New Technology HGH

Remaining true to the spirit of innovation that possesses us, we continue to try to seek for more and better products. In this context, we are pleased to offer you the new HGH, based on a **new production process**. That makes our already high-standard product named EVOGENE, **even better**.

As it is widely known, until now the HGH is made from Colon Bacillus (Escherichia coli). We introduce a new technology in HGH manufacturing from **Pichia Pastoris** (which belongs to methylotropic yeast). The HGH produced in this way has many advantages over the old technology. Most important to be mentioned are:

★ With the old technology, the greater purity that can be achieved is about 92% (which means about 8% impurities that cannot be removed). With our new technology **the purity of the product is 99%**!

★ New technology HGH has **larger activity coefficient**. It is more active for IU to IU comparing to the "traditional" way made HGH.

★ The new technology HGH has shown **no immune-reaction problems**. The human body doesn't form and produce antibodies after 6-8 months of use. This was the case with the old-way made HGH. So, with the new HGH there is no need to take more and more quantities just to have the same results.

★ The HGH molecule is **more stable**. As a result, it can be stored for longer time without been decayed.

EVOGENE

3,33 mg (10IU) injection

Alley

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1. Description
Evogene (recombinant Human Growth Hormone – rDNA origin) is a human growth hormone produced by recombinant DNA technology. It has 191 amino acid sequence and its structure are identical to the dominant form of this human pituitary growth hormone. It has a molecular weight of 22,125 daltons.
Evogene(rHGH) is a sterile, non-pyrogenic, white lyophilized powder intended for subcutaneous or intramuscular injection, after reconstitution with sterile Water for Injection (0,3% m-Cresol)

2. Clinical pharmacology
2.1 Mechanism of Action
Somatropin (as well as endogenous HGH) binds to a dimeric GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by IGF-I produced in the liver and also locally (e.g., skeletal growth, protein synthesis), while others are primarily a consequence of the direct effects of somatropin (e.g., lipolysis) [see Clinical Pharmacology (2.2)].

2.2 Pharmacodynamics
Tissue Growth
The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in children with GHD.

Skeletal Growth
The measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies in vitro have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGFs). The somatomedins, among them IGF-I, are polypeptide hormones which are synthesized in the liver, kidney,

and various other tissues. IGF-I levels are low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, and increase after treatment with somatropin.

Cell Growth
It has been shown that the total number of skeletal muscle cells is markedly decreased in children with short stature lackin endogenous GH compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

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

Protein Metabolism
Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention which can be quantitated by observing the decline in urinary nitrogen excretion and blood urea nitrogen following the initiation of somatropin therapy.

Carbohydrate Metabolism
Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, large doses of somatropin may impair glucose tolerance.
Although the precise mechanism of the diabetogenic effect of somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase. Administration of human growth hormone to normal adults and patients with growth hormone deficiency results in increases in mean serum fasting and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A1c levels remain in the normal range.

Lipid Metabolism
Somatropin stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids and triglycerides. Untreated GHD is associated with increased body fat stores, including increased abdominal visceral and subcutaneous adipose tissue. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, and decreased serum levels of low density lipoprotein (LDL) cholesterol.

Mineral Metabolism
Administration of somatropin results in an increase in total body potassium and phosphorus and to a lesser extent sodium. This retention is thought to be the result of cell growth. Serum levels of phosphate increase in children with GHD after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

Connective Tissue Metabolism
Somatropin stimulates the synthesis of chondroitin sulfate and collagen, and increases the urinary excretion of hydroxyproline.

3. Indications

Evogene is a prescription product for the treatment of growth failure in children:
Who do not make enough growth hormone on their own. This condition is called growth hormone deficiency (GHD).
With a genetic condition called Prader-Willi syndrome (PWS). Growth hormone is not right for all children with PWS. Check with your doctor.
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).
With a genetic condition called Turner syndrome (TS).
With idiopathic short stature (ISS), which means that they are shorter than 98.8% of other children of the same age and sex; they are growing at a rate that is not likely to allow them to reach normal adult height, and their growth plates have not closed. Other causes of short height should be ruled out. ISS has no known cause.
Evogene is a prescription product for the replacement of growth hormone in adults with growth hormone deficiency (GHD) that started either in childhood or as an adult. Your doctor should do tests to be sure you have GHD, as appropriate.

