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

℞ only

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/Somatomedin-C) 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. Concentrations 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 only for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

CONTRAINDICATIONS

Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see **WARNINGS**). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN™ is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone-deficient adult patients (n = 522) with these conditions 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**).

TEV-TROPIN™ should not be used in patients with closed epiphyses.

Patients with evidence of progression of an underlying intracranial lesion should not receive TEV-TROPIN™, intracranial tumors must be inactive and antitumor therapy completed.

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.

WARNINGS

See **CONTRAINDICATIONS** for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing growth hormone 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 growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with growth hormone 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 growth hormone. If during treatment with growth hormone, 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 growth hormone 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**).

Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN™ is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

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. WHEN RECONSTITUTING WITH STERILE NORMAL SALINE, USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNUSED PORTION.

PRECAUTIONS

Therapy with TEV-TROPIN™ should be directed by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Patients with growth hormone deficiency secondary to intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Patients should be observed for evidence of glucose intolerance because human growth hormone may induce a state of insulin resistance.

Glucocorticoid therapy may inhibit the growth-promoting effect of human growth hormone. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

Hypothyroidism may become manifest during treatment with human growth hormone. Inadequate treatment of hypothyroidism may negate optimal response to human growth hormone. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders. Physicians and parents should be alert to the development of a limp or complaint of hip or knee pain in patients treated with TEV-TROPIN™.

Intracranial hypertension (IH) has not been reported in any patients treated with TEV-TROPIN™. Nevertheless, IH with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with other growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

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

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

Nursing Mothers
There have been no studies conducted with TEV-TROPIN™ 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 TEV-TROPIN™ is administered to a nursing woman.

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

ADVERSE REACTIONS
Utilizing a double-antibody immunoassay, no antibodies to growth hormone could be detected in a group of 164 naïve and previously treated clinical trial patients after treatment with TEV-TROPIN™ for up to 40 months. However, utilizing the less specific polyethelene glycol (PEG) precipitation immunoassay, 27 of the 164 patient group were tested after treatment with TEV-TROPIN™ for 4 to 6 months and antibodies to growth hormone were detected in two patients (7.4%). The binding capacity of the antibodies from the two antibody positive patients was not determined.

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. 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.

In studies of growth hormone-deficient children, headaches occurred infrequently. 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.

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. Long-term 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. The dosage schedule for TEV-TROPIN™ should be reconstituted with 1 to 5 mL 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™ growth hormone. 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. It is recommended that TEV-TROPIN™ be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

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.

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