TEV-TROPIN®
[somatropin (rDNA origin) for injection]
5 mg (15 IU)

DESCRIPTION

TEV-TROPIN® (somatropin, rDNA origin, for injection), a polypeptide of recombinant DNA origin, has 191 amino acid residues and a molecular weight of about 22,124 daltons. It has an amino acid sequence identical to that of human growth hormone of pituitary origin. TEV-TROPIN® is a strain of *Escherichia coli* modified by insertion of the human growth hormone gene.

TEV-TROPIN® is a sterile, white, lyophilized powder, intended for subcutaneous administration, after reconstitution with bacteriostatic 0.9% sodium chloride injection, USP, (normal saline) (benzyl alcohol preserved). The quantitative composition of the lyophilized drug per vial is:

5 mg (15 IU) vial:

Somatropin	5 mg (15 IU)
Mannitol	30 mg

The diluent contains bacteriostatic 0.9% sodium chloride injection, USP, (normal saline), 0.9% benzyl alcohol as a preservative, and water for injection. A 5 mL vial of the diluent will be supplied with each dispensed vial of TEV-TROPIN®.

TEV-TROPIN® is a highly-purified preparation. Reconstituted solutions have a pH in the range of 7.0 to 9.0.

CLINICAL PHARMACOLOGY

Clinical trials have demonstrated that TEV-TROPIN® is equivalent in its therapeutic effectiveness and in its pharmacokinetic profile to those of human growth hormone of pituitary origin (somatropin). TEV-TROPIN® stimulates linear growth in children who lack adequate levels of endogenous growth hormone. Treatment of growth hormone-deficient children with TEV-TROPIN® produces increased growth rates and IGF-1 (Insulin-Like Growth Factor-1) concentrations that are similar to those seen after therapy with human growth hormone of pituitary origin.

Both TEV-TROPIN® and somatropin have also been shown to have other actions including:

A. *Tissue Growth*

1. Skeletal Growth. TEV-TROPIN® stimulates skeletal growth in patients with growth hormone deficiency. The measurable increase in body length after administration of TEV-TROPIN® results from its effect on the epiphyseal growth plates of long bones. Concentration of IGF-1, which may play a role in skeletal growth, are low in the serum of growth hormone-deficient children but increase during treatment with TEV-TROPIN®. Mean serum alkaline phosphatase concentrations are increased.
2. Cell Growth. It has been shown that there are fewer skeletal muscle cells in short statured children who lack endogenous growth hormone

as compared with normal children. Treatment with somatropin results in an increase in both the number and size of muscle cells.

3. Organ Growth. Somatropin influences the size of internal organs and it also increases red cell mass.

B. *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, results from treatment with somatropin.

C. *Carbohydrate Metabolism*

Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. Large doses of somatropin may impair glucose tolerance.

D. *Lipid Metabolism*

Administration of somatropin to growth hormone-deficient patients mobilizes lipid, reduces body fat stores, and increases plasma fatty acids.

E. *Mineral Metabolism*

Sodium, potassium, and phosphorous are conserved by somatropin. Serum concentrations of inorganic phosphates increased in patients with growth hormone deficiency after therapy with TEV-TROPIN® or somatropin. Serum calcium concentrations are not significantly altered in patients treated with either somatropin or TEV-TROPIN®.

F. *Connective Tissue Metabolism*

Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

PHARMACOKINETICS

Following intravenous administration of 0.1 mg/kg of TEV-TROPIN®, the elimination half-life was about 0.42 hours (approximately 25 minutes) and the mean plasma clearance (±SD) was 133 (±16) mL/min in healthy male volunteers.

In the same volunteers, after a subcutaneous injection of 0.1 mg/kg TEV-TROPIN to the forearm, the mean peak serum concentration (±SD) was 80 (±50) ng/mL which occurred approximately 7 hours post-injection and the apparent elimination half-life was approximately 2.7 hours. Compared to intravenous administration, the extent of systemic availability from subcutaneous administration was approximately 70%.

INDICATION AND USAGE

TEV-TROPIN® is indicated for the treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

CONTRAINDICATIONS

TEV-TROPIN® reconstituted with bacteriostatic 0.9% sodium chloride injection, USP (normal saline) (benzyl alcohol preserved) should not be administered to patients with a known sensitivity to benzyl alcohol (see **WARNINGS**).

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

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

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.

Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n = 522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3 to 8 mg/day) compared to those receiving placebo (see **WARNINGS**).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see **WARNINGS**). TEV-TROPIN® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

WARNINGS

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 doses of somatropin (see **CONTRAINDICATIONS**). 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 experiencing acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstructions or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible an treated aggressively (see **CONTRAINDICATIONS**). TEV-TROPIN® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

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.

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

When administering TEV-TROPIN® to newborns, reconstitute with sterile normal saline for injection, USP. WHEN RECONSTITUTING WITH STERILE NORMAL SALINE, USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNUSED PORTION.

