Injecting the medicine

- Disinfect the metal/rubber tip of the cartridge by again wiping it with an alcohol swab. This must be done each time before the medicine is taken from the cartridge.
- Take out an insulin syringe and remove its needle guard. Hold the GENOTROPIN Mixer upside down so the metal/rubber tip is pointing downward.
- Stick the needle of the syringe through the rubber tip of the cartridge in the GENOTROPIN Mixer. Make sure the needle tip always stays below the level of the liquid. This will help keep air from entering the syringe.
- Hold the side of the syringe body and the end of the syringe plunger rod. Pull the plunger of the syringe back slowly. This will draw out your prescribed dose.
- Hold the GENOTROPIN Mixer and syringe with its needle pointing up. Gently tap the side of the syringe to move any air bubbles to the top. Then, push the syringe's plunger gently. This will force the air bubbles out. Check the dosage again to make sure you have withdrawn the prescribed amount of medicine. Remove the syringe. It is now ready for your injection.
- Clean your skin of germs where you plan to inject, as your health care provider has taught you. Pinch the skin firmly between your thumb and forefinger. Hold the syringe close to your injection.
- Gently and smoothly inject the medicine until the syringe is empty. Pull the needle straight out, quickly. Press firmly on the injection area with a dry gauze pad.
- Put the needle in a proper disposal container.
- Choose a different injection site each day.

Storing the GENOTROPIN Mixer

The GENOTROPIN Mixer and cartridges must be stored under refrigeration at 36°F to 46°F (2°C to 8°C). Do not freeze. Protect from light.

Reusing the GENOTROPIN Mixer

The cartridge of medicine can be used again for up to 28 days after mixing. Simply follow the instructions above. You can get more needles with a new cartridge.

Changing the cartridge

When the cartridge is empty, you can use the GENOTROPIN Mixer with a new cartridge:
- Unscrew the plunger rod from the GENOTROPIN Mixer.
- Remove and throw out the old cartridge.
- Follow the steps beginning with Step 2 for your next injection.

Questions about how to use the GENOTROPIN Mixer®?

Contact your health care provider, call the Pfizer Bridge Program® at 1-800-645-1280, or visit our Web site at www.genotropin.com

GENOTROPIN cartridges contain m-Cresol and should not be used by patients allergic to it.

Use a different place on the body each day for growth hormone injections. This can help to prevent skin problems such as lumpiness or soreness.

A health care provider will help you with the first injection. He or she will also train you on how to inject GENOTROPIN.

Rx only

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full prescribing information and full Instructions for Use.

www.genotropin.com

Since your medicine comes in a 2-chamber cartridge, it needs to be mixed. The GENOTROPIN Mixer is a device to mix your drug.

To inject your medicine, you will need the following:
- GENOTROPIN Mixer with pressure-release needle
- One cartridge containing drug and liquid
- Alcohol swab
- Insulin syringe for injection
- Container for proper disposal

Before you begin

- First, wash and dry your hands.
- Unscrew the dark green plunger rod from the light green holder of the GENOTROPIN Mixer.
- Remove the cartridge of drug from its package.

Mixing the drug

- Put the cartridge into the GENOTROPIN Mixer with its metal/rubber tip facing into the open end of the holder. You should be able to see the metal/rubber tip. It should stick out from the opening at the front of the holder.
- Screw the plunger rod back into the holder. This will mix the drug and the liquid.

Caution: Look in the window of the GENOTROPIN Mixer to make sure the medicine is completely dissolved. If it is not, gently tip the GENOTROPIN Mixer from side to side. Do this until the liquid is clear. Do not shake!

Look carefully at the now-mixed medicine. Nothing should be floating in it, and it should be clear.

Releasing pressure

- Disinfect the metal/rubber tip of the cartridge by wiping it with an alcohol swab.
- Remove the cap from the pressure-release needle. Do not touch the needle. With the metal/rubber tip of the cartridge pointing up, pierce the rubber tip with the needle. This will release extra pressure in the cartridge. Be sure the cartridge is upright when pierced. This is to make sure the medicine doesn't spill out. (Only do this step the first time you use a new cartridge.)
- Remove the needle from the cartridge and replace its cap. Put it in a proper disposal container.
Injecting the medicine
• Disinfect the metal/rubber tip of the cartridge by again wiping it with an alcohol swab. This must be done each time before the medicine is taken from the cartridge.
• Take out an insulin syringe and remove its needle guard. Hold the GENOTROPIN Mixer upside down so the metal/rubber tip is pointing downward.
• Stick the needle of the syringe through the rubber tip of the cartridge in the GENOTROPIN Mixer. Make sure the needle tip always stays below the level of the liquid. This will help keep air from entering the syringe.
• Hold the side of the syringe body and the end of the syringe plunger rod. Pull the plunger of the syringe back slowly. This will draw out your prescribed dose.
• Hold the GENOTROPIN Mixer and syringe with its needle pointing up. Gently tap the side of the syringe to move any air bubbles to the top. Then, push the syringe's plunger gently. This will force the air bubbles out. Check the dosage again to make sure you have withdrawn the prescribed amount of medicine. Remove the syringe. It is now ready for your injection.
• Clean your skin of germs where you plan to inject, as your health care provider has taught you. Pinch the skin firmly between your thumb and forefinger. Hold the syringes close to the needle — like a dart. Push it into the skin straight up or at a slight tilt with a quick, firm action.
• Gently and smoothly inject the medicine until the syringe is empty. Pull the needle straight out, quickly. Press firmly on the injection area with a dry gauze pad.
• Put the needle in a proper disposal container.
• Choose a different injection site each day.

Storing the GENOTROPIN Mixer
The GENOTROPIN Mixer and cartridges must be stored under refrigeration at 36°F to 46°F (2°C to 8°C). Do not freeze. Protect from light.

Mixing the drug
• Put the cartridge into the GENOTROPIN Mixer with its metal/rubber tip facing into the open end of the holder. You should be able to see the metal/rubber tip. It should stick out from the opening at the front of the holder.
• Screw the plunger rod back into the holder. This will mix the drug and the liquid.

Caution: Look in the window of the GENOTROPIN Mixer to make sure the medicine is completely dissolved. If it is not, gently tip the GENOTROPIN Mixer from side to side. Do this until the liquid is clear. Do not shake!
Look carefully at the now-mixed medicine. Nothing should be floating in it, and it should be clear.

GENOTROPIN cartridges contain m-Cresol and should not be used by patients allergic to it.

