HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GENOTROPIN® (somatropin [rDNA origin] for injection)
Initial U.S. Approval: 1987

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Pancreatitis (5.14)	03/2011
Warnings and Precautions, Impaired Glucose Tolerance and Diabetes Mellitus (5.4)	03/2011

----------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 (1.1)
- ***Adult:*** Treatment of adults with either adult onset or childhood onset GHD (1.2)

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

GENOTROPIN should be administered subcutaneously (2)

- ***Pediatric GHD:*** 0.16 to 0.24 mg/kg/week (2.1)
- ***Prader-Willi Syndrome:*** 0.24 mg/kg/week (2.1)
- ***Small for Gestational Age:*** Up to 0.48 mg/kg/week (2.1)
- ***Turner Syndrome:*** 0.33 mg/kg/week (2.1)
- ***Idiopathic Short Stature:*** up to 0.47 mg/kg/week (2.1)
- ***Adult GHD:*** Either a non-weight based or a weight based dosing regimen may be followed, with doses adjusted based on treatment response and IGF-I concentrations (2.2)
- Non-weight based dosing: A starting dose of approximately 0.2mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight, and increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day. (2.2)
- Weight based dosing: The recommended initial dose is not more than 0.04 mg/kg/week; the dose may be increased as tolerated to not more than 0.08 mg/kg/week at 4–8 week intervals. (2.2)
- GENOTROPIN cartridges are color-coded to correspond to a specific GENOTROPIN PEN delivery device (2.3)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

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

GENOTROPIN lyophilized powder in a two-chamber color-coded cartridge (3):

- 5 mg (green tip) and 12 mg (purple tip) (with preservative)

GENOTROPIN MINIQUICK Growth Hormone Delivery Device containing a two-chamber cartridge (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

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

- Acute Critical Illness (4.1, 5.1)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment – reports of sudden death (4.2, 5.2)
- Active Malignancy (4.3)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4.4)
- Children with closed epiphyses (4.5)
- Known hypersensitivity to somatropin or m-cresol (4.6)

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

Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk (5.1).

- 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 (5.2).
- Neoplasm: 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 (5.3).
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary (5.6).
- Hypopituitarism: Closely monitor other hormone replacement therapies (5.7)
- Hypothyroidism: May first become evident or worsen (5.8).
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.9).
- Progression of Preexisting Scoliosis: May develop (5.10)
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.14).

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

Other common somatropin-related adverse reactions include injection site reactions/rashes and lipoatrophy (6.1) and headaches (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1, 7.2).

- Glucocorticoid Replacement: Should be carefully adjusted (7.2)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.3)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.4)
- Insulin and/or Oral/Injectable Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2012

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
- 4.1 Acute Critical Illness
- 4.2 Prader-Willi Syndrome in Children
- 4.3 Active Malignancy
- 4.4 Diabetic Retinopathy
- 4.5 Closed Epiphyses
- 4.6 Hypersensitivity

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 Fluid Retention
- 5.7 Hypopituitarism
- 5.8 Hypothyroidism
- 5.9 Slipped Capital Femoral Epiphysis in Pediatric Patients
- 5.10 Progression of Preexisting Scoliosis in Pediatric Patients
- 5.11 Otitis Media and Cardiovascular Disorders in Turner Syndrome
- 5.12 Local and Systemic Reactions
- 5.13 Laboratory Tests
- 5.14 Pancreatitis

6 ADVERSE REACTIONS
- 6.1 Most Serious and/or Most Frequently Observed Adverse Reactions
- 6.2 Clinical Trials Experience
- 6.3 Post-Marketing Experience

7 DRUG INTERACTIONS
- 7.1 11 β-Hydroxysteroid Dehydrogenase Type 1
- 7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocortioid 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.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients

GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for the treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.

GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for the treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS). The diagnosis of PWS should be confirmed by appropriate genetic testing (see CONTRAINDICATIONS).

GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for the treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2 years.

GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for the treatment of growth failure associated with Turner syndrome.

GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for the treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature, defined by height standard deviation score (SDS) $\leq$-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

1.2 Adult Patients

GENOTROPIN (somatropin [rDNA origin] for injection) is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

Adult Onset (AO): Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or

Childhood Onset (CO): Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Patients who were treated with somatropin for growth hormone deficiency in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. According to current standards, confirmation of the diagnosis of adult growth hormone deficiency in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

2 DOSAGE AND ADMINISTRATION

The weekly dose should be divided into 6 or 7 **subcutaneous** injections. **GENOTROPIN must not be injected intravenously.**

Therapy with GENOTROPIN should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with growth failure associated with growth hormone deficiency (GHD), Prader-Willi syndrome (PWS), Turner syndrome (TS), those who were born small for gestational age (SGA) or Idiopathic Short Stature (ISS), and adult patients with either childhood onset or adult onset GHD.

2.1 Dosing of Pediatric Patients

General Pediatric Dosing Information
The GENOTROPIN dosage and administration schedule should be individualized based on the growth response of each patient.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human GH (rhGH).

Treatment with GENOTROPIN for short stature should be discontinued when the epiphyses are fused.

Pediatric Growth Hormone Deficiency (GHD)
Generally, a dose of 0.16 to 0.24 mg/kg body weight/week is recommended.

Prader-Willi Syndrome
Generally, a dose of 0.24 mg/kg body weight/week is recommended.

Turner Syndrome
Generally, a dose of 0.33 mg/kg body weight/week is recommended.

Idiopathic Short Stature
Generally, a dose up to 0.47 mg/kg body weight/week is recommended.

Small for Gestational Age[a]
Generally, a dose of up to 0.48 mg/kg body weight/week is recommended.

[a] Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.48 mg/kg/week), especially in very short children (i.e., height SDS <–3), and/or older/ pubertal children, and that a reduction in dosage (e.g., gradually towards 0.24 mg/kg/week) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g., approximately <4 years) (who respond the best in general) with less severe short stature (i.e., baseline height SDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.24 mg/kg/week), and titrating the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the somatropin dose as necessary.

2.2 Dosing of Adult Patients

Adult Growth Hormone Deficiency (GHD)

Either of two approaches to GENOTROPIN dosing may be followed: a non-weight based regimen or a weight based regimen.

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 I (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, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

3 DOSAGE 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

4.1 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. 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 (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3–8 mg/day) compared to those receiving placebo *[see Warnings and Precautions (5.1)]*.

4.2 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)]*.

4.3 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.

4.4 Diabetic Retinopathy

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

4.5 Closed Epiphyses

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

4.6 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. These products should not be used by patients with a known sensitivity to this preservative. The GENOTROPIN MINIQUICK presentations are preservative-free (see HOW SUPPLIED). Localized reactions are the most common hypersensitivity reactions.

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 (4.1)]*. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.

5.2 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: severe obesity, 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 have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively *[see Contraindications (4.2)]*.

5.3 Neoplasms

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, 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.

Patients should be monitored carefully for any malignant transformation of skin lesions.

5.4 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 2 diabetes mellitus has been reported. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral/injectable agents) may require adjustment when somatropin therapy is instituted in these patients.

5.5 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or 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 preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, 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.

5.6 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

5.7 Hypopituitarism

Patients with hypopituitarism (multiple pituitary hormone deficiencies) should have their other hormonal replacement treatments closely monitored during somatropin treatment.

5.8 Hypothyroidism

Undiagnosed/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 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.

5.10 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.

5.11 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 treatment 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.

5.12 Local and Systemic Reactions

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)]*.

