Small for Gestational Age and Growth Hormone Treatment

GENOTROPIN is a prescription product for the treatment of growth failure in children who were born smaller than most other babies born after the same number of weeks of pregnancy. Some of these babies may not show catch-up growth by age 2 years. This condition is called small for gestational age (SGA).
Deciding to go ahead with growth hormone treatment is a big decision. You and your family are sure to have questions about Small for Gestational Age (SGA) 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.

Our patient support program is here to help. Call the Pfizer Bridge Program® at 1-800-645-1280 if you have questions about insurance or your child’s device.

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Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
Small for Gestational Age and Growth Hormone Treatment

What is SGA?
SGA stands for "small for gestational age." It is used to describe a child born smaller in size than normal for the child's gender and gestational age (the number of weeks of pregnancy at birth). SGA children are smaller than most kids who were born after the same number of weeks of pregnancy.

Why is a baby born SGA?
Often, it is unclear why a baby is born SGA. Sometimes a fetal growth problem occurring during pregnancy is a cause, as well as genetic factors.

Do SGA babies stay small?
Most children born SGA "catch up" to other children by age 2. They catch up by growing faster than usual during the first 2 years.

But 10% of these children don't catch up by age 2. These children may be helped by growth hormone therapy.

How does my child's doctor know if my child is SGA?
Your child's health care provider should track growth using standard charts. These charts contain curved lines which are the average growth rates of US children. Your child's health care provider measures your child at each checkup and marks the chart. With SGA children, the health care provider sees that the child's growth is not keeping up with most other children.

If your child is not catching up by age 2, there are tests that may be able to show why.

These tests include:
- A full physical exam
- Blood and urine tests to help rule out other disorders that could affect growth

If no other cause can be found, the child may need growth hormone therapy.

Example of a standard growth chart

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 his or her body needs help growing. Taking GENOTROPIN should help your child grow.

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 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 who were born smaller than most other babies born after the same number of weeks of pregnancy. Some of these babies may not show catch-up growth by age 2 years. This condition is called small for gestational age (SGA). Growth hormone can help them approach their growth potential.

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.

More than 83,000 children all over the world have taken GENOTROPIN over the last 30 years.*

*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?

Along with its benefits, any medical treatment may cause some unwanted effects. In studies of GENOTROPIN in children born SGA, side effects included temporarily elevated blood sugar, increased pressure in the brain, early puberty, abnormal jaw growth, injection site reactions, growth of moles, and worsening of scoliosis (curvature of the spine).

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 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 professional 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.

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. You will have regular appointments with your health care provider, measure your child’s growth, and monitor 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.

Please see Important Safety Information on pages 7, 8, 9, 16, and 17 and accompanying full Prescribing Information in pocket.
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 SGA?
If you would like more information about SGA, you can contact your health care provider or refer to the websites listed below.

There are also a number of patient support groups.
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.
GENOTROPIN® (somatropin) for injection, for subcutaneous use

Initial U.S. Approval: 1987

--- INDICATIONS AND USAGE ---

Warnings and Precautions, Severe Hypersensitivity (5.6)
Warnings and Precautions, Acute Critical Illness (5.1)

--- DOSAGE FORMS AND STRENGTHS ---

--- CONTRAINDICATIONS ---

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)

--- NONCLINICAL TOXICOLOGY ---

--- 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).

--- 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.

--- PATIENT COUNSELING INFORMATION ---

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.
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) to -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 (AD): 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.

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.

*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.
patients (doses 5.3–8 mg/day) compared to those receiving placebo. 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: somatotropin, history of upper airway obstruction or sleep apnea, or unidentifiable 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)].

5.3 Neoplasms

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

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms.

Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes, of preexisting nevi.

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. In addition, glucose intolerance, type 1 diabetes mellitus, and overt diabetes mellitus have been reported in children with Turner syndrome, type 1 diabetes mellitus, and 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 or IH. In patients who develop new symptoms of IH, funduscopic examination should be performed 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.

5.6 Severe Hypersensitivity

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

5.7 Fluid Retention

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

5.8 Hypoadrenalism

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

5.9 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 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.

5.10 Slipped Capital Femoral Epiphyses in Pediatric Patients

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

5.11 Progression of Preexisting Scoliosis in Pediatric Patients

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

5.12 Otitis Media and Cardiovascular Disorders in Turner Syndrome

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

5.13 Lipatrophy

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

5.14 Laboratory Tests

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

5.15 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults.

Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops persistent severe abdominal pain.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under variable 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; 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 hypoglycemia in patients 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 IFG-1 standard deviation (SD) scores were maintained in the normal range. IFG-1 SD scores above +2 SD were observed as follows: 1 subject (3%), 10 subjects (20%), and 16 subjects (38%) in the untreated group, 0.23 and the 0.47 mg/kg/week groups, respectively, had at least one measurement; while 0 subjects (0%), 2 subjects (7%) and 6 subjects (14%) had two or more consecutive IFG-1 measurements above +2 SD.

Clinical Trials in adults with GHD

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

Table 1 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>
<thead>
<tr>
<th>Adverse Event</th>
<th>Double Blind Phase</th>
<th>Open Label Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n = 572</td>
<td>GENOTROPIN n = 573</td>
</tr>
<tr>
<td>Swelling, peripheral</td>
<td>5.1</td>
<td>17.5*</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.2</td>
<td>17.3*</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>14.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Pain, extremities</td>
<td>5.9</td>
<td>14.7*</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>2.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.9</td>
<td>9.6*</td>
</tr>
<tr>
<td>Headache</td>
<td>7.7</td>
<td>9.9</td>
</tr>
<tr>
<td>Stiffness of extremities</td>
<td>1.6</td>
<td>7.9*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.6</td>
<td>4.9*</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.4</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* Increased significantly when compared to placebo, P ≤ 0.05.