Use a different place on the body each day for growth hormone injections. This can help to prevent skin problems such as lumpiness or soreness.
A health care provider will help you with the first injection. He or she will also train you on how to inject.

Steps for releasing pressure
• Disinfect the metal/rubber tip of the cartridge by wiping it with an alcohol swab.
• Remove the cap from the pressure-release needle. Do not touch the needle. With the metal/rubber tip of the cartridge pointing up, pierce the rubber tip with the needle. This will release extra pressure in the cartridge. Be sure the cartridge is upright when pierced. This is so the medicine doesn’t spill out. (Only do this step the first time you use a new cartridge.)
• Remove the needle from the cartridge and replace its cap. Put it in a proper disposal container.

Questions about how to use the GENOTROPIN Mixer®?
Contact your health care provider, call the Pfizer Bridge Program® at 1-800-645-1280, or visit our Web site at www.genotropin.com.

www.genotropin.com

Since your medicine comes in a 2-chamber cartridge, it needs to be mixed. The GENOTROPIN Mixer is a device to mix your drug.
To inject your medicine, you will need the following:
• GENOTROPIN Mixer with pressure-release needle
• One cartridge containing drug and liquid
• Alcohol swab
• Insulin syringe for injection
• Container for proper disposal

Before you begin
• First, wash and dry your hands.
• Unscrew the dark green plunger rod from the light green holder of the GENOTROPIN Mixer.
• Remove the cartridge of drug from its package.

Changing the cartridge
When the cartridge is empty, you can use the GENOTROPIN Mixer with a new cartridge:
• Unscrew the plunger rod from the GENOTROPIN Mixer.
• Remove and throw out the old cartridge.
• Follow the steps beginning with Step 2 for your next injection.

Changing the cartridge from your supplier.
When the cartridge is empty, you can use the GENOTROPIN Mixer. Simply follow the instructions above. You can get more needles.

Rx only
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full prescribing information and full Instructions for Use.

[Image: Diagram of GENOTROPIN Mixer and instructions]
GENOTROPIN® (somatropin) for injection, for subcutaneous use

Initial U.S. Approval: 1987

--- INDICATIONS AND USAGE ---

GENOTROPIN is a recombinant human growth hormone indicated for:

- **Pediatric**: Treatment of children with growth failure due to growth hormone deficiency (GHD), Prader-Willi syndrome, Small for Gestational Age, Turner syndrome, and Idiopathic Short Stature.
- **Adult**: Treatment of adults with either adult onset or childhood onset GHD.

--- CONTRAINDICATIONS ---

- Hypersensitivity to somatropin or excipients
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy
- Children with closed epiphyses

--- WARNINGS AND PRECAUTIONS ---

- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk.
- Prader-Willi syndrome in Children: Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment. Discontinue treatment if these signs occur.
- Neoplasms: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin in particular meningiomas in patients treated with radiation to the head for their first neoplasm.
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked periodically.
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain.
- Progression of Preexisting Scoliosis: Monitor any child with scoliosis for progression of the curve.
- Prader-Willi Syndrome in Children: Evaluate for signs of upper airway obstruction.

--- ADVERSE REACTIONS ---

- Other common somatropin-related adverse reactions include injection site reactions/flushes and lipatrophy.

--- HOW SUPPLIED/STORAGE AND HANDLING ---

- New cartridge provides a pen delivery system. Each cartridge contains:
  - 0.2 mg (green tip)
  - 0.4 mg
  - 0.6 mg
  - 0.8 mg
  - 1.0 mg
  - 1.2 mg
  - 1.4 mg
  - 1.6 mg
  - 1.8 mg
  - 2.0 mg

--- PATIENT COUNSELING INFORMATION ---

--- FULL PRESCRIBING INFORMATION: CONTENTS ---

1 INDICATIONS AND USAGE
1.1 Pediatric Patients
1.2 Adult Patients

2 DOSAGE AND ADMINISTRATION
2.1 Dosing of Pediatric Patients
2.2 Dosing of Adult Patients
2.3 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Acute Critical Illness
5.2 Prader-Willi Syndrome in Children
5.3 Neoplasms
5.4 Impaired Glucose Tolerance and Diabetes Mellitus
5.5 Intracranial Hypertension
5.6 Severe Hypersensitivity
5.7 Fluid Retention
5.8 Hypoadrenalism
5.9 Hypothyroidism
5.10 Slipped Capital Femoral Epiphysis in Pediatric Patients
5.11 Progression of Preexisting Scoliosis in Pediatric Patients
5.12 Otitis Media and Cardiovascular Disorders in Turner Syndrome
5.13 Lipoatrophy
5.14 Laboratory Tests
5.15 Pancreatitis

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience

7 DRUG INTERACTIONS
7.1 11β-Hydroxysteroid Dehydrogenase Type 1
7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment
7.3 Cytochrome P450-Metabolized Drugs
7.4 Oral Estrogen
7.5 Insulin and/or Oral/Injectable Hypoglycemic Agents

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Adult Growth Hormone Deficiency
14.2 Prader-Willi Syndrome
14.3 SGA
14.4 Turner Syndrome
14.5 Idiopathic Short Stature

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.*
Non-weight based — based on published consensus guidelines, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor 1 (IGF-I) concentrations. The dose should be decreased as necessary on the basis of adverse events and/or serum IGF-I concentrations above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person, and between male and female patients.

Weight based — based on the dosing regimen used in the original adult GHD registration trials, the recommended dosage at the start of treatment is not more than 0.04 mg/kg/week. The dose may be increased according to individual patient requirements to not more than 0.08 mg/kg/week at 4-8 week intervals. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I concentrations should be used as guidance in dose titration. A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

2.3 Preparation and Administration

The GENOTROPIN 5 and 12 mg cartridges are color-coded to help ensure proper use with the GENOTROPIN Pen delivery device. The 5 mg cartridge has a green tip to match the green pen window on the Pen 5, while the 12 mg cartridge has a purple tip to match the purple pen window on the Pen 12.

Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. GENOTROPIN MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

GENOTROPIN may be given in the thigh, buttoks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

3 DOSE FORMS AND STRENGTHS

GENOTROPIN lyophilized powder:
- 5 mg two-chamber cartridge (green tip, with preservative) concentration of 5 mg/mL
- 12 mg two-chamber cartridge (purple tip, with preservative) concentration of 12 mg/mL

GENOTROPIN MINIQUICK Growth Hormone Delivery Device containing a two-chamber cartridge of GENOTROPIN (without preservative):
- 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg

4 CONTRAINDICATIONS

Acute Critical Illness

Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure [see Warnings and Precautions (5.1)].