As with any protein, local or systemic allergic reactions may occur. Parents/Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

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

5.14 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

6.1 Most Serious and/or Most Frequently Observed Adverse Reactions
This list presents the most serious[b] and/or most frequently observed[a] adverse reactions during treatment with somatropin:
• [b] Sudden death in pediatric patients with Prader-Willi syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection *[see Contraindications (4.2) and Warnings andPrecautions (5.2)]*
• [b] Intracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*
• [a], [b] Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus *[see Warnings and Precautions (5.4)]*
• [b] Intracranial hypertension *[see Warnings and Precautions (5.5)]*
• [b] Significant diabetic retinopathy *[see Contraindications (4.4)]*
• [b] Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions (5.8)]*
• [b] Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions (5.9)]*
• [a]Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias *[see Warnings and Precautions (5.6)]*
• [a]Unmasking of latent central hypothyroidism *[see Warnings and Precautions (5.7)]*
• [a]Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) *[see Warnings andPrecautions (5.11)]*
• [b] Pancreatitis *[see Warnings and Precautions (5.14)]*

6.2 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; lipoatrophy; headache; hematuria; 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 hyperglycemia, one patient with benign 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 IGF-1 standard deviation (SD) scores were maintained in the normal range. IGF-1 SD scores above +2 SD were observed as follows: 1 subject (3%), 10 subjects (30%) 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 IGF-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 displays the adverse events reported by 5% or more of adult GHD patients in clinical trials after various durations of treatment with GENOTROPIN. Also presented are the corresponding incidence rates of these adverse events in placebo patients during the 6-month double-blind portion of the clinical trials.

Table 1
Adverse Events Reported by ≥ 5% of 1,145 Adult GHD Patients During Clinical Trials of GENOTROPIN and Placebo, Grouped by Duration of Treatment

Adverse Event	Double Blind Phase		Open Label Phase GENOTROPIN		
	Placebo 0–6 mo. n = 572 % Patients	GENOTROPIN 0–6 mo. n = 573 % Patients	6–12 mo. n = 504 % Patients	12–18 mo. n = 63 % Patients	18–24 mo. n = 60 % Patients
Swelling, peripheral	**5.1**	**17.5***	**5.6**	**0**	**1.7**
Arthralgia	**4.2**	**17.3***	**6.9**	**6.3**	**3.3**
Upper respiratory infection	**14.5**	**15.5**	**13.1**	**15.9**	**13.3**
Pain, extremities	**5.9**	**14.7***	**6.7**	**1.6**	**3.3**
Edema, peripheral	**2.6**	**10.8***	**3.0**	**0**	**0**
Paresthesia	**1.9**	**9.6***	**2.2**	**3.2**	**0**
Headache	**7.7**	**9.9**	**6.2**	**0**	**0**
Stiffness of extremities	**1.6**	**7.9***	**2.4**	**1.6**	**0**
Fatigue	**3.8**	**5.8**	**4.6**	**6.3**	**1.7**
Myalgia	**1.6**	**4.9***	**2.0**	**4.8**	**6.7**
Back pain	**4.4**	**2.8**	**3.4**	**4.8**	**5.0**

* Increased significantly when compared to placebo, $P \leq .025$: Fisher´s Exact Test (one-sided)
n = number of patients receiving treatment during the indicated period.
% = percentage of patients who reported the event during the indicated period.

Post-Trial Extension Studies in Adults
In expanded post-trial extension studies, diabetes mellitus developed in 12 of 3,031 patients (0.4%) during treatment with GENOTROPIN. All 12 patients had predisposing factors, e.g., elevated glycated hemoglobin levels and/or marked obesity, prior to receiving GENOTROPIN. Of the 3,031 patients receiving GENOTROPIN, 61 (2%) developed symptoms of carpal tunnel syndrome, which lessened after dosage reduction or treatment interruption (52) or surgery (9). Other adverse events that have been reported include generalized edema and hypoesthesia.

Anti-hGH Antibodies
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to GENOTROPIN with the incidence of antibodies to other products may be misleading. In the case of growth hormone, antibodies with binding capacities lower than 2 mg/mL have not been associated with growth attenuation. In a very small number of patients treated with somatropin, when binding capacity was greater than 2 mg/mL, interference with the growth response was observed.

In 419 pediatric patients evaluated in clinical studies with GENOTROPIN lyophilized powder, 244 had been treated previously with GENOTROPIN or other growth hormone preparations and 175 had received no previous growth hormone therapy. Antibodies to growth hormone (anti-hGH antibodies) were present in six previously treated patients at baseline. Three of the six became negative for anti-hGH antibodies during 6 to 12 months of treatment with GENOTROPIN. Of the remaining 413 patients, eight (1.9%) developed detectable anti-hGH antibodies during treatment with GENOTROPIN; none had an antibody binding capacity > 2 mg/L. There was no evidence that the growth response to GENOTROPIN was affected in these antibody-positive patients.

Periplasmic Escherichia coli Peptides
Preparations of GENOTROPIN contain a small amount of periplasmic *Escherichia coli* peptides (PECP). Anti-PECP antibodies are found in a small number of patients treated with GENOTROPIN, but these appear to be of no clinical significance.

6.3 Post-Marketing Experience

Because these adverse events 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. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in Sections 6.1 and 6.2 in children and adults.

Leukemia has been reported in a small number of GHD children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy *per se* was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*.

The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children and adults, *see Warnings and Precautions [5.14]*).

New-onset type 2 diabetes mellitus has been reported.

7 DRUG INTERACTIONS

7.1 11 β-Hydroxysteroid Dehydrogenase Type 1
The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone 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) hypoadrenalism 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 these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocortioid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement dosing 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 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 offsprings 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 [rDNA origin], 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-chambered cartridge contains 5.8 mg of somatropin. The reconstituted concentration is 5mg/ml . The cartridge contains overfill to allow for delivery of 1ml containing the stated amount of GENOTROPIN – 5 mg.

GENOTROPIN 12mg 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-chambered 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), have Prader-Willi 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 also normalizes concentrations of IGF-I (Insulin-like Growth Factor-I/Somatomedin C). In adults with GHD, treatment with GENOTROPIN results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism, and normalization of IGF-I concentrations.

In addition, the following actions have been demonstrated for GENOTROPIN and/or somatropin.

12.2 Pharmacodynamics

Tissue Growth

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 calciuria.

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 (C_{max}) serum levels were 23.0 (± 9.4) ng/mL and 17.4 (± 9.2) ng/mL, respectively.

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 C_{max} 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 C_{max} 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 patients was 0.3 (± 0.11) L/hrs/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
Mean SC Pharmacokinetic Parameters in Adult GHD Patients

	Bioavailability (%) (N=15)	**T_{max} (hours) (N=16)**	**CL/F (L/hr x kg) (N=16)**	**Vss/F (L/kg) (N=16)**	**$T_{1/2}$ (hours) (N=16)**
Mean (± SD)	80.5 *	5.9 (± 1.65)	0.3 (± 0.11)	1.3 (± 0.80)	3.0 (± 1.44)
95% CI	70.5 – 92.1	5.0 – 6.7	0.2 – 0.4	0.9 – 1.8	2.2 – 3.7

T_{max} = time of maximum plasma concentration $T_{1/2}$ = terminal half-life
CL/F = plasma clearance SD = standard deviation
Vss/F = volume of distribution CI = confidence interval

* 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) were 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 0.48 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)

	Study 1		Study 2	
	GENOTROPIN (0.24 mg/kg/week) n=15	Untreated Control n=12	GENOTROPIN (0.36 mg/kg/week) n=7	Untreated Control n=9
Linear growth (cm) Baseline height	112.7 ± 14.9	109.5 ± 12.0	120.3 ± 17.5	120.5 ± 11.2
Growth from months 0 to 12	11.6* ± 2.3	5.0 ± 1.2	10.7* ± 2.3	4.3 ± 1.5
Height Standard Deviation Score (SDS) for age Baseline SDS	-1.6 ± 1.3	-1.8 ± 1.5	-2.6 ± 1.7	-2.1 ± 1.4
SDS at 12 months	-0.5† ± 1.3	-1.9 ± 1.4	-1.4† ± 1.5	-2.2 ± 1.4

* $p \leq 0.001$

† $p \leq 0.002$ (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)

	GENOTROPIN n=14	Untreated Control n=10
Fat mass (kg) Baseline	12.3 ± 6.8	9.4 ± 4.9
Change from months 0 to 12	-0.9* ± 2.2	2.3 ± 2.4
Lean body mass (kg) Baseline	15.6 ± 5.7	14.3 ± 4.0
Change from months 0 to 12	4.7* ± 1.9	0.7 ± 2.4
Lean body mass/Fat mass Baseline	1.4 ± 0.4	1.8 ± 0.8
Change from months 0 to 12	1.0* ± 1.4	-0.1 ± 0.6
Body weight (kg) † Baseline	27.2 ± 12.0	23.2 ± 7.0
Change from months 0 to 12	3.7‡ ± 2.0	3.5 ± 1.9

* $p < 0.005$

† 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) as a daily SC injection or no treatment for the first 24 months of the studies. After 24 months in the studies, all patients received GENOTROPIN.

