GENOTROPIN is a prescription product for the treatment of growth failure in children with a genetic condition called Turner Syndrome (TS).

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
Deciding to go ahead with growth hormone treatment is a big decision. You and your family are sure to have questions about Turner Syndrome (TS) and its treatment. This booklet will answer many of those questions. If you still need more information about GENOTROPIN, you can visit www.GENOTROPIN.com or call your child’s health care provider.

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Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
**Turner Syndrome and Growth Hormone Treatment**

**What is Turner Syndrome?**

Turner Syndrome (TS) is a complex disorder. It is caused by changes in or absence of one of the X chromosomes. It affects only girls. About one out of every 2500 girls born each year are affected by TS. There can be many features with TS; not all girls with TS will have all of these features, and the features may be more serious in one patient and less serious in another.

Almost all girls with TS have short stature and loss of ovarian function. Other symptoms of TS may include:

- Puffy hands and feet at birth
- Low hairline on the back of the neck
- Webbed neck
- Low-set ears
- Soft nails that turn up at the ends
- Multiple small, brown moles
- Lazy eye
- Osteoporosis (thin or weak bones) later in life
- Kidney problems
- Diabetes
- Heart problems
- High blood pressure

**How are patients with TS treated?**

TS cannot be cured, but there are ways to help with many of the symptoms. Short stature can be treated with growth hormone. Other hormones can help with pubertal development and preventing bone weakness. Some girls with TS may have heart problems and may need to have their heart checked each year. Additionally, some TS patients may need surgery for kidney problems, and blood pressure must be checked regularly. Many TS patients may have diabetes and need their health care providers to monitor their blood sugar. Thyroid disorders may also occur. These conditions can be treated with drugs.

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
**Why does my child need growth hormone?**

Your child’s health care provider has prescribed growth hormone for your child because her body needs help growing. Taking GENOTROPIN should help your child grow.

GENOTROPIN is intended to treat growth and body mass. It does not treat all of the symptoms listed on page 4.

**What is a growth hormone?**

Hormones are substances made by glands in the body. They travel in the blood and help with important bodily functions. Natural growth hormone is a substance made by the body’s pituitary (pit-TOO-it-tair-ee) gland. This pea-sized gland found at the base of the brain makes a group of hormones that control many of the body’s functions. It helps children grow, and adults need it to stay healthy.

**What is GENOTROPIN?**

GENOTROPIN is the name of one growth hormone therapy your child’s health care provider may prescribe for your child. It is just like the natural growth hormone that our bodies make. The main difference is that GENOTROPIN is man-made.

GENOTROPIN is a prescription product for the treatment of growth failure in children with a genetic condition called Turner Syndrome (TS).

GENOTROPIN should not be used by patients who have had an allergy or bad reaction to somatropin or any of the other ingredients in GENOTROPIN. In the event of an allergic reaction, seek prompt medical attention.

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*Includes use in all approved indications.*

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
Who should not take GENOTROPIN?

Growth hormone should not be used:

• To increase height in children after the growth plates have closed

• In patients with diabetes who have certain types of diabetic retinopathy (eye problems)

• In patients who have been recently diagnosed with cancer, with cancer, or who are being treated for cancer. Growth hormone deficiency can be caused by brain tumors. So, the presence of these brain tumors should be ruled out before treatment is started. Growth hormone should not be used if it is shown that a previous brain tumor has come back or is getting larger

• In patients who are critically ill because of surgery, trauma, or respiratory failure

• In children with Prader-Willi syndrome who are very overweight or have severe breathing problems

• By patients who have had an allergy or bad reaction to somatropin or any of the other ingredients in GENOTROPIN. In the event of an allergic reaction, seek prompt medical attention

What are the common side effects of GENOTROPIN?

Turner Syndrome patients taking growth hormone therapy may be more likely to get ear infections. This is also called otitis media.

In studies of GENOTROPIN in children with Turner Syndrome, side effects included flu, throat, ear, or sinus infection, runny nose, joint pain, and urinary tract infection.