Prader-Willi Syndrome in Children
Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients [see Warnings and Precautions (5.2)].

Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

Hypersensitivity

GENOTROPIN is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. The 5 mg and 12 mg presentations of GENOTROPIN lyophilized powder contain m-cresol as a preservative. Systemic hypersensitivity reactions have been reported with post-marketing use of somatropin products [see Warnings and Precautions (5.6)].

Diabetic Retinopathy
Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

Closed Epiphyses
Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin [see Contraindications (4)]. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated
5.1 Prader-Willi Syndrome in Children

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: somatotropin resistance, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also be followed for weight control and monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively [see Contraindications (4)].

5.2 Neoplasms

In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence [see Contraindications (4)]. Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor.

5.3 Impaired Glucose Tolerance and Diabetes Mellitus

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. New-onset Type 1 and 2 diabetes mellitus and glucose intolerance have been reported. In susceptible patients, hypoglycemia was the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence [see Contraindications (4)]. Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor.

5.4 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude premature increases in intracranial pressure due to intermittent monitoring. If papilledema is observed by funduscopic examination before initiating treatment with somatropin, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome and Prader-Willi syndrome may be at increased risk for the development of IH.

5.5 Severe Hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs [see Contraindications (4)].

5.6 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention (e.g., edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias) are usually transient and dose dependent.

5.7 Hypoadrenalism

Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of secondary (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment [see Section 7.1, 11-β Hydroxysteroid Dehydrogenase Type 1].

5.8 Hypothyroidism

Untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

5.9 Hyperglycemia

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs [see Contraindications (4)].

5.10 Slipped Capital Femoral Epiphyses in Pediatric Patients

Slipped capital femoral epiphyses may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

5.11 Progression of Preexisting Scoliosis in Pediatric Patients

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

5.12 Otitis Media and Cardiovascular Disorders in Turner Syndrome

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin therapy may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

5.13 Lipatrophy

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site [see Dosage and Administration. (2.3)].

5.14 Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 may increase during somatropin therapy.

5.15 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops persistent severe abdominal pain.

6. ADVERSE REACTIONS

The following important adverse reactions are also described elsewhere in the labeling:

- Increased mortality in patients with acute critical illness [see Warnings and Precautions (5.1)]
- Fatalities in children with Prader-Willi syndrome [see Warnings and Precautions (5.2)]
- Neoplasms [see Warnings and Precautions (5.3)]
- Hypothyroidism [see Warnings and Precautions (5.4)]
- Intracranial hypertension [see Warnings and Precautions (5.5)]
- Severe hypersensitivity [see Warnings and Precautions (5.6)]
- Fluid retention [see Warnings and Precautions (5.7)]
- Hypoadrenalism [see Warnings and Precautions (5.8)]
- Hypothyroidism [see Warnings and Precautions (5.9)]
- Slipped capital femoral epiphysis in pediatric patients [see Warnings and Precautions (5.10)]
- Progression of preexisting scoliosis in pediatric patients [see Warnings and Precautions (5.11)]
- Otitis media and cardiovascular disorders in patients with Turner syndrome [see Warnings and Precautions (5.12)]
- Lipatroph [see Warnings and Precautions (5.13)]
- Pancreatitis [see Warnings and Precautions (5.15)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatropin formulation, and may not reflect the adverse reaction rates observed in practice.

Clinical Trials in children with GHD

In clinical studies with GENOTROPIN in pediatric GHD patients, the following events were reported infrequently: injection site reactions, including pain or burning associated with the injection, fibrosis, nodules, rash, inflammation, pigmentation, or bleeding; lipatrophy; headache; hematoma; hypothyroidism; and mild hyperglycemia.

Clinical Trials in PWS

In two clinical studies with GENOTROPIN in pediatric patients with Prader-Willi syndrome, the following drug-related events were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.

Clinical Trials in children with SGA

In clinical studies of 273 pediatric patients born small for gestational age treated with GENOTROPIN, the following clinically significant events were reported: mild transient intracranial hypertension, two patients with central precocious puberty, two patients with jaw prominence, and several patients with aggravation of preexisting scoliosis, injection site reactions, and self-limited progression of pigmented nevi. Anti-hGH antibodies were not detected in any of the patients treated with GENOTROPIN.

Clinical Trials in children with Turner Syndrome

In two clinical studies with GENOTROPIN in pediatric patients with Turner syndrome, the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain, and urinary tract infection. The only treatment-related adverse event that occurred in more than 1 patient was joint pain.
Clinical Trials in children with Idiopathic Short Stature

In two open-label clinical studies with GENOTROPIN in pediatric patients with ISS, the most commonly encountered adverse events include upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia. In one of the two studies, during GENOTROPIN treatment, the mean IFG-1 standard deviation (SD) scores were maintained in the normal range. IFG-1 SD scores above +2 SD were observed as follows: 1 subject (3%), 10 subjects (20%) and 16 subjects (38%) in the untreated control. 0.23 and the 0.47 mg/kg/week groups, respectively, had at least one measurement; while 0 subjects (0%), 2 subjects (7%) and 6 subjects (14%) had two or more consecutive IFG-1 measurements above +2 SD.

Clinical Trials in adults with GHD

In clinical trials with GENOTROPIN in 1,145 GHD adults, the majority of the adverse events consisted of mild to moderate symptoms of fluid retention, including peripheral swelling, arthralgia, pain and stiffness of the extremities, peripheral edema, myalgia, paresthesia, and hypoesthesia. These events were reported early during therapy, and tended to be transient and/or responsive to dosage reduction.

Table 1:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Double Blind Phase</th>
<th>Open Label Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n = 572</td>
<td>GENOTROPIN n = 573</td>
</tr>
<tr>
<td></td>
<td>6–12 mo. % Patients</td>
<td>6–12 mo. % Patients</td>
</tr>
<tr>
<td></td>
<td>0–6 mo. % Patients</td>
<td>12–18 mo. % Patients</td>
</tr>
<tr>
<td></td>
<td>0–6 mo. % Patients</td>
<td>18–24 mo. % Patients</td>
</tr>
<tr>
<td>Swelling, peripheral</td>
<td>5.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>14.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Pain, extremities</td>
<td>5.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>2.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Headache</td>
<td>7.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Stiffness of extremities</td>
<td>1.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.4</td>
<td>3.4</td>
</tr>
</tbody>
</table>

* Increased significantly when compared to placebo. P<0.05. Fisher's Exact Test (one-sided)

7. DRUG INTERACTIONS

7.1 11β-Hydroxysteroid Dehydrogenase Type 1

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypogonadism, may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of the drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1 [see Warnings and Precautions (5.8)].