Patients who received any dose of GENOTROPIN showed significant increases in growth during the first 24 months of study, compared with patients who received no treatment (see Table 5). Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height standard deviation score (SDS) compared with children treated with 0.24 mg/kg/week. Both of these doses resulted in a slower but constant increase in growth between months 24 to 72 (data not shown).

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

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

* 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.

SDS 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 Ranke standard (both studies) for age-matched, untreated Turner syndrome patients. As seen in Table 5, 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.

Table 6
Growth Parameters (mean ± SD) after 12 Months of Treatment with GENOTROPIN in Pediatric Patients with Turner Syndrome in Two Open Label Studies

	GENOTROPIN 0.33 mg/kg/week Study 055^ n=22	GENOTROPIN 0.13–0.23 mg/kg/week Study 092# n=16
Height Velocity (cm/yr)		
Baseline	4.1 ± 1.5	3.9 ± 1.0
Month 12	7.8 ± 1.6	6.1 ± 0.9
Change from baseline (95% CI)	3.7 (3.0, 4.3)	2.2 (1.5, 2.9)
Height Velocity SDS (Tanner^/Sempé# Standards)	(n=20)	
Baseline	-2.3 ± 1.4	-1.6 ± 0.6
Month 12	2.2 ± 2.3	0.7 ± 1.3
Change from baseline (95% CI)	4.6 (3.5, 5.6)	2.2 (1.4, 3.0)
Height Velocity SDS (Ranke Standard)		
Baseline	-0.1 ± 1.2	-0.4 ± 0.6
Month 12	4.2 ± 1.2	2.3 ± 1.2
Change from baseline (95% CI)	4.3 (3.5, 5.0)	2.7 (1.8, 3.5)
Height SDS (Tanner^/Sempé# Standards)		
Baseline	-3.1 ± 1.0	-3.2 ± 1.0
Month 12	-2.7 ± 1.1	-2.9 ± 1.0
Change from baseline (95% CI)	0.4 (0.3, 0.6)	0.3 (0.1, 0.4)
Height SDS (Ranke Standard)		
Baseline	-0.2 ± 0.8	-0.3 ± 0.8
Month 12	0.6 ± 0.9	0.1 ± 0.8
Change from baseline (95% CI)	0.8 (0.7, 0.9)	0.5 (0.4, 0.5)

SDS = Standard Deviation Score
Ranke standard based on age-matched, untreated Turner syndrome patients
Tanner^/Sempé# standards based on age-matched normal children
$p<0.05$, for all changes from baseline

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 for the ISS patients who remained prepubertal at randomization (n= 105) were: mean (± SD): chronological age 11.4 (1.3) years, height SDS -2.4 (0.4), height velocity SDS -1.1 (0.8), and height velocity 4.4 (0.9) cm/yr, IGF-1 SDS -0.8 (1.4). Patients were treated for a median duration of 5.7 years. Results for final height SDS are displayed by treatment arm in Table 7. GENOTROPIN therapy improved final height in ISS children relative to untreated controls. The observed mean gain in final height was 9.8 cm for females and 5.0 cm for males for both doses combined compared to untreated control subjects. A height gain of 1 SDS was observed in 10 % of untreated subjects, 50% of subjects receiving 0.23 mg/kg/week and 69% of subjects receiving 0.47 mg/kg/week

Table 7. Final height SDS results for pre-pubertal patients with ISS*

	Untreated (n=30)	GEN 0.033 (n=30)	GEN 0.067 (n=42)	GEN 0.033 vs. Untreated (95% CI)	GEN 0.067 vs. Untreated (95% CI)
Baseline height SDS					
Final height SDS minus baseline	0.41 (0.58)	0.95 (0.75)	1.36 (0.64)	+0.53 (0.20, 0.87) p=0.0022	+0.94 (0.63, 1.26) p<0.0001
Baseline predicted ht					
Final height SDS minus baseline predicted final height SDS	0.23 (0.66)	0.73 (0.63)	1.05 (0.83)	+0.60 (0.09, 1.11) p=0.0217	+0.90 (0.42, 1.39) p=0.0004

*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 *[in particular, see Adverse Reactions (6.1) for a listing of the most serious and/or most frequently observed adverse reactions associated with somatropin treatment in children and adults].* 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

Rx only

LAB-0222-18.0
Revised February 2012

Instructions for Use
GENOTROPIN MINIQUICK (JEEN-o-tro-pin MIN-ee-kwik)
Growth Hormone Delivery Device containing Genotropin® Lyophilized powder (somatropin [rDNA] for injection)

Important Note

Please read these instructions completely before using GENOTROPIN MINIQUICK. 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.

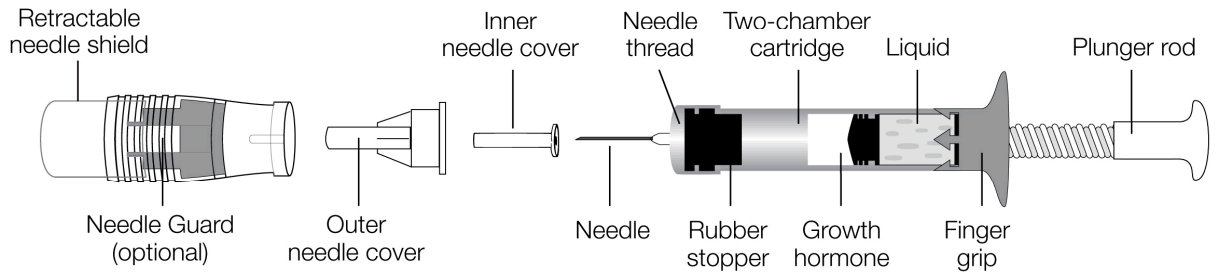
GENOTROPIN MINIQUICK is available in 10 dose strengths.
Check your GENOTROPIN MINIQUICK to be sure you have the dose your doctor prescribed.

GENOTROPIN MINIQUICK is a device holding a 2-chamber cartridge of GENOTROPIN, used to mix and inject a single dose of GENOTROPIN.

For each injection you will need:
- 2 alcohol pads (not included)
- the GENOTROPIN MINIQUICK device with the 2-chamber cartridge of GENOTROPIN inside it. The 2-chamber cartridge of GENOTROPIN contains the growth hormone powder in one chamber and the liquid in the other.
- an injection needle. A needle for injection is provided with each device. If you need additional needles, ask for Becton Dickinson Ultra-Fine pen needles, either 29 gauge, 30 gauge or 31 gauge.
- the reusable Needle Guard (optional, not included)
- a proper disposal container (not included)

The diagram below identifies the different components of the GENOTROPIN MINIQUICK. (See Figure A)

FIGURE A



Storage instructions for your GENOTROPIN MINIQUICK
- Keep your GENOTROPIN MINIQUICK in the original carton to protect it from light.
- Before you mix the growth hormone powder with the liquid in the syringe, you can store the GENOTROPIN MINIQUICK in the refrigerator [36ºF to 46ºF (2ºC to 8ºC)]. However, you can also store the GENOTROPIN MINIQUICK at room temperature [68°F to 77ºF (20ºC to 25ºC)] for up to three months. Do not freeze.
- Inject the GENOTROPIN right after you mix it. If that is not possible, you can keep the GENOTROPIN MINIQUICK in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC) for up to 24 hours after mixing it. Do not freeze.

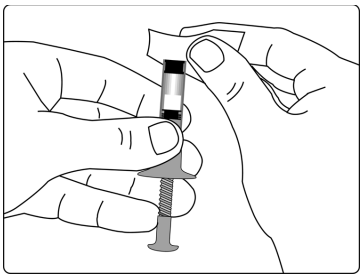
Using your GENOTROPIN MINIQUICK

Step 1.
Wash your hands well with soap and water before using the GENOTROPIN MINIQUICK.