This does not mean that your child will have any of these reactions. It's just that they are possible based on reactions some children have had. Tell your child’s health care provider about these or any other side effects that you notice.

How long has GENOTROPIN been available in the United States?

GENOTROPIN has been available in the United States for more than 20 years. However, if your child experiences anything unusual, let your child’s health care provider know right away.

GENOTROPIN has been available in the United States for more than 20 years.

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
Taking GENOTROPIN

How will my child take GENOTROPIN?

GENOTROPIN is injected daily, just below the skin. It doesn't come in a pill because it can't do its work when taken by mouth. Injecting GENOTROPIN lets it stay active and help your child grow.

GENOTROPIN is given with a short, thin needle. Only a very small amount of GENOTROPIN is injected. A needle guard is available so the needle is not seen when injected.

Flexible device options are available to fit a range of individual needs. Your child’s health care provider will decide which one is right for your child.

A health care provider may help you and your child with the first injection. He or she can also train you to inject GENOTROPIN on your own.

Will I hurt my child with a painful injection?

Many people say the injections feel like a pinch, and the needle is very thin. Naturally, you don't want to do anything that will cause your child discomfort, and it's normal to be a little nervous at first about giving an injection to your child.

When is the best time to give GENOTROPIN?

Your child's health care provider can tell you the best time to take GENOTROPIN. Many find the best time to inject GENOTROPIN is just before bedtime. This works well for two reasons.

- First, the body releases the most growth hormone naturally at night. Taking GENOTROPIN at night imitates your body’s pattern
- Second, nighttime is when most people brush their teeth and do other things to get ready for bed. Taking GENOTROPIN at this time makes it part of the normal bedtime routine and helps avoid missing a dose

Try to inject GENOTROPIN at the same time each day.

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
Taking GENOTROPIN (continued)

Where on the body should the injections be given?
GENOTROPIN is injected just below the skin. The health care provider who teaches you how to inject GENOTROPIN can tell you where to inject it. Most often, he or she will tell you to use the thigh, the stomach, or the rear end.

He or she will also tell you it is important to change to a different injection area each day.

Change to a different injection area each day.
This helps keep injection sites from getting sore or lumpy.

To help you change the injection site each time, divide an area into smaller spots. Keep track of the places you have already used so you know to pick a different one.

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
**How do I store GENOTROPIN?**

- You should store the GENOTROPIN cartridges, GENOTROPIN Pen®, and GENOTROPIN Mixer® in the refrigerator (36ºF to 46ºF) but not in the freezer. Protect it from light.
- If the GENOTROPIN cartridges, Pen, or Mixer are left out of the refrigerator, contact your health care provider or pharmacy.
- The GENOTROPIN MiniQuick® does not require refrigeration for up to 3 months before mixing.

**What if I have questions about my child’s device?**

If you have any other questions, you can call the Device Support Hotline at **1-800-645-1280**, available 24 hours a day, 7 days a week, including holidays. You can also get information and answers anytime at [www.GENOTROPIN.com](http://www.GENOTROPIN.com).

**How long will my child have to take GENOTROPIN?**

Your child’s health care provider will determine the length of time for GENOTROPIN therapy. He or she will monitor progress regularly.

**How will we know if GENOTROPIN is working?**

Your child’s health care provider will tell you if GENOTROPIN is working. He or she will monitor your child regularly. Also, you and your child can make a growth chart to follow your child’s progress. It’s important to keep these appointments so your child’s health care provider knows whether or not GENOTROPIN is working.

**What if I have additional questions?**

Through the Pfizer Bridge Program® your dedicated Patient Care Consultant will:

- Familiarize himself or herself with your child’s case.
- Offer help with the insurance reimbursement process.
- Confirm if you are eligible for the GENOTROPIN Savings Program.
- Serve as a coordinating liaison between you and your health care provider, your insurance provider, and your pharmacy.
- Call your pharmacy to arrange the first shipment of GENOTROPIN and request shipment to you every month.
- Set up training for you or a caregiver to learn how to give injections, when available and requested by your child’s health care provider.
What other safety information should I know?