PRECAUTIONS

General

TEV-TROPIN® therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of pediatric patients with growth hormone deficiency.

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has not revealed a relationship between somatropin replacement therapy and recurrence of CNS tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

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

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 patients. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin,

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

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered. 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.

Patients with endocrine disorders, including growth hormone deficiency, may have an increased incidence of slipped capital femoral epiphysis. Any child who develops a limp or complains of hip or knee pain during somatropin therapy should be evaluated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. IH has been reported more frequently after treatment with IGF-1. Symptoms usually occur within the first eight weeks after the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved rapidly after temporary suspension or termination of therapy. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin induced idiopathic IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved.

Progression of scoliosis can occur in children 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.

Bone age should be monitored periodically during somatropin administration, especially in patients who are pubertal and/or receiving concomitant thyroid hormone replacement therapy. Under these circumstances, epiphyseal maturation may progress rapidly.

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

Information for Patients
Patients being treated with TEV-TROPIN and/or their caregivers should be informed about the potential benefits and risks associated with treatment. See the patient information included with the product and/or injection device. This information is intended to aid in the safe and effective administration of the medication. It is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer TEV-TROPIN should receive appropriate training and instruction on the proper use of TEV-TROPIN from the physician or other suitable qualified health care professional. A puncture-resistant container for the disposal of used needles and syringes should be strongly recommended. Patients and/or caregivers should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes.

Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, and IGF-1 may increase after somatropin therapy.

Drug Interactions
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. Growth hormone and somatropin inhibit 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

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.

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 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 CP450 liver enzymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis, mutagenesis and reproduction studies have not been conducted with TEV-TROPIN®.

Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted withTEV-TROPIN. It is also not known whether TEV-TROPIN can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. TEV-TROPIN®should be given to a pregnant woman only if clearly needed.

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 TEV-TROPIN® is administered to a nursing woman.

Geriatric Use
The safety and effectiveness of somatropin in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and may be more prone to develop adverse reactions.

ADVERSE REACTIONS
The following adverse reactions have been observed during appropriate use of somatropin: headaches (children and adults), gynecomastia (children) and pancreatitis (children and adults). See WARNINGS section.

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 influences 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 TEV-TROPIN with the incidence of antibodies to other products may be misleading. With respect to growth hormone, antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases, when binding capacity exceeds 2 mg/L, growth attenuation has been observed.

None of the patients with anti-GH antibodies in the clinical studies experienced decreased linear growth response to TEV-TROPIN® or any other associated adverse event. Injection site reactions (e.g., pain, bruise) occurred in 8 of the 164 treated patients.

Leukemia has been reported in a small number of patients treated with other growth hormone products. It is uncertain whether this risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors.

New-onset type 2 diabetes mellitus has been reported.

OVERDOSAGE
The recommended dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight 3 times per week should not be exceeded. Acute overdose could cause initial hypoglycemia and subsequent hyperglycemia. Repeated use of doses in excess of those recommended could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

DOSAGE AND ADMINISTRATION

A dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight administered 3 times per week by subcutaneous injection is recommended. TEV-TROPIN® should be reconstituted with 1-5mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved).* The stream of normal saline should be aimed against the side of the vial to prevent foaming. Swirl the vial with a GENTLE rotary motion until the contents are completely dissolved and the solution is clear. DO NOT SHAKE. Since TEV-TROPIN® is a protein, shaking or vigorous mixing will cause the solution to be cloudy. If the resulting solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

* Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN® to newborns, reconstitute with sterile normal saline for injection, USP.

Occasionally, after refrigeration, some cloudiness may occur. This is not unusual for proteins like TEV-TROPIN®. Allow the product to warm to room temperature. If cloudiness persists or particulate matter is noted, the contents MUST NOT be used.

Before and after injection, the septum of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions.

TEV-TROPIN® can be administered using (1) a standard sterile disposable syringe or (2) using a Tjet Needle-Free injection device. For proper use, please refer to the **User's Manual** provided with the administration device.

STABILITY AND STORAGE

Before Reconstitution – Vials of TEV-TROPIN® are stable when refrigerated at 36° to 46°F (2° to 8°C). Expiration dates are stated on the labels.

After Reconstitution – Vials of TEV-TROPIN® are stable for up to 14 days when reconstituted with bacteriostatic 0.9% sodium chloride (normal saline), USP, and stored in a refrigerator at 36° to 46°F (2° to 8°C). Do not freeze the reconstituted solution.

HOW SUPPLIED

TEV-TROPIN® (somatropin, rDNA origin, for injection) is supplied as 5 mg (15 IU) of lyophilized, sterile somatropin per vial.

Each 5 mg carton contains one vial of TEV-TROPIN® (5 mg per vial) and one vial of diluent [5-mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved)], and is supplied in single cartons or cartons of six.

Rx only.

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