Step 2.
Open the plastic bag that contains your GENOTROPIN MINIQUICK, by tearing the bag along the perforated line on the plastic.

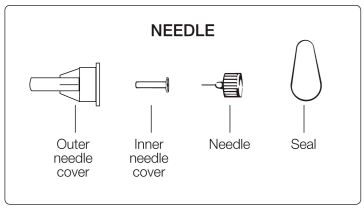
Step 3.
Wipe the rubber stopper on the GENOTROPIN MINIQUICK with a pad or swab moistened with rubbing alcohol. (See Figure B)

FIGURE B



Step 4.
Peel the seal from the back of the injection needle. Leave both needle covers (inner and outer) on the needle. (See Figure C)

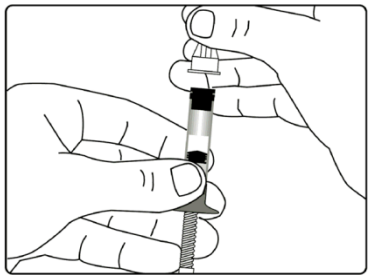
FIGURE C



Step 5.

- Attach the needle onto the GENOTROPIN MINIQUICK by pushing it down and turning it clockwise (to the right) until it will no longer turn.
- Make sure the needle is positioned squarely, not at an angle, onto the end of the rubber stopper before screwing it onto the GENOTROPIN MINIQUICK. (See Figure D)

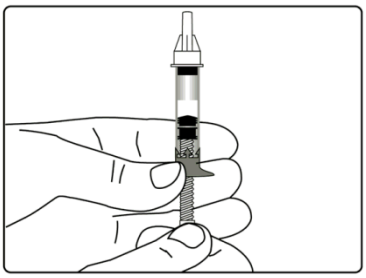
FIGURE D



Step 6.

- Hold the GENOTROPIN MINIQUICK with the needle pointing up. To mix the growth hormone powder with the liquid, turn the plunger rod clockwise (to the right) until it will not go any further. (See Figure E)
- When you turn the plunger rod clockwise (to the right), the GENOTROPIN MINIQUICK automatically mixes the growth hormone powder and the liquid.
- **Do not shake** the GENOTROPIN MINIQUICK. Shaking may cause the growth hormone to not work as well.
- Make sure the solution is clear, and that the growth hormone powder is completely dissolved. If you see particles in the solution, or if the solution is discolored, **do not inject it**. Call the toll-free number listed at the beginning of this leaflet.

FIGURE E



Step 7.

- Select your injection site and wipe that area of your skin with an alcohol pad, as instructed by your healthcare provider.

- **If you are using the reusable Needle Guard to hide the needle, go to Step 8.**

- **If you are not using the reusable Needle Guard, go to Step 9.**

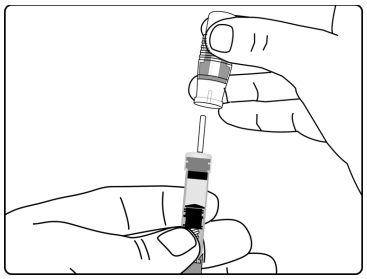
Step 8. – With Needle Guard

- Remove the outer needle cover from the needle, place the Needle Guard onto the GENOTROPIN MINIQUICK, and press gently until the Needle Guard snaps into place. Save the outer needle cover. (See Figure F)

- Remove the inner needle cover from the needle.

- Go to Step 10.

FIGURE F

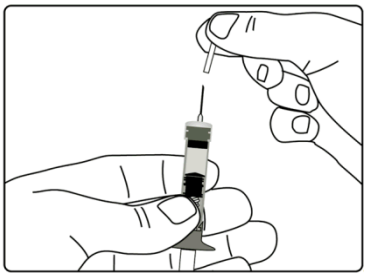


Step 9. – Without Needle Guard

- Remove the outer and inner needle covers from the needle. Save the outer needle cover. (See Figure G)

- Go to Step 10.

FIGURE G

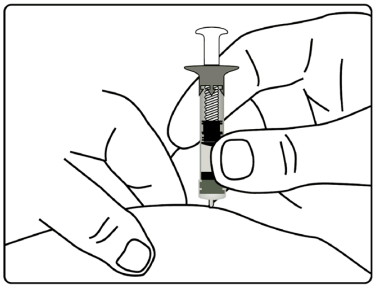


Step 10.

- Pinch a fold of skin at the injection site firmly, and push the needle straight into the skin at a 90-degree angle. (See Figure H)

- If you are using the optional Needle Guard, the retractable plastic needle shield will push in as the GENOTROPIN MINIQUICK is pushed against your skin.

FIGURE H

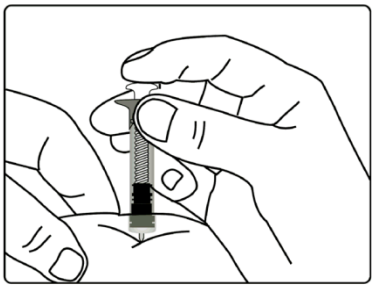


Step 11

- Push the plunger rod in as far as it will go, to inject all the medicine in the GENOTROPIN MINIQUICK. (See Figure I)

- Wait a few seconds to be sure that all the growth hormone has been injected. Pull out the needle.

FIGURE I

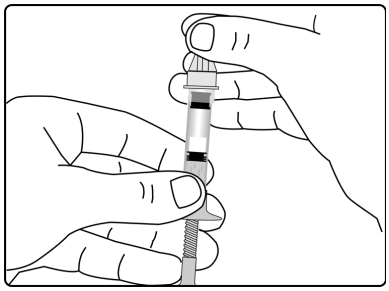


Step 12.

- If you are using the Needle Guard, remove the Needle Guard and then carefully replace the outer needle cover on the needle. **Save the Needle Guard for future use.** (See Figure J)

- If you are not using the Needle Guard, carefully replace the outer needle cover on the needle.

FIGURE J



Step 13. Disposing of your GENOTROPIN MINIQUICK

- Your doctor or healthcare provider will instruct you on how to discard your used syringes and needles and other medical waste in an appropriate puncture resistant disposal container such as a 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, syringes, other medical waste, and sharps containers.

- **Do not** throw needles, syringes, or sharps containers in the household trash without first checking your state and local laws.

- **Do not** recycle the sharps container.

- Always keep your sharps container in a safe place and out of the reach of children.

Questions and Answers	
Question	**Answer**
Is it a problem if I see air bubbles in the syringe?	No. There is no need to remove the air from the GENOTROPIN MINIQUICK. The small amount of air in the syringe does not affect your injection.
What should I do if I have problems turning the plunger rod (Step 6)?	The problem could be because the needle has been inserted at an angle onto the rubber stopper. Carefully replace the outer needle cover on the needle and unscrew counterclockwise to remove the needle. Hold the GENOTROPIN MINIQUICK with the needle-end pointing up, and re-attach and screw the needle squarely on top of the device.
What should I do if I have problems pushing the	The problem could be because the needle has

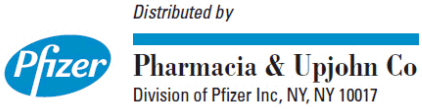
plunger when making the injection (Step 11)?	been inserted at an angle onto the rubber stopper. Carefully replace the outer needle cover on the needle and unscrew counterclockwise to remove the needle. Hold the GENOTROPIN MINIQUICK with the needle-end pointing up, and re-attach and screw the needle squarely on top of the device.
What should I do if the needle is damaged or bent?	Throw away the needle and use a new needle with the GENOTROPIN MINIQUICK.
How do I care for my Needle Guard?	Clean the Needle Guard by wiping with a damp cloth or alcohol swab. If your Needle Guard does not function properly, call the Pfizer Bridge Program at 1-800-645-1280.

If you have any questions about your dose or your treatment with GENOTROPIN, call your healthcare provider right away.

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.