Some patients have developed diabetes mellitus while taking GENOTROPIN. Dosage of diabetes medicines may need to be adjusted during growth hormone treatment. Patients should be watched carefully if growth hormone is given along with glucocorticoid therapy and/or other drugs that are processed by the body in the same way.

In childhood cancer survivors, treatment with growth hormone may increase the risk of a new tumor, particularly certain benign brain tumors. This risk may be higher in patients who were treated with cranial radiation. Also, patients and their doctors should check regularly for skin changes.

A small number of patients treated with growth hormone have had increased pressure in the brain. This can cause headaches and problems with vision. Treatment should be stopped and reassessed in these patients. Patients with Turner Syndrome and Prader-Willi syndrome may be at higher risk of developing increased pressure in the brain.

Thyroid function should be checked regularly during growth hormone therapy. Thyroid hormone replacement therapy should be started or adjusted if needed.

Patients treated with growth hormone should be checked regularly for low serum cortisol levels and/or the need to increase the dose of the glucocorticoids they are taking.

In children experiencing rapid growth, curvature of the spine may develop or worsen. This is also called scoliosis. Patients with scoliosis should be checked regularly to make sure their scoliosis does not get worse during their growth hormone therapy.

In children experiencing rapid growth, limping or hip or knee pain may occur. If a child getting growth hormone therapy starts to limp or gets hip or knee pain, the child's doctor should be notified and the child should be examined.

Growth hormone should only be used during pregnancy if clearly needed. It should be used with caution in nursing mothers because it is not known whether growth hormone is passed into human milk.

Some cases of pancreatitis (inflamed pancreas) have been reported rarely in children and adults receiving growth hormone. There is some evidence that there is a greater risk of this in children than in adults. Literature suggests that girls who have Turner Syndrome may have a greater risk of pancreatitis than other children taking growth hormone. In any child who develops lasting, severe abdominal pain, pancreatitis should be considered.

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

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

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

Rx only

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
What if I have more questions about my child’s TS?
If you would like more information about TS, you can contact your health care provider or refer to the websites below.

There are also a number of patient support groups.
Turner Syndrome Society: www.turnersyndrome.org
Human Growth Foundation: www.hgfound.org
The MAGIC Foundation: www.MAGICfoundation.org

These websites are neither owned nor controlled by Pfizer. Pfizer does not endorse and is not responsible for the content or services of these sites.

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
Visit our website at www.GENOTROPIN.com
Contact the Pfizer Bridge Program® at 1-800-645-1280

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

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
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) for injection, for subcutaneous use
Initial U.S. Approval: 1987

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

• Hypersensitivity to somatropin or excipients (4)
• Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4)
• Children with closed epiphyses (4)

• 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)
• Neoplasms: Monitor patients with preexisting tumors for progression or recurrence.
• Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin in particular meningiomas in patients treated with radiation to the head for their first neoplasm (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)
• Hypersensitivity: Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention (5.6)
• Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary (5.7)
• Hypoadrenalism: Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (5.8)
• Hypothyroidism: May first become evident or worsen. Monitor thyroid function periodically (5.9)
• Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.10)
• Progression of Preexisting Scoliosis: Monitor any child with scoliosis for progression of the curve (5.11)
• Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.15)

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2016

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Full Prescribing Information

1 INDIcATIONS AND USAGE

1.1 Pediatric Patients

GENOTROPIN is indicated for the treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. GENOTROPIN 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 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 is indicated for the treatment of growth failure associated with Turner syndrome.

GENOTROPIN 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) < -2.5, 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 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 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.

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 (rGH).

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

Generally, a dose of up to 0.48 mg/kg body weight/week is recommended.

Note: 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 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 (rGH).

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

Generally, a dose of up to 0.48 mg/kg body weight/week is recommended.

Non-weight based — based on published consensus guidelines, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor 1 (IGF-I) concentrations. The dose should be decreased as necessary on the basis of adverse events and/or serum IGF-I concentrations above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person, and between male and female patients.