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement doses should be carefully adjusted in children receiving concomitant somatropin and glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.

7.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)-mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.4 Oral Estrogen

In patients on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal [see Dosage and Administration (2.2)].

7.5 Insulin and/or Oral/Injectable Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated [see Warnings and Precautions (5.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies carried out with GENOTROPIN at doses of 0.3, 1, and 3.3 mg/kg/day administered SC in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving SC doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times the human dose) produced anestrus or extended estrus cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted.

In perinatal and postnatal studies in rats, GENOTROPIN doses of 0.3, 1 and 3.3 mg/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offspring due to GENOTROPIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
8.3 Nursing Mothers

There have been no studies conducted with GENOTROPIN in nursing mothers. It is not
known whether this drug is excreted in human milk. Because many drugs are excreted
in human milk, caution should be exercised when GENOTROPIN is administered to a
nursing woman.

8.5 Geriatric Use

The safety and effectiveness of GENOTROPIN in patients aged 65 and over have not
been evaluated in clinical studies. Elderly patients may be more sensitive to the action
of GENOTROPIN, and therefore may be more prone to develop adverse reactions. A lower
starting dose and smaller dose increments should be considered for older patients [see Dosage and Administration (2.2)].

10 OVERDOSAGE

Short-Term

Short-term overdosage could lead initially to hypoglycemia and subsequently to
hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention.

Long-Term

Long-term overdosage could result in signs and symptoms of gigantism and/or
acromegaly consistent with the known effects of excess growth hormone [see Dosage and Administration (2)].

11 DESCRIPTION

GENOTROPIN lyophilized powder contains somatropin, which is a polypeptide hormone
of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of
22,124 daltons. The amino acid sequence of the product is identical to that of human
growth hormone of pituitary origin (somatropin). GENOTROPIN is synthesized in a strain
of Escherichia coli that has been modified by the addition of the gene for human growth
hormone. GENOTROPIN is a sterile white lyophilized powder intended for subcutaneous
injection.

GENOTROPIN 5 mg is dispensed in a two-chamber cartridge. The front chamber contains
recombinant somatropin 5.8 mg, glycine 2.2 mg, mannitol 1.8 mg, sodium dihydrogen
phosphate anhydrous 0.32 mg, and disodium phosphate anhydrous 0.31 mg; the rear
chamber contains 0.3% m-Cresol (as a preservative) and mannitol 45 mg in 1.14 mL
water for injection. The GENOTROPIN 5 mg two-chamber cartridge contains 5.8 mg of
somatropin. The reconstituted concentration is 5 mg/mL. The cartridge contains overfill
to allow for delivery of 1mL containing the stated amount of GENOTROPIN – 5 mg.

GENOTROPIN 12 mg is dispensed in a two-chamber cartridge. The front chamber contains
recombinant somatropin 13.8 mg, glycine 2.3 mg, mannitol 14.0 mg, sodium dihydrogen
phosphate anhydrous 0.47 mg, and disodium phosphate anhydrous 0.46 mg; the rear
chamber contains 0.3% m-Cresol (as a preservative) and mannitol 32 mg in 1.13 mL
water for injection. The GENOTROPIN 12 mg two-chamber cartridge contains 13.8 mg
of somatropin. The reconstituted concentration is 12 mg/mL. The cartridge contains overfill
to allow for delivery of 1mL containing the stated amount of GENOTROPIN – 12 mg.

GENOTROPIN MINIQUICK® is dispensed as a single-use syringe device containing a
two-chamber cartridge. GENOTROPIN MINIQUICK is available as individual doses of 0.2 mg to
2.0 mg in 0.2 mg increments. The front chamber contains recombinant somatropin 0.22 to
2.2 mg, glycine 0.23 mg, mannitol 1.14 mg, sodium dihydrogen phosphate 0.05 mg, and
disodium phosphate anhydrous 0.027 mg; the rear chamber contains mannitol 12.6 mg in
water for injection 0.275 mL. The reconstituted GENOTROPIN MINIQUICK two-chamber
cartridge contains overfill to allow for delivery of 0.25 mL containing the stated amount
of GENOTROPIN.

GENOTROPIN is a highly purified preparation. The reconstituted recombinant somatropin
solution has an osmolality of approximately 300 mosm/kg, and a pH of approximately 6.7.
The concentration of the reconstituted solution varies by strength and presentation (see HOW SUPPLIED).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In vitro, preclinical, and clinical tests have demonstrated that GENOTROPIN lyophilized
powder is therapeutically equivalent to human growth hormone of pituitary origin and
achieves similar pharmacokinetic profiles in normal adults. In pediatric patients who have
growth hormone deficiency (GHD), Frader-Willis syndrome (PWS), were born small for
gestational age (SGA), have Turner syndrome (TS), or have idiopathic short stature
(ISS), treatment with GENOTROPIN stimulates linear growth. In patients with GHD or PWS,
treatment with GENOTROPIN achieves similar pharmacokinetic profiles in normal adults. In pediatric patients who have

12.2 Pharmacodynamics

A. Skeletal Growth: GENOTROPIN stimulates skeletal growth in pediatric patients
with GHD, PWS, SGA, TS, or ISS. The measurable increase in body length after
administration of GENOTROPIN results from an effect on the epiphyseal plates of long
bones. Concentrations of IGF-I, which may play a role in skeletal growth, are generally
low in the serum of pediatric patients with GHD, PWS, or SGA, but tend to increase
during treatment with GENOTROPIN. Elevations in mean serum alkaline phosphatase
concentration are also seen.

B. Cell Growth: It has been shown that there are fewer skeletal muscle cells in short-
statured pediatric patients who lack endogenous growth hormone as compared with
the normal pediatric population. Treatment with somatropin results in an increase in
both the number and size of muscle cells.

Protein Metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention,
as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows
the initiation of therapy with GENOTROPIN.

Carbohydrate Metabolism

Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia that
is improved by treatment with GENOTROPIN. Large doses of growth hormone may impair
glucose tolerance.