Manufactured by:
Vetter Pharma-Fertigung GmbH & Co. KG
Ravensburg, Germany



LAB-0227-5.0
Revised February 2012

Growth Hormone Delivery Device containing Genotropin®
Lyophilized Powder (somatropin [rDNA origin] for injection)

Genotropin Pen® 12

Growth Hormone Delivery Device for use with Genotropin®
Lyophilized Powder (somatropin [rDNA origin] for injection)

Instructions for Use

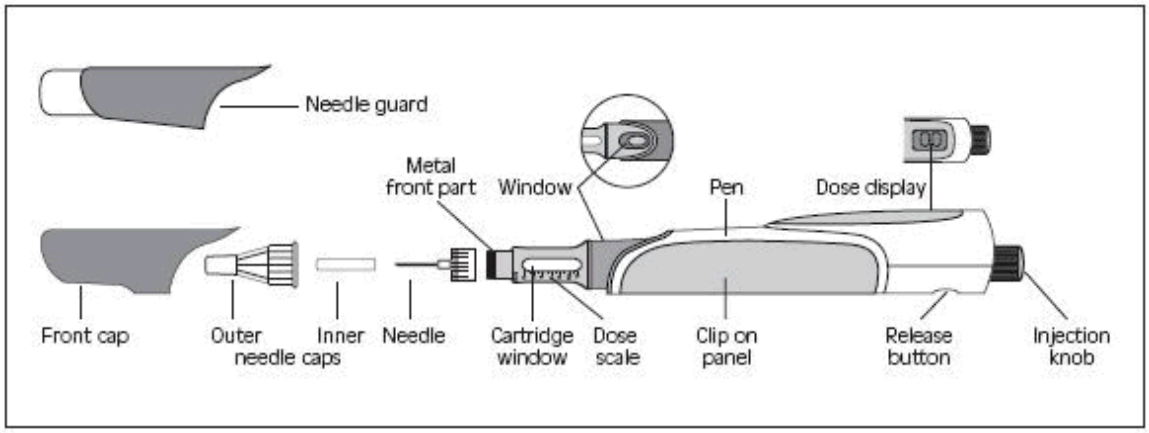
Important Note
Please read these instructions completely before using the GENOTROPIN PEN 12. If there is anything you do not understand or cannot do, call the toll-free number listed at the end of these instructions.
If you have any questions about your dose or your treatment with GENOTROPIN, call your healthcare provider.

GENOTROPIN PEN 12 is a device used to mix and inject doses of GENOTROPIN Lyophilized Powder (somatropin [rDNA origin] for injection). Use this device **only** for administration of GENOTROPIN.

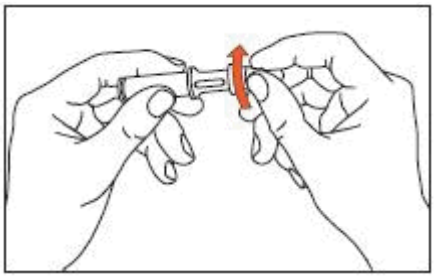
What You Will Need

- GENOTROPIN PEN 12
- 12 mg two-chamber cartridge of GENOTROPIN
- Alcohol swab
- 29-gauge, 30-gauge, or 31-gauge Becton Dickinson pen needle
- Proper disposal container for used needles

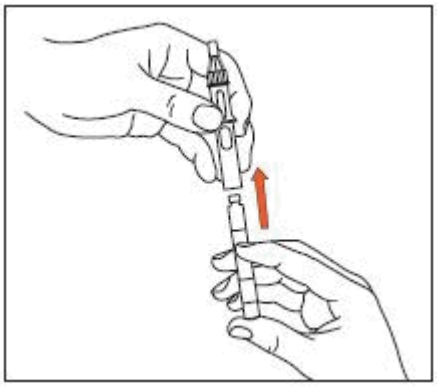
Components of the GENOTROPIN PEN 12



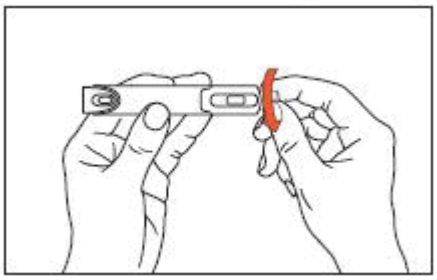
Before You Begin
To help prevent infection, **always** wash your hands with soap and water before preparing or using the GENOTROPIN PEN 12.



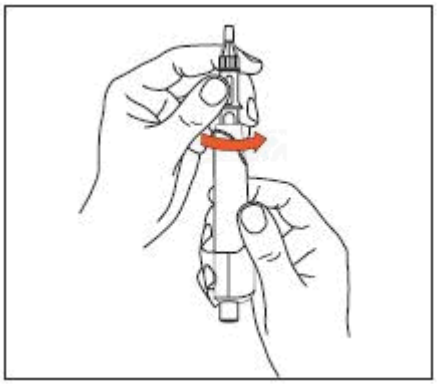
1. **Attach the Needle**
   - Remove the front cap from the GENOTROPIN PEN 12.
   - Unscrew the metal front part and detach it from the plastic body of the pen.
   - Remove the paper covering from the back of a new needle.
   - Screw the needle onto the metal front part by gently turning it clockwise (to the right).



2. **Insert the Two-Chamber Cartridge of GENOTROPIN**
   - Use only the 12mg cartridge.
   - Wipe the metal/rubber tip of the cartridge with an alcohol swab.
   - Insert the cartridge into the metal front part of the pen, with the metal/rubber tip towards the needle end. Push the cartridge firmly into place.

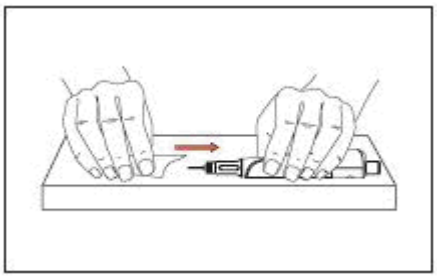


3. **Prepare the Body of the Pen**
   - Press the red release button to release the black/white injection knob.
   - **Turn the black/white injection knob counterclockwise (to the left) as far as it will go.**
   - Check that the plunger rod is not visible through the window at the top of the plastic body of the pen. Do NOT proceed if the plunger rod is visible, as the medication will not be properly mixed. Instead, press the red release button again to draw back the plunger rod. After the rod is no longer visible through the window, proceed to the next step.



4. **Screw the GENOTROPIN PEN 12 Together**
   - Hold the metal front part upright.
   - While holding upright, gently screw the metal front part and the plastic body back together. This mixes the diluent in the rear chamber of the cartridge with the growth hormone powder in the front chamber.
   - Gently tip the assembled GENOTROPIN PEN 12 from side to side to help dissolve the powder completely. **DO NOT SHAKE** as that might inactivate the growth hormone.

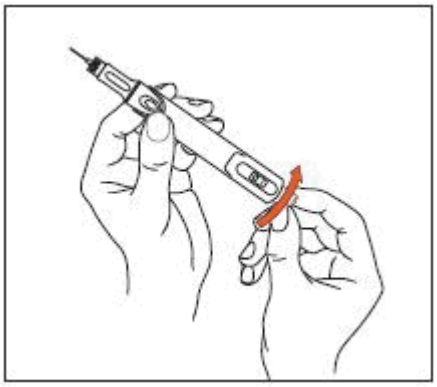
5. **Examine Solution and Release Trapped Air**
   - Look through the cartridge windows in the metal front part of the pen and make sure the drug solution is clear. If you see particles or if the solution is discolored, **DO NOT INJECT IT**. Instead, call the toll-free number listed at the end of these instructions.
   - Remove the outer needle cap and save it for later.
   - Remove and discard the inner needle cap. **Be careful not to touch the exposed needle.**
   - Remove any trapped air from the solution as follows:
     a) Turn the black/white injection knob clockwise (to the right) one click. This will line up the white mark on the injection knob and the black mark on the body of the pen.
     b) Hold the GENOTROPIN PEN 12 upright and gently tap the metal front part with your finger to move any air bubbles to the top.



c) Push the black/white injection knob all the way in. You will see a drop of liquid appear at the needle point. Any trapped air has now been released.