Weight based — based on the dosing regimen used in the original adult GHD registration trials, the recommended dosage at the start of treatment is not more than 0.04 mg/kg/week. The dose may be increased according to individual patient requirements to not more than 0.08 mg/kg/week at 4–8 week intervals. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I concentrations should be used as guidance in dose titration.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

2.3 Preparation and Administration

The GENOTROPIN 5 and 12 mg cartridges are color-coded to help ensure proper use with the GENOTROPIN Pen delivery device. The 5 mg cartridge has a green tip to match the green pen window on the Pen 3, 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 lipodystrophy.

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 (see Warnings and Precautions (5.1)).

- Prader-Willi Syndrome in Children

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

- Active Malignancy

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

- Hypersensitivity

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

- Diabetic Retinopathy

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

- Closed Epiphyses

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

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

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

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

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

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

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

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

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

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

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

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

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

Clinical Trials in children with SGA
In clinical studies of 273 pediatric patients born small for gestational age treated with GENOTROPIN, the following clinically significant events were reported: mild transient hypertension (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, fractures, 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 (20%) and 16 subjects (38%) in the untreated controls, 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 hypothyroidism. 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Double Blind Phase</th>
<th>Open Label Phase GENOTROPIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 6–18 mo. n = 572</td>
<td>GENOTROPIN 6–18 mo. n = 573</td>
</tr>
<tr>
<td></td>
<td>6–12 mo. n = 504</td>
<td>12–18 mo. n = 63</td>
</tr>
<tr>
<td></td>
<td>18–24 mo. n = 60</td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td>% Patients</td>
<td>% Patients</td>
</tr>
<tr>
<td>Swelling, peripheral</td>
<td>5.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17.5*</td>
<td>6.9</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>15.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Pain, extremities</td>
<td>14.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>10.8*</td>
<td>3.0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>9.6*</td>
<td>2.2</td>
</tr>
<tr>
<td>Headache</td>
<td>7.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Stiffness of extremities</td>
<td>7.8*</td>
<td>2.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.9*</td>
<td>2.0</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.4</td>
<td>3.4</td>
</tr>
</tbody>
</table>

* Increased significantly when compared to placebo, P < 0.05. Fisher’s Exact Test (one-sided) 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 (5). Other adverse events that have been reported include generalized edema and hypothyroidism.

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 lypophilized 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.

Perispinal Escherichia coli Peptides

Preparations of GENOTROPIN contain a small amount of perispinal 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.

6.2 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.

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products [see Warnings and Precautions (5.6)].

Leukemia has been reported in a small number of GHD children treated with somatropin, somatrem (methionylrhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GH itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not concluded that exogenous GH is a causative factor for leukemia. However, in certain cases of leukemia, it is possible that the diagnosis was established after the child had already received therapy with exogenous GH. The risk for children with GHD, if any, remains to be established [see Contraindications (4) and Warnings and Precautions (5.3)].

The following serious adverse reactions have been observed with use of somatropin (including events observed in patients who received brands of somatropin other than GENOTROPIN): acute critical illness [see Warnings and Precautions (5.1)], sudden death [see Warnings and Precautions (5.2)], intracranial tumors [see Warnings and Precautions (5.3)], central nervous system disorders (including hypothyroidism) [see Warnings and Precautions (5.9)], cardiovascular disorders, and pancreatitis [see Warnings and Precautions (5.15)].

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease (osteonecrosis/vascular necrosis) occasionally associated with slipped capital femoral epiphysis have been reported in children treated with growth hormone [see Warnings and Precautions (5.10)]. Cases have been reported with GENOTROPIN.

The following additional adverse reactions have been observed during the approved use of somatropin: headaches (children and adults), gynecomastia (children), and significant diabetic retinopathy. New-onset type 2 diabetes mellitus has been reported.

7. DRUG INTERACTIONS

7.1 11β-Hydroxysteroid Dehydrogenase Type 1

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of 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) hypogonadal men may have unmask or develop increased androgenic activity. In the event of increased androgenic activity, replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of the drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1 [see Warnings and Precautions (5.8)].