Lipid Metabolism

In GHD patients, administration of somatropin has resulted in lipid mobilization, reduction
in body fat stores, and increased plasma fatty acids.

Mineral Metabolism

Somatropin induces retention of sodium, potassium, and phosphorus. Serum
concentrations of inorganic phosphate are increased in patients with GHD after therapy
with GENOTROPIN. Serum calcium is not significantly altered by GENOTROPIN. Growth
hormone could increase calcitriol.

Body Composition

Adult GHD patients treated with GENOTROPIN at the recommended adult dose (see DOSAGE AND ADMINISTRATION) demonstrate a decrease in fat mass and an increase in
lean body mass. When these alterations are coupled with the increase in total body
water, the overall effect of GENOTROPIN is to modify body composition, an effect that
is maintained with continued treatment.

12.3 Pharmacokinetics

Absorption

Following a 0.03 mg/kg subcutaneous (SC) injection in the thigh of 1.3 mg/mL
GENOTROPIN to adult GHD patients, approximately 80% of the dose was systemically
available as compared with that available following intravenous dosing. Results were
comparable in both male and female patients. Similar bioavailability has been observed in
healthy adult male subjects.

In healthy adult males, following an SC injection in the thigh of 0.03 mg/kg, the extent of
absorption (AUC) of a concentration of 5.3 mg/mL GENOTROPIN was 35% greater than
that for 1.3 mg/mL GENOTROPIN. The mean ± (standard deviation) peak (Cmax) serum
levels were 23.0 (± 9.4) ng/mL and 17.4 (± 9.2) ng/mL.

In a similar study involving pediatric GHD patients, 5.3 mg/mL GENOTROPIN yielded a
mean AUC that was 17% greater than that for 1.3 mg/mL GENOTROPIN. The mean Cmax
levels were 21.0 ng/mL and 16.3 ng/mL, respectively.

Adult GHD patients received two single SC doses of 0.03 mg/kg of GENOTROPIN at a
concentration of 1.3 mg/mL; with a one- to four-week washout period between injections.
Mean Cmax levels were 12.4 ng/mL (first injection) and 12.2 ng/mL (second injection),
achieved at approximately six hours after dosing.

There are no data on the bioequivalence between the 12 mg/mL formulation and either the
1.3 mg/mL or the 5.3 mg/mL formulations.

Distribution

The mean volume of distribution of GENOTROPIN following administration to GHD adults
was estimated to be 1.3 (± 0.8) L/kg.

Metabolism

The metabolic fate of GENOTROPIN involves classical protein catabolism in both the liver
and kidneys. In renal cells, at least a portion of the breakdown products are returned to
the systemic circulation. The mean terminal half-life of intravenous GENOTROPIN in normal
adults is 0.4 hours, whereas subcutaneously administered GENOTROPIN has a half-life
of 3.0 hours in GHD adults. The observed difference is due to slow absorption from the
subcutaneous injection site.

Excretion

The mean clearance of subcutaneously administered GENOTROPIN in 16 GHD adult
days was 0.3 (± 0.11) L/hr/kg.

Special Populations

Pediatric: The pharmacokinetics of GENOTROPIN are similar in GHD pediatric and adult
patients.

Gender: No gender studies have been performed in pediatric patients; however, in
GHD adults, the absolute bioavailability of GENOTROPIN was similar in males and females.

Race: No studies have been conducted with GENOTROPIN to assess pharmacokinetic
differences among races.

Renal or hepatic insufficiency: No studies have been conducted with GENOTROPIN in
these patient populations.

Table 2

<table>
<thead>
<tr>
<th>Mean SC Pharmacokinetic Parameters in Adult GHD Patients</th>
<th>Bioavailability (%) (N=15)</th>
<th>T_max (hours) (N=16)</th>
<th>CL/F (L/hr x kg) (N=16)</th>
<th>Vss/F (L/kg) (N=16)</th>
<th>T1/2 (hours) (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD)</td>
<td>80.5 (± 1.65)</td>
<td>5.9 (± 1.65)</td>
<td>0.3 (± 0.11)</td>
<td>1.3 (± 0.80)</td>
<td>3.0 (± 1.44)</td>
</tr>
<tr>
<td>95% CI</td>
<td>70.5 – 92.1</td>
<td>5.0 – 6.7</td>
<td>0.2 – 0.4</td>
<td>0.9 – 1.8</td>
<td>2.2 – 3.7</td>
</tr>
</tbody>
</table>

T_max: time of maximum plasma concentration

Vss/F: volume of distribution

The absolute bioavailability was estimated under the assumption that the
log-transformed data follow a normal distribution. The mean and standard
deviation of the log-transformed data were mean = 0.22 (± 0.241).
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with GENOTROPIN. No potential mutagenicity of GENOTROPIN was revealed in a battery of tests including induction of gene mutations in bacteria (the Ames test), gene mutations in mammalian cells grown in vitro (mouse L5178Y cells), and chromosomal damage in intact animals (bone marrow cells in rats). See PREGNANCY section for effect on fertility.

14 CLINICAL STUDIES

14.1 Adult Growth Hormone Deficiency (GHD)

GENOTROPIN lyophilized powder was compared with placebo in six randomized clinical trials involving a total of 172 adult GHD patients. These trials included a 6-month double-blind treatment period, during which 85 patients received GENOTROPIN and 87 patients received placebo, followed by an open-label treatment period in which participating patients received GENOTROPIN for up to a total of 24 months. GENOTROPIN was administered as a daily SC injection at a dose of 0.04 mg/kg/week for the first month of treatment and 0.08 mg/kg/week for subsequent months.

Beneficial changes in body composition were observed at the end of the 6-month treatment period for the patients receiving GENOTROPIN as compared with the placebo patients. Lean body mass, total body water, and lean/fat ratio increased while total body fat mass and waist circumference decreased. These effects on body composition were maintained when treatment was continued beyond 6 months. Bone mineral density declined after 6 months of treatment but returned to baseline values after 12 months of treatment.

14.2 Prader-Willi Syndrome (PWS)

The safety and efficacy of GENOTROPIN in the treatment of pediatric patients with Prader-Willi syndrome (PWS) was evaluated in two randomized, open-label, controlled clinical trials. Patients received either GENOTROPIN or no treatment for the first year of the studies, while all patients received GENOTROPIN during the second year. GENOTROPIN was administered as a daily SC injection, and the dose was calculated for each patient every 3 months. In Study 1, the treatment group received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week. In Study 2, the treatment group received GENOTROPIN at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week.