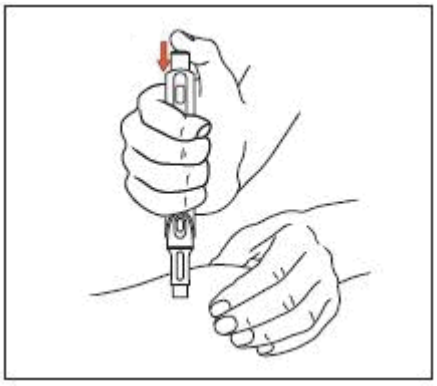
d) If no liquid squirts out, press the red release button and turn the black/white injection knob clockwise (to the right) until it clicks once. Repeat steps b) and c).

- If desired, attach the reusable needle guard over the needle—push until it snaps in place. Again, be careful not to touch the exposed needle. To avoid an accidental needle stick, grip the sides of the needle guard; never push on the end.



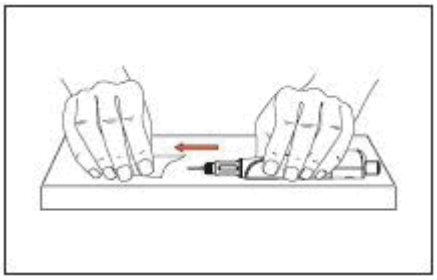
6. <u>Dial Your Prescribed Dose</u>

- Press the red release button to reset the device.
- The black/white injection knob will pop out and the dose display window will read **0.0.**
- With the dose display activated, turn the black/white injection knob clockwise (to the right) until your prescribed dose is displayed.
- If you go too far, just turn the knob back the other way until the correct dose is displayed. NOTE: If you turn the black/white injection knob backwards beyond zero after a cartridge has been inserted, the pen display will show (- -). Just turn the injection knob forward (clockwise) until numbers reappear on the dose display.
- The GENOTROPIN PEN 12 contains a battery for the dose display. To save the battery's energy, the dose display is activated for two minutes and then automatically disappears. **Although the display is no longer visible, the dose remains available for delivery.** NOTE: Each click of the black/white injection knob equals a two-tenth-of-a milligram dose (or 0.2 mg). One click—or 0.2 mg—is the minimum possible dose per injection; 20 clicks—or 4.0 mg—is the maximum possible dose per injection. If you accidentally dial more than the maximum 4.0 mg dose, some liquid may emerge from the tip. This is normal and will not affect your injection—simply dial back to the correct dose.



7. <u>Inject your GENOTROPIN</u>

- Select and prepare an appropriate injection site, as directed by your healthcare provider.
- Pinch a fold of skin at the injection site firmly, and push the GENOTROPIN PEN 12 into the skinfold at a 90° angle. Push the pen down as far as possible.
- Push the black/white injection knob until it clicks. Wait at least 5 seconds and then withdraw the GENOTROPIN PEN 12.



8. **Discard the Needle and Store the GENOTROPIN PEN 12**
   - Remove and store the needle guard, if you used one.
   - **Carefully** replace the outer protective cap on the needle, as instructed by your healthcare provider.
   - Unscrew the needle and discard it in a proper disposal container. **NEVER REUSE A NEEDLE.**
   - Replace the front cap, then put the GENOTROPIN PEN 12 back in its protective case. Store it in the refrigerator at 36° to 46°F (2° to 8°C) until your next injection.

Your Next Injection

If you already have a drug cartridge in your GENOTROPIN PEN 12, prepare the pen and administer your dose as follows:

- Remove the front cap of the GENOTROPIN PEN 12.
- Remove the paper covering from the back of a new needle.
- Screw the needle onto the metal front part of the pen by turning it clockwise (to the right).
- Remove the outer and inner needle caps.
- Follow the instructions above, starting with step 6.

To Replace the Cartridge

- Press the red release button to reset the GENOTROPIN PEN 12.
- **Turn the black/white injection knob counterclockwise (to the left) as far as it will go.**
- Unscrew the metal front part and remove the empty cartridge.
- Discard the empty cartridge as instructed by your healthcare provider.
- To insert a new cartridge and prepare the GENOTROPIN PEN 12 for use, follow the instructions above.

Storage

Between uses, store your GENOTROPIN PEN 12 in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in its protective case. **Always remove the needle before storing**. Do not freeze. Protect from light. Discard the cartridge in your GENOTROPIN PEN 12 within 28 days after reconstitution (mixing of the growth hormone powder with the diluent) even if the cartridge is not empty.

When traveling, keep your GENOTROPIN PEN 12 in its protective case and carry it in an insulated bag to protect it from heat or freezing. Put it back in the refrigerator as soon as possible.

Caring For Your GENOTROPIN PEN 12

No special maintenance is required. To clean the GENOTROPIN PEN 12, wipe the outside surface with a damp cloth. Do not immerse. Do not use alcohol or any other cleaning agents, as they may damage the plastic body.

To clean the reusable needle guard, wipe it with a damp cloth or alcohol swab.

Disposing of your GENOTROPIN PEN 12

- Your doctor or healthcare provider will instruct you on how to discard your used syringes and needles and other medical waste in an appropriate puncture resistant disposal container such as a 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, syringes, other medical waste, and sharps containers.
- Do not throw needles, syringes, or sharps containers in the household trash without first checking your state and local laws.

COMMON QUESTIONS

How do I tell how much GENOTROPIN is left in the GENOTROPIN PEN 12?

Look at the dose scale imprinted along the side of the window on the metal front part of the pen. The front edge of the gray rubber plunger lines up with the number of milligrams remaining in the cartridge.

What happens when the battery runs low?

The battery in the GENOTROPIN PEN 12 should run for two years. When it begins to run low due to the end of the battery´s life, you will see a flashing symbol (⚌) in the dose display. This means the battery will last about another month. When the battery is dead, the

dose display will show a steady ≡≡. A flashing "bt" means the battery is running very low for some other reason and will last for about another month. When the battery is dead, the display will then show a steady "bt".

In either case, call the Pfizer Bridge Program at the toll-free number listed below to exchange your GENOTROPIN PEN 12 for a new one.

<u>If the battery suddenly dies, can the GENOTROPIN PEN 12 still be used?</u>
Yes. Call the Pfizer Bridge Program at the toll-free number listed below for instructions on how to determine the dose without the electronic dose display.

Questions about how to use the GENOTROPIN PEN 12?
Call the Pfizer Bridge Program toll-free at (800) 645-1280

Manufactured by:
Ypsomed AG
Burgdorf, Switzerland

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

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

LAB-0224-7.0
Revised February 2012

Genotropin Pen® 5

Growth Hormone Delivery Device for use with Genotropin®
Lyophilized Powder (somatropin [rDNA origin] for injection)

Instructions for Use

Important Note

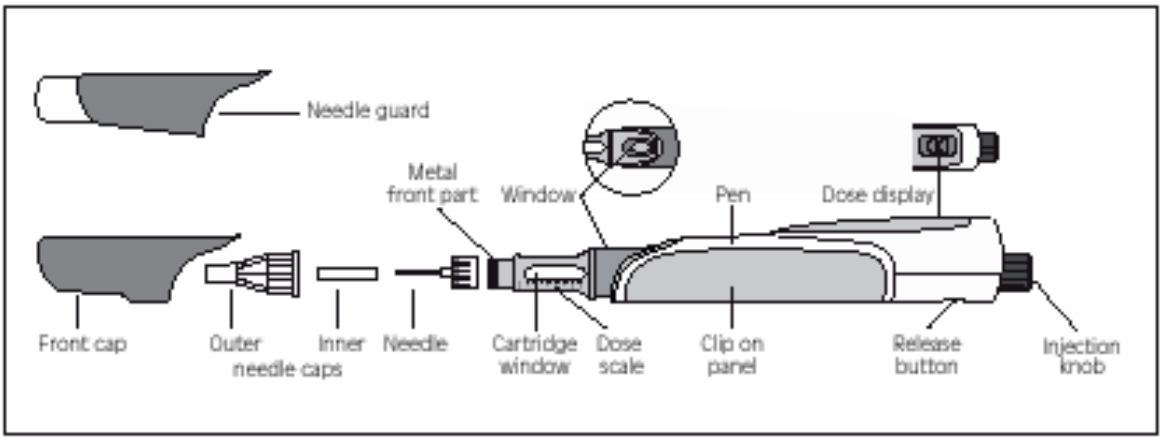
Please read these instructions completely before using the GENOTROPIN PEN 5. If there is anything you do not understand or cannot do, call the toll-free number listed at the end of these instructions.
If you have any questions about your dose or your treatment with GENOTROPIN, call your healthcare provider.