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement 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 hypoglycemic 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 anestrous or extended estrous cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted. In perinatal and postnatal studies in rats, GENOTROPIN doses of 0.3, 1, and 3.3 mg/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offspring due to GENOTROPIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
12.2 Pharmacodynamics

A. Skeletal Growth: GENOTROPIN stimulates skeletal growth in pediatric patients with GHD, PWS, SGA, TS, or ISSN. 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 (Cmax) 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 Cmax levels were 21.0 ng/mL and 16.3 ng/mL, respectively.

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

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

Distribution

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

Metabolism

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

Excretion

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

Special Populations

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

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

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

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

Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean SC Pharmacokinetic Parameters in Adult GHD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hours)</td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>80.5 * (± 5.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>70.5 – 92.1</td>
</tr>
</tbody>
</table>

* 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).
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 0.24 mg/kg/week for the remainder of the study.

During the second year of treatment, the control 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 0.48 mg/kg/week. In Study 2, the treatment group received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week.

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

14.2 Prader-Willi Syndrome (PWS)

The safety and efficacy of GENOTROPIN in the treatment of pediatric patients with Prader-Willi syndrome (PWS) was evaluated in two randomized, open-label, controlled clinical trials. Patients received either GENOTROPIN or no treatment for the first year of the studies, while all patients received GENOTROPIN during the second year. GENOTROPIN was administered as a daily SC injection, and the dose was calculated for each patient every 3 months. In Study 1, the treatment group received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.48 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)

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

* p ≤ 0.01  † p ≤ 0.001 (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 | Untreated Control |
| | n=14 | 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 4

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). Beneficial changes in body composition were observed at the end of the 6-month treatment period, compared with patients who received no treatment. Treatment with GENOTROPIN vs Untreated Control group was statistically significant at p=0.0001. Both of these doses resulted in a slower but consistent 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) | GENOTROPIN (0.48 mg/kg/week) | Untreated Control |
| | n=76 | n=93 | 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 6, height velocity SDS and height SDS values were smaller at baseline and after treatment with GENOTROPIN when the normative standards were utilized as opposed to the Turner syndrome standard.

Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with GENOTROPIN (see Table 6). The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of GENOTROPIN.

### Table 6: Effect of GENOTROPIN on Growth in Turner Syndrome (Mean ± SD)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Study 055</th>
<th>Study 092</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height velocity SDS</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 0.3</td>
</tr>
</tbody>
</table>
16  HOW SUPPLIED/STORAGE AND HANDLING
GENOTROPIN® lyophilized powder is available in the following packages:
5 mg two-chamber cartridge (with preservative)
Concentration of 5 mg/mL
For use with the GENOTROPIN® PEN® 5 Growth Hormone Delivery Device and/or the GENOTROPIN® MIXER™ Growth Hormone Reconstitution Device.
Package of 1 NDC 0013-2626-81

12 mg two-chamber cartridge (with preservative)
Concentration of 12 mg/mL
For use with the GENOTROPIN® PEN 12 Growth Hormone Delivery Device and/or the GENOTROPIN® MIXER Growth Hormone Reconstitution Device.
Package of 1 NDC 0013-2646-81

GENOTROPIN® MINIQUICK® Growth Hormone Delivery Device containing a two-chamber cartridge of GENOTROPIN® (without preservative)
After reconstitution, each GENOTROPIN® MINIQUICK® delivers 0.25 mL, regardless of strength. Available in the following strengths, each in a package of 7:
0.2 mg NDC 0013-2649-02
0.4 mg NDC 0013-2650-02
0.6 mg NDC 0013-2651-02
0.8 mg NDC 0013-2652-02
1.0 mg NDC 0013-2653-02
1.2 mg NDC 0013-2654-02
1.4 mg NDC 0013-2655-02
1.6 mg NDC 0013-2656-02
1.8 mg NDC 0013-2657-02
2.0 mg NDC 0013-2658-02

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

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

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

Or
Vetter Pharma-Fertigung GmbH & Co. KG
Langenargen, Germany

Or
Pfizer Manufacturing Belgium N.V.
Puurs, Belgium

Rx only

Pharmacia & Upjohn Co
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