Patients who received GENOTROPIN showed significant increases in linear growth during the first year of study, compared with patients who received no treatment (see Table 3). Linear growth continued to increase in the second year, when both groups received treatment with GENOTROPIN.

### Table 3
Efficacy of GENOTROPIN in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GENOTROPIN (0.24 mg/kg/week) n=15</td>
<td>Untreated Control n=12</td>
</tr>
<tr>
<td>Linear growth (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline height</td>
<td>112.7 ± 14.9</td>
<td>109.5 ± 12.0</td>
</tr>
<tr>
<td>Growth from months 0 to 12</td>
<td>11.6* ± 2.3</td>
<td>5.0 ± 1.2</td>
</tr>
<tr>
<td>Height Standard Deviation Score (SDF) for age Baseline SDF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.6 ± 1.3</td>
<td>-1.8 ± 1.5</td>
<td>-2.6 ± 1.7</td>
</tr>
<tr>
<td>SDS at 12 months</td>
<td>-0.5* ± 1.3</td>
<td>-1.9 ± 1.4</td>
</tr>
</tbody>
</table>

* p < 0.001
† p < 0.002 (when comparing SDS change at 12 months)

Changes in body composition were also observed in the patients receiving GENOTROPIN (see Table 4). These changes included a decrease in the amount of fat mass, and increases in the amount of lean body mass and the ratio of lean-to-fat tissue, while changes in body weight were similar to those seen in patients who received no treatment. Treatment with GENOTROPIN did not accelerate bone age, compared with patients who received no treatment.

### Table 4
Effect of GENOTROPIN on Body Composition in Pediatric Patients with Prader-Willi Syndrome (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>GENOTROPIN n=14</th>
<th>Untreated Control n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat mass (kg) Baseline</td>
<td>12.3 ± 6.8</td>
<td>9.4 ± 4.9</td>
</tr>
<tr>
<td>Change from months 0 to 12</td>
<td>-0.9* ± 2.2</td>
<td>2.3 ± 2.4</td>
</tr>
<tr>
<td>Lean body mass (kg) Baseline</td>
<td>15.6 ± 5.7</td>
<td>14.3 ± 4.0</td>
</tr>
<tr>
<td>Change from months 0 to 12</td>
<td>4.7* ± 1.9</td>
<td>0.7 ± 2.4</td>
</tr>
<tr>
<td>Lean body mass/ Fat mass Baseline</td>
<td>1.4 ± 1.4</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Change from months 0 to 12</td>
<td>0.10* ± 0.6</td>
<td>-0.1 ± 0.6</td>
</tr>
<tr>
<td>Body weight (kg) Baseline</td>
<td>27.2 ± 12.0</td>
<td>23.2 ± 7.0</td>
</tr>
<tr>
<td>Change from months 0 to 12</td>
<td>3.7* ± 2.0</td>
<td>3.5 ± 1.9</td>
</tr>
</tbody>
</table>

* p < 0.005
† n=15 for the group receiving GENOTROPIN; n=12 for the Control group
‡ n.s.

14.3 SGA

Pediatric Patients Born Small for Gestational Age (SGA) Who Fail to Manifest Catch-up Growth by Age 2

The safety and efficacy of GENOTROPIN in the treatment of children born small for gestational age (SGA) were evaluated in 4 randomized, open-label, controlled clinical trials. Patients (age range of 2 to 8 years) were observed for 12 months before being randomized to receive either GENOTROPIN (two doses per study, most often 0.24 and 0.48 mg/kg/week) or placebo, followed by 2 months of open-label treatment with GENOTROPIN (see Table 5). Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height standard deviation score (SDS) with a median increase of 2.4 SDS units (p = 0.001) compared with children treated with 0.24 mg/kg/week.

### Table 5
Efficacy of GENOTROPIN in Children Born Small for Gestational Age (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>GENOTROPIN (0.24 mg/kg/week) n=76</th>
<th>GENOTROPIN (0.48 mg/kg/week) n=93</th>
<th>Untreated Control n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height Standard Deviation Score (SDS) Baseline SDS</td>
<td>-3.2 ± 0.8</td>
<td>-3.4 ± 1.0</td>
<td>-3.1 ± 0.9</td>
</tr>
<tr>
<td>SDS at 24 months</td>
<td>-2.0 ± 0.8</td>
<td>-1.7 ± 1.0</td>
<td>-2.9 ± 0.9</td>
</tr>
<tr>
<td>Change in SDS from baseline to month 24</td>
<td>1.2* ± 0.5</td>
<td>1.7*± 0.6</td>
<td>0.1 ± 0.3</td>
</tr>
</tbody>
</table>

* p = 0.0001 vs Untreated Control group
† p = 0.0001 vs group treated with GENOTROPIN 0.24 mg/kg/week

14.4 Turner Syndrome

Two randomized, open-label, clinical trials were conducted that evaluated the efficacy and safety of GENOTROPIN in Turner syndrome patients with short stature. Turner syndrome patients were treated with GENOTROPIN alone or GENOTROPIN plus adjunctive hormonal therapy (ethinylestradiol or oxandrolone). A total of 38 patients were treated with GENOTROPIN alone in the two studies. In Study 055, 22 patients were treated for 12 months, and in Study 092, 16 patients were treated for 12 months. Patients received GENOTROPIN at a dose between 0.13 to 0.33 mg/kg/week.

For height velocity and height are expressed using either the Tanner (Study 055) or Sempé (Study 092) standards for age-matched normal children as well as the Randé standard (both studies) for age-matched, untreated Turner syndrome patients. As seen in Table 6, height velocity SDS and height SDS values were smaller at baseline and after treatment with GENOTROPIN when the normative standards were utilized as opposed to the Turner syndrome standard.

Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with GENOTROPIN (see Table 6). The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of GENOTROPIN.
The long-term efficacy and safety of GENOTROPIN in patients with idiopathic short stature (ISS) were evaluated in a randomized, open-label, clinical trial that enrolled 177 children. Patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL, and prepubertal status. Baseline patient characteristics (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months

**Table 6**

<table>
<thead>
<tr>
<th></th>
<th>GENOTROPIN</th>
<th>GENOTROPIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.33 mg/kg/week</td>
<td>0.13–0.23 mg/kg/week</td>
</tr>
<tr>
<td></td>
<td>Study 055* n=22</td>
<td>Study 092# n=16</td>
</tr>
<tr>
<td><strong>Height Velocity (cm/yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.1 ± 1.5</td>
<td>3.9 ± 1.0</td>
</tr>
<tr>
<td>Month 12</td>
<td>7.8 ± 1.6</td>
<td>6.1 ± 0.9</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>3.7 (3.0, 4.3)</td>
<td>2.2 (1.5, 2.9)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td><em><em>Height Velocity SDS (Tanner</em>/Sempé# Standards)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-2.3 ± 1.4</td>
<td>-1.6 ± 0.6</td>
</tr>
<tr>
<td>Month 12</td>
<td>2.2 ± 2.3</td>
<td>0.7 ± 1.3</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>4.6 (3.5, 5.6)</td>
<td>2.2 (1.4, 3.0)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Height SDS (Ranke Standard)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-0.1 ± 1.2</td>
<td>-0.4 ± 0.6</td>
</tr>
<tr>
<td>Month 12</td>
<td>4.2 ± 1.2</td>
<td>2.3 ± 1.2</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>4.3 (3.5, 5.0)</td>
<td>2.7 (1.8, 3.5)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td><em><em>Height SDS (Tanner</em>/Sempé# Standards)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-3.1 ± 1.0</td>
<td>-3.2 ± 1.0</td>
</tr>
<tr>
<td>Month 12</td>
<td>-2.7 ± 1.1</td>
<td>-2.9 ± 1.0</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.4 (0.3, 0.6)</td>
<td>0.3 (0.1, 0.4)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Height SDS (Ranke Standard)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-0.2 ± 0.8</td>
<td>-0.3 ± 0.8</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.6 ± 0.9</td>
<td>0.1 ± 0.8</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.8 (0.7, 0.9)</td>
<td>0.5 (0.4, 0.5)</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
</tbody>
</table>

SDS = Standard Deviation Score
Ranke standard based on age-matched, untreated Turner syndrome patients
Tanner*/Sempé# standards based on age-matched normal children

14.5 Idiopathic Short Stature
The long-term efficacy and safety of GENOTROPIN in patients with idiopathic short stature (ISS) were evaluated in one randomized, open-label, clinical trial that enrolled 177 children. Patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL, and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and were subsequently randomized to GENOTROPIN or observation only and followed to final height. Two GENOTROPIN doses were evaluated in this trial: 0.23 mg/kg/week (0.033 mg/kg/day) and 0.47 mg/kg/week (0.067 mg/kg/day). Baseline patient characteristics (n=105) were: mean (SD) 14.5 ± 1.5 years; median duration of 5.7 years. Results for final height SDS are displayed by treatment arm for the ISS patients who remained prepubertal at randomization (n=105). All patients were observed for height progression for 12 months and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients).

**Table 7**

<table>
<thead>
<tr>
<th></th>
<th>GEN 0.033 vs. Unreated</th>
<th>GEN 0.067 vs. Unreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Baseline height SDS</td>
<td>+0.53 (0.20, 0.87) p=0.0022</td>
<td>+0.94 (0.63, 1.26) p&lt;0.0001</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>1.36 (0.64)</td>
<td>0.94 (0.63, 1.26)</td>
</tr>
<tr>
<td>minus baseline</td>
<td></td>
<td>(p&lt;0.0001)</td>
</tr>
<tr>
<td>Baseline predicted ht</td>
<td>0.53 (0.20, 0.87) p=0.0022</td>
<td>+0.94 (0.63, 1.26) p&lt;0.0001</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>1.36 (0.64)</td>
<td>0.94 (0.63, 1.26)</td>
</tr>
<tr>
<td>minus baseline</td>
<td></td>
<td>(p&lt;0.0001)</td>
</tr>
</tbody>
</table>

*Mean (SD) are observed values.
**Least square means based on ANCOVA (final height SDS and final height SDS minus baseline predicted height SDS were adjusted for baseline height SDS)

16 HOW SUPPLIED/STORAGE AND HANDLING
GENOTROPIN lyophilized powder is available in the following packages:
5 mg two-chamber cartridge (with preservative)
Concentration of 5 mg/mL
For use with the GENOTROPIN PEN® 5 Growth Hormone Delivery Device and/or the GENOTROPIN MIXER™ Growth Hormone Reconstitution Device.
Package of 1 NDC 0013-2626-81
12 mg two-chamber cartridge (with preservative)
Concentration of 12 mg/mL
For use with the GENOTROPIN PEN 12 Growth Hormone Delivery Device and/or the GENOTROPIN MIXER Growth Hormone Reconstitution Device.
Package of 1 NDC 0013-2646-81
GENOTROPIN MINIQUICK Growth Hormone Delivery Device containing a two-chamber cartridge of GENOTROPIN (without preservative)
After reconstitution, each GENOTROPIN MINIQUICK delivers 0.25 mL, regardless of strength. Available in the following strengths, each in a package of 7:
0.2 mg NDC 0013-2649-02
0.4 mg NDC 0013-2650-02
0.6 mg NDC 0013-2651-02
0.8 mg NDC 0013-2652-02
1.0 mg NDC 0013-2653-02
1.2 mg NDC 0013-2654-02
1.4 mg NDC 0013-2655-02
1.6 mg NDC 0013-2656-02
1.8 mg NDC 0013-2657-02
2.0 mg NDC 0013-2658-02

Storage and Handling
Except as noted below, store GENOTROPIN lyophilized powder under refrigeration at 36°F to 46°F (2°C to 8°C). Do not freeze. Protect from light.
The 5 mg and 12 mg cartridges of GENOTROPIN contain a diluent with a preservative. Thus, after reconstitution, they may be stored under refrigeration for up to 28 days.
The GENOTROPIN MINIQUICK Growth Hormone Delivery Device should be refrigerated prior to dispensing, but may be stored at or below 77°F (25°C) for up to three months after dispensing. The diluent has no preservative. After reconstitution, the GENOTROPIN MINIQUICK may be stored under refrigeration for up to 24 hours before use.
The GENOTROPIN MINIQUICK should be used only once and then discarded.