GENOTROPIN PEN 5 is a device used to mix and inject doses of GENOTROPIN Lyophilized Powder (somatropin [rDNA origin] for injection). Use this device **only** for administration of GENOTROPIN.

What You Will Need

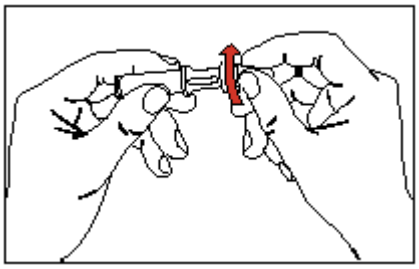
- GENOTROPIN PEN 5
- 5mg two-chamber cartridge of GENOTROPIN
- Alcohol swab
- 29-gauge, 30-gauge, or 31-gauge Becton Dickinson pen needle
- Proper disposal container for used needles

Components of the GENOTROPIN PEN 5



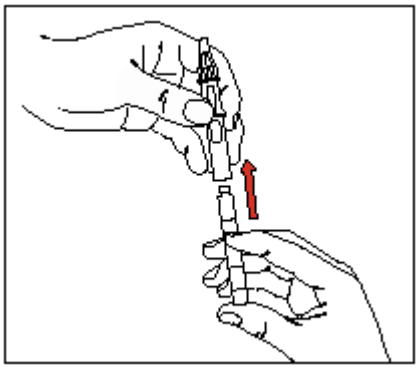
Before You Begin

To help prevent infection, **always** wash your hands with soap and water before preparing or using the GENOTROPIN PEN 5.



1. **Attach the Needle**

- Remove the front cap from the GENOTROPIN PEN 5.
- Unscrew the metal front part and detach it from the plastic body of the pen.
- Remove the paper covering from the back of a new needle.
- Screw the needle onto the metal front part by gently turning it clockwise (to the right).

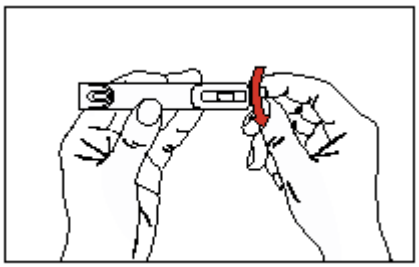


2. Insert the Two-Chamber Cartridge of GENOTROPIN

• Use only the 5 mg cartridge.

• Wipe the metal/rubber tip of the cartridge with an alcohol swab.

• Insert the cartridge into the metal front part of the pen, with the metal/rubber tip towards the needle end. Push the cartridge firmly into place.

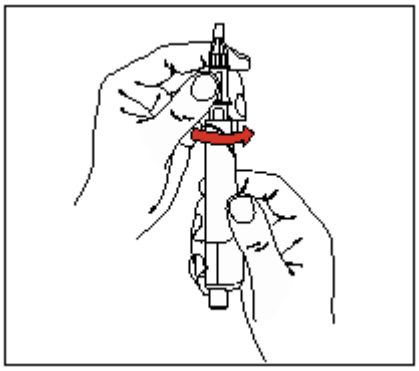


3. Prepare the Body of the Pen

• Press the red release button to release the black/white injection knob.

• **Turn the black/white injection knob counterclockwise (to the left) as far as it will go.**

• Check that the plunger rod is not visible through the window at the top of the plastic body of the pen. DO NOT proceed if the plunger rod is visible, as the medication will not be properly mixed. Instead, press the red release button again to draw back the plunger rod. After the rod is no longer visible through the window, proceed to the next step.

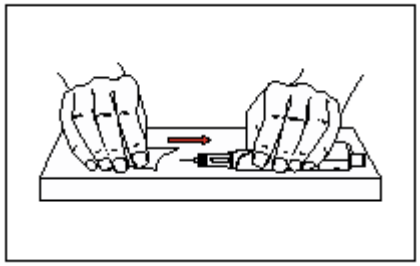


4. Screw the GENOTROPIN PEN 5 Together

• Hold the metal front part upright

• While holding upright, gently screw the metal front part and the plastic body back together. This mixes the diluent in the rear chamber of the cartridge with the growth hormone powder in the front chamber.

• Gently tip the assembled GENOTROPIN PEN 5 from side to side to help dissolve the powder completely. **DO NOT SHAKE** as that might inactivate the growth hormone.



5. Examine Solution and Release Trapped Air

• Look through the cartridge windows in the metal front part of the pen and make sure the drug solution is clear. If you see particles or if the solution is discolored, **DO NOT INJECT IT.** Instead, call the toll-free number listed at the end of these instructions.

• Remove the outer needle cap and save it for later.

• Remove and discard the inner needle cap. **Be careful not to touch the exposed needle.**

• Remove any trapped air from the solution as follows:

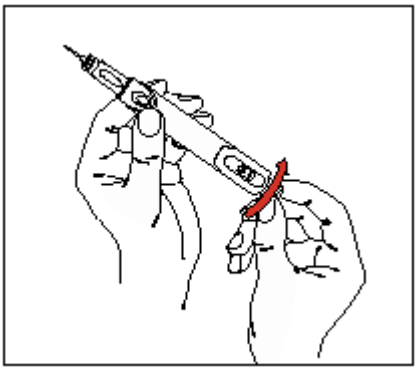
a) Turn the black/white injection knob clockwise (to the right) one click. This will line up the white mark on the injection knob and the black mark on the body of the pen.

b) Hold the GENOTROPIN PEN 5 upright and gently tap the metal front part with your finger to move any air bubbles to the top.

c) Push the black/white injection knob all the way in. You will see a drop of liquid appear at the needle point. Any trapped air has now been released.

d) If no liquid squirts out, press the red release button and turn the black/white injection knob clockwise (to the right) until it clicks once. Repeat steps b) and c).

• If desired, attach the reusable needle guard over the needle—push until it snaps in place. Again, be careful not to touch the exposed needle. To avoid an accidental needle stick, grip the sides of the needle guard; never push on the end.



6. Dial Your Prescribed Dose

• Press the red release button to reset the device.

• The black/white injection knob will pop out and the dose display window will read **0.0.**

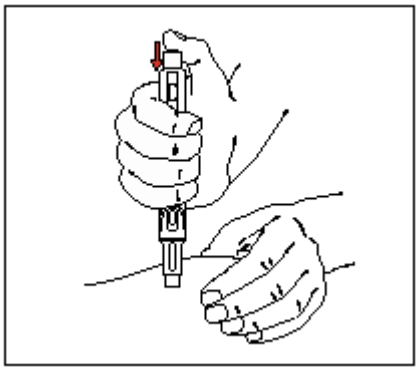
• With the dose display activated, turn the black/white injection knob clockwise (to the right) until your prescribed dose is displayed.

• If you go too far, just turn the knob back the other way until the correct dose is displayed.

NOTE: If you turn the black/white injection knob backwards beyond zero after a cartridge has been inserted, the pen display will show (--). Just turn the injection knob forward (clockwise) until numbers reappear on the dose display.

• The GENOTROPIN PEN 5 contains a battery for the dose display. To save the battery's energy, the dose display is activated for two minutes and then automatically disappears. **Although the display is no longer visible, the dose remains available for delivery.**

NOTE: Each click of the black/white injection knob equals a one-tenth-of-a milligram dose (or 0.1 mg). One click—or 0.1 mg—is the minimum possible dose per injection; 20 clicks—or 2.0 mg—is the maximum possible dose per injection. If you accidentally dial more than the maximum 2.0 mg dose, some liquid may emerge from the tip. This is normal and will not affect your injection—simply dial back to the correct dose.

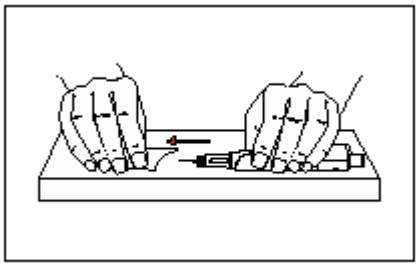


7. Inject your GENOTROPIN

• Select and prepare an appropriate injection site, as directed by your healthcare provider.