<table>
<thead>
<tr>
<th>% Patients reporting the event during the indicated period.</th>
<th>% = percentage of patients who reported the event during the indicated period.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 mo.</td>
<td>6–12 mo.</td>
</tr>
<tr>
<td>14.7*</td>
<td>17.3*</td>
</tr>
<tr>
<td>14.3*</td>
<td>17.3*</td>
</tr>
<tr>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>1.7</td>
<td>3.7</td>
</tr>
<tr>
<td>4.6</td>
<td>6.1</td>
</tr>
<tr>
<td>4.0</td>
<td>6.8</td>
</tr>
</tbody>
</table>

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 (11β-HSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11β-HSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11β-HSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11β-HSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypogonadal males may have unmasked and glucocorticoid-mediated 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 11β-HSD-1 [see Warnings and Precautions (5.3)].

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 antiprerenal 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 affected 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/parenteral agents may require adjustment when somatropin therapy is initiated [see Warnings and Precautions (5.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies carried out with GENOTROPIN at doses of 0.3, 1, and 3.3 mg/kg/day administered SC in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving SC doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times the human dose) produced 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.
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)].

10 OVERDOSAGE

10.1 Short-Term

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

10.1.2 Long-Term

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

11 DESCRIPTION

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
In vitro, preclinical, and clinical tests have demonstrated that GENOTROPIN 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 5 mg/mL. The cartridge contains overﬁll
to allow for delivery of 1 mL containing the stated amount of GENOTROPIN – 5 mg.

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

12.2 Pharmacodynamics

A. Tissue Growth

12.2.1 Skeletal Growth: GENOTROPIN stimulates skeletal growth in pediatric patients
with GHD, PWS, SGA, TS, or ISS. The measureable increase in body length after
administration of GENOTROPIN results from an effect on the epiphyseal plates of long
bones. Concentrations of IGf-I, which 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.

12.2.2 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

Adaptation: GH-deﬁcient 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 21.0 ng/mL and 16.3 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.

Adaptation: GH-deﬁcient 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.

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
donors was 0.3 (± 0.11) L/hr/kg.

Special Populations

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

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

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

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

Table 2

<table>
<thead>
<tr>
<th>Mean Sc Pharmacokinetic Parameters in Adult GHD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%) (N=15)</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Mean (± SD)</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
<tr>
<td>Tmax = time of maximum plasma concentration</td>
</tr>
<tr>
<td>* 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).</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Study</th>
<th>GENOTROPIN (0.24 mg/kg/week)</th>
<th>Untreated Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=15</td>
<td>112.7 ± 14.9</td>
<td>109.5 ± 12.0</td>
</tr>
<tr>
<td>Study 2</td>
<td>GENOTROPIN (0.36 mg/kg/week)</td>
<td>Untreated Control</td>
</tr>
<tr>
<td>n=7</td>
<td>120.3 ± 17.5</td>
<td>120.5 ± 11.2</td>
</tr>
<tr>
<td>n=9</td>
<td>11.6 ± 2.3</td>
<td>5.0 ± 1.2</td>
</tr>
<tr>
<td>Growth from months 0 to 12</td>
<td>10.7 ± 2.3</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Height Standard Deviation Score (SDS) for age Baseline SDS</td>
<td>-1.6 ± 1.3</td>
<td>-1.8 ± 1.5</td>
</tr>
<tr>
<td>SDS at 12 months</td>
<td>-0.5 ± 1.3</td>
<td>-1.9 ± 1.4</td>
</tr>
</tbody>
</table>

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

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). 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)

<table>
<thead>
<tr>
<th>Study</th>
<th>GENOTROPIN (0.24 mg/kg/week)</th>
<th>Untreated Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=76</td>
<td>-3.2 ± 0.8</td>
<td>-3.4 ± 1.0</td>
</tr>
<tr>
<td>n=93</td>
<td>-2.0 ± 0.8</td>
<td>-1.7 ± 1.0</td>
</tr>
<tr>
<td>Height Standard Deviation Score (SDS) Baseline SDS</td>
<td>-2.1 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>SDS at 24 months</td>
<td>2.1 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Change in SDS from baseline to month 24</td>
<td>1.7 ± 0.6</td>
<td></td>
</tr>
</tbody>
</table>

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

14.4 Turner Syndrome

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

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

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

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

**14.5 Idiopathic Short Stature**

The long-term efficacy and safety of GENOTROPIN in patients with idiopathic short stature (ISS) were evaluated in one randomized, open-label, clinical trial that enrolled 177 children. Patients were enrolled on the basis of short stature, stimulated GH secretion > 10 ng/mL, and prepubertal status (criteria for idiopathic short stature were retrospectively applied and included 126 patients). All patients were observed for height progression for 12 months and were subsequently randomized to GENOTROPIN or observation only and followed to final height. Two GENOTROPIN doses were evaluated in this trial: 0.23 mg/kg/week (0.033 mg/kg/day) and 0.47 mg/kg/week (0.067 mg/kg/day). Baseline patient characteristics 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.

**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 diuluent 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 diuluent 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.
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