17 PATIENT COUNSELING INFORMATION
Patients being treated with GENOTROPIN (and/or their parents) should be informed about the potential benefits and risks associated with GENOTROPIN treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.
Patients and caregivers who will administer GENOTROPIN should receive appropriate training and instruction on the proper use of GENOTROPIN from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.
GENOTROPIN is supplied in a two-chamber cartridge, with the lyophilized powder in the front chamber and a diluent in the rear chamber. A reconstitution device is used to mix the diluent and powder. The two-chamber cartridge contains overfill in order to deliver the stated amount of GENOTROPIN.
The GENOTROPIN 5 mg and 12 mg cartridges are color-coded to help ensure proper use with the GENOTROPIN Pen delivery device. The 5 mg cartridge has a green tip to match the green pen window on the Pen 5, while the 12 mg cartridge has a purple tip to match the purple pen window on the Pen 12.
Follow the directions for reconstitution provided with each device. Do not shake; shaking may cause denaturation of the active ingredient.
Please see accompanying directions for use of the reconstitution and/or delivery device.
Manufactured by:
Vetter Pharma-Fertigung GmbH & Co. KG
Ravensburg, Germany
Or
Vetter Pharma-Fertigung GmbH & Co. KG
Langenargen, Germany
Or
Pfizer Manufacturing Belgium N.V.
Puurs, Belgium
Rx only
Distributed by
Pharmacia & Upjohn Co
Division of Pfizer Inc. N.Y., N.Y. 10017

LAB-0222-23.0
Genotropin Mixer®
Growth Hormone Reconstitution Device

Instructions for Use
GENOTROPIN Mixer (JEEN-o-tro-pin MIX-er)
Growth Hormone Delivery Device for Mixing Genotropin®
Lyophilized powder (somatropin) for injection

Storage instructions for your GENOTROPIN MIXER
• Store your GENOTROPIN MIXER (with cartridge) in the refrigerator [36°F to 46°F (2°C to 8°C)]. Always remove the needle before storing.

Using your GENOTROPIN MIXER
Step 1. Before you begin
• First, wash and dry your hands.
• Completely unscrew the dark green plunger rod from the light green holder of the GENOTROPIN MIXER.
• Remove the two-chamber cartridge of GENOTROPIN from its package.

Step 2. Mixing GENOTROPIN
Insert the cartridge into the GENOTROPIN MIXER with the metallic/rubber tip of the cartridge facing into the open end of the holder. The metallic/rubber tip of the cartridge should be visible sticking out from the opening at the front of the holder.
• Screw the plunger rod back into the holder. When the two halves are completely screwed together, the growth hormone and the diluent are automatically mixed. (See Figure B)

CAUTION: Look in the window of the GENOTROPIN MIXER to make sure the growth hormone is completely dissolved. If it is not, gently tip the GENOTROPIN MIXER from side to side until the liquid is clear. DO NOT SHAKE. The solution should be inspected visually for particulate matter and discoloration prior to administration. If the solution is still cloudy, do not inject it. Remove the cartridge and return it to your supplier. Repeat the procedure using a new cartridge.

Step 3. Releasing Pressure
• Disinfect the metallic/rubber tip of the cartridge by wiping it with an alcohol swab.
• Remove the protective cap from the pressure-release needle. Do not touch the exposed needle. With the metallic/rubber tip of the cartridge pointing upwards, pierce the rubber tip with the needle. This will release the excess pressure in the cartridge. Be sure the cartridge is vertical when pierced, to avoid spilling the growth hormone. (This step is only performed the first time you use a new cartridge.) (See Figure C)
• Remove the pressure-release needle from the cartridge and discard the needle in a proper disposal container.

Step 4. Injecting GENOTROPIN
• Disinfect the metallic/rubber tip of the cartridge by wiping it with an alcohol swab. This must be done each time before the solution is taken from the cartridge.
• Take out an insulin syringe and remove its needle guard. Hold the GENOTROPIN MIXER upside down so that the metallic/rubber tip is pointing downwards.
• Insert the needle of the syringe through the rubber tip of the cartridge contained in the GENOTROPIN MIXER, making sure that the needle tip always stays below the fluid level. This will minimize air from entering your syringe.
• Holding the side of the syringe body and the end of the syringe plunger rod, pull the plunger of the syringe back slowly to draw out your prescribed dose of growth hormone.
• Still holding the GENOTROPIN MIXER and syringe with its needle pointing upwards, gently tap the side of the syringe to move any air bubbles to the top of the syringe. Then push the syringe’s plunger gently to force the air bubbles out of the syringe. Remove the syringe. It is now ready for your injection. (See Figure D)
• Disinfect the area to be injected as directed by your healthcare provider. Pinch the skin firmly between your thumb and forefinger. Hold the syringe close to the needle—like a dart—and push it into the skin at a 45° to 90° angle with a quick, firm action.
• Gently and smoothly inject the growth hormone until the syringe is empty. Withdraw the needle quickly, by pulling it straight out, and apply pressure over the injection site with a dry gauze pad.
• Discard the needle in a proper disposal container.
• The site of the injection should be changed each day.

Step 5. Reusing the GENOTROPIN MIXER
The cartridge of GENOTROPIN can be reused for up to 28 days after reconstitution. Simply follow the instructions in the “Injecting GENOTROPIN” section. Additional pressure-release needles may be obtained by calling the Pfizer Bridge Program at 1-800-645-1280.

Important Note
Please read these instructions completely before using GENOTROPIN MIXER. If there is anything you do not understand or cannot do, call the Pfizer Bridge Program’s toll-free number at 1-800-645-1280.

The GENOTROPIN MIXER is a device used to mix growth hormone that is provided in a 2-chamber cartridge of GENOTROPIN.
Step 6. Changing the cartridge
When the cartridge of GENOTROPIN is empty, you can reuse the GENOTROPIN MIXER with your next cartridge, as follows:
• Unscrew the plunger rod from the GENOTROPIN MIXER.
• Remove and discard the old cartridge.
• Follow the steps beginning with the “Before You Begin” section.

Step 7. Disposing of used needles and cartridges
• Your Healthcare provider will instruct you on how to discard your used needles and other medical waste in an appropriate puncture resistant disposal container such as sharps (medical waste) container. 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, other medical waste and sharps containers.
• **Do not** throw needles 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 reach of children.

If you have any questions regarding the GENOTROPIN MIXER, contact your healthcare provider or call the Pfizer Bridge Program at 1-800-645-1280.

Use this device only for the person for whom it was prescribed.

These Instructions for use have been approved by the U.S. Food and Drug Administration.

Caution: Federal law restricts this device to sale by or on the order of a physician.

Pfizer Manufacturing Belgium NV, Rijksweg 12, B-2870 Puurs, Belgium

Distributed by Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017

LAB-0228-4.0
Revised September 2016