• Pinch a fold of skin at the injection site firmly, and push the GENOTROPIN PEN 5 into the skinfold at a 90° angle. Push the pen down as far as possible.

• Push the black/white injection knob until it clicks. Wait at least 5 seconds and then withdraw the GENOTROPIN PEN 5.



8. Discard the Needle and Store the GENOTROPIN PEN 5

• Remove and store the needle guard, if you used one.

• **Carefully** replace the outer protective cap on the needle, as instructed by your healthcare provider.

• Unscrew the needle and discard it in a proper disposal container. **NEVER REUSE A NEEDLE.**

• Replace the front cap, then put the GENOTROPIN PEN 5 back in its protective case. Store it in the refrigerator at 36°F to 46°F (2°C to 8°C) until your next injection.

Your Next Injection

If you already have a drug cartridge in your GENOTROPIN PEN 5, prepare the pen and administer your dose as follows:

• Remove the front cap of the GENOTROPIN PEN 5.
• Remove the paper covering from the back of a new needle.
• Screw the needle onto the metal front part of the pen by turning it clockwise (to the right).
• Remove the outer and inner needle caps.
• Follow the instructions above, starting with step 6.

To Replace the Cartridge

• Press the red release button to reset the GENOTROPIN PEN 5.
• **Turn the black/white injection knob counterclockwise (to the left) as far as it will go.**
• Unscrew the metal front part and remove the empty cartridge.
• Discard the empty cartridge as instructed by your healthcare provider.
• To insert a new cartridge and prepare the GENOTROPIN PEN 5 for use, follow the instructions above.

Storage

Between uses, store your GENOTROPIN PEN 5 in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in its protective case. **Always remove the needle** before storing. Do not freeze. Protect from light. Discard the cartridge in your GENOTROPIN PEN 5 within 28 days after reconstitution (mixing of the growth hormone powder with the liquid) even if the cartridge is not empty.

When traveling, keep your GENOTROPIN PEN 5 in its protective case and carry it in an insulated bag to protect it from heat or freezing. Put it back in the refrigerator as soon as possible.

Caring For Your GENOTROPIN PEN 5

No special maintenance is required. To clean the GENOTROPIN PEN 5, wipe the outside surface with a damp cloth. Do not immerse. Do not use alcohol or any other cleaning agents, as they may damage the plastic body.

To clean the reusable needle guard, wipe it with a damp cloth or alcohol swab.

Disposing of your GENOTROPIN PEN 5

- Your doctor or healthcare provider will instruct you on how to discard your used syringes and needles and other medical waste in an appropriate puncture resistant disposal container such as a 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, syringes, other medical waste, and sharps containers.
- Do not throw needles, syringes, or sharps containers in the household trash without first checking your state and local laws.

COMMON QUESTIONS

How do I tell how much GENOTROPIN is left in the GENOTROPIN PEN 5?

Look at the dose scale imprinted along the side of the window on the metal front part of the pen. The front edge of the gray rubber plunger lines up with the number of milligrams remaining in the cartridge.

What happens when the battery runs low?

The battery in the GENOTROPIN PEN 5 should run for two years. When it begins to run low due to the end of the battery's life, you will see a flashing symbol (≡) in the dose display. This means the battery will last about another month. When the battery is dead, the dose display will show a steady≡ ≡. A flashing "bt" means the battery is running very low for some other reason and will last for about another month. When the battery is dead, the display will then show a steady "bt".

In either case, call the Pfizer Bridge Program at the toll-free number listed below to exchange your GENOTROPIN PEN 5 for a new one.

If the battery suddenly dies, can the GENOTROPIN PEN 5 still be used?

Yes. Call the Pfizer Bridge Program at the toll-free number listed below for instructions on how to determine the dose without the electronic dose display.

Questions about how to use the GENOTROPIN PEN 5?
Call the Pfizer Bridge Program toll-free at (800) 645-1280

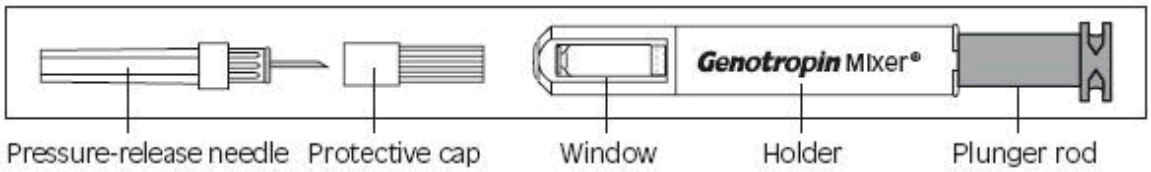
Manufactured by:
Ypsomed AG
Burgdorf, Switzerland

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

LAB-0225-6.0
Revised February 2012

Genotropin Mixer®

Growth Hormone Reconstitution Device

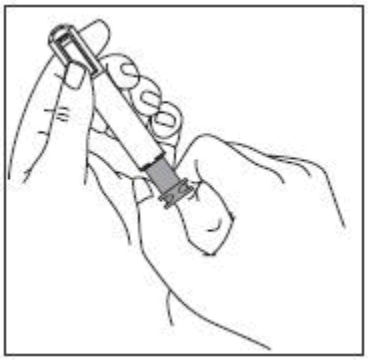


The GENOTROPIN MIXER is a device used to mix growth hormone that is provided in a two-chamber cartridge. Materials needed for injection using the GENOTROPIN MIXER:

- GENOTROPIN MIXER with a pressure-release needle
- One cartridge of GENOTROPIN® Lyophilized Powder (somatropin [rDNA origin] for injection), which contains growth hormone and diluent
- Alcohol swab
- Insulin syringe for injection
- Proper disposal container

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.



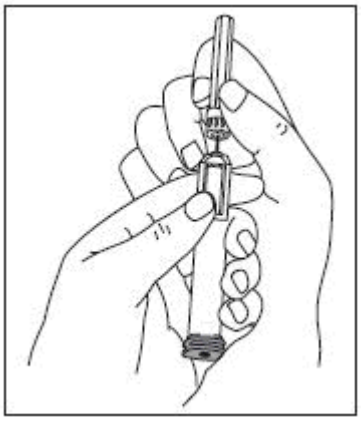
MIXING GENOTROPIN

- 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.

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.

RELEASING PRESSURE

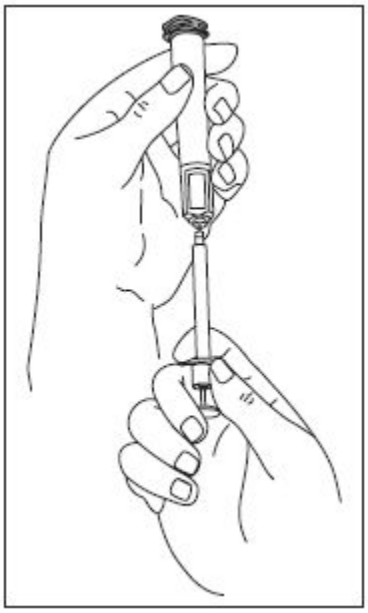
- Disinfect the metallic/rubber tip of the cartridge by wiping it with an alcohol swab.
- Remove the **protective cap** from the **pressure-release needle**. **Do not touch the exposed needle**. With the metallic/rubber tip of the **cartridge pointing upwards**, pierce the rubber tip with the needle.



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**.)

- Remove the pressure-release needle from the cartridge and discard the needle in a proper disposal container.

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.
- 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.

STORING THE GENOTROPIN MIXER

The GENOTROPIN MIXER with cartridge must be stored in a refrigerator at 36°F to 46°F (2°C to 8°C).

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.

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.

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

DISPOSING OF YOUR GENOTROPIN MIXER

- Your doctor or healthcare provider will instruct you on how to discard your used syringes and needles and other medical waste in an appropriate puncture resistant disposal container such as a 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, syringes, other medical waste, and sharps containers.
- Do not throw needles, syringes, or sharps containers in the household trash without first checking your state and local laws.

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

LAB-0228-3.0
Revised February 2012