4. Contraindications

Do not use Evogene, if:
- you are allergic to any ingredient in **Evogene** or in the diluent, including metacresol

- you have active or recurring cancer or brain tumor, or you currently receive treatment for cancer

- you have severe breathing problems (e.g., respiratory failure) or a serious illness caused by complications from a surgery or injury

- you have a certain type of eye problem caused by diabetes (diabetic retinopathy)

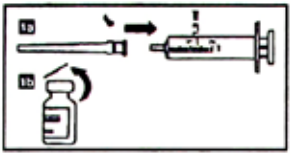
- the patient is a child who has Prader-Willi syndrome and is severely overweight or has severe breathing problems (e.g., respiratory infection, history of airway blockage or sleep apnea)

- the patient is a child who has epiphyseal closure (bone growth is complete)

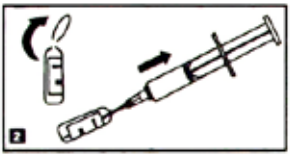
Contact your doctor or health care provider right away if any of these apply to you.

5. Instructions for reconstitution

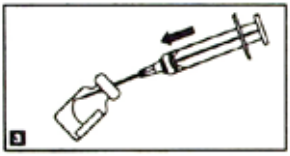
Powder must be dissolved only with the solvent provided.



Picture 1
1a. Apply the needle to the syringe
1b. Remove the plastic cover from the vial



Picture 2
Break the top of the ampoule containing the solvent. Remove the plastic cover of the needle. Make sure the needle is well applied to the syringe. Slowly absorb all the solvent.



Picture 3
Inject all the solvent to the vial. This will create a 3,33mg/ml solution. To prevent foaming, the solvent should be injected into the vial by aiming the stream of liquid against the glass wall.

Picture 4
Following reconstitution, the vial should be swirled with a GENTLE rotary motion until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be clear and colorless, without particulate matter.

6. Adverse reactions

This list presents the most serious and/or most frequently observed adverse reactions during treatment with somatropin:

- Sudden death in pediatric patients with Prader-Willi syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection
- Intracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin
- Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus
- Intracranial hypertension
- Significant diabetic retinopathy
- Slipped capital femoral epiphysis in pediatric patients
- Progression of preexisting scoliosis in pediatric patients

- Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome / paraesthesias
- Unmasking of latent central hypothyroidism
- Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions)
- Pancreatitis

7. Warnings and precautions

• **Acute Critical Illness:** Potential benefit of treatment continuation should be weighed against the potential risk

• **Prader-Willi Syndrome in Children:** Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment for GHD. Discontinue treatment if these signs occur

• **Neoplasm:** Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin – in particular meningiomas in patients treated with radiation to the head for their first neoplasm

• **Impaired Glucose Tolerance and Diabetes Mellitus:** May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment

• **Intracranial Hypertension:** Exclude preexisting papilledema.
May develop and is usually reversible after discontinuation or dose reduction

• **Fluid Retention** (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary

• **Hypothyroidism:** May first become evident or worsen

• **Slipped Capital Femoral Epiphysis:** May develop. Evaluate children with the onset of a limp or hip/knee pain

• **Progression of Preexisting Scoliosis:** May develop

• **Pancreatitis:** Consider pancreatitis in patients with persistent severe abdominal pain.

8. Interaction with other drugs

8.1 Inhibition of 11í-Hydroxysteroid Dehydrogenase Type 1

The microsomal enzyme 11í-hydroxysteroid dehydrogenase type 1 (11íHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11íHSD-1. Consequently, individuals with untreated GHD have relative increases in 11íHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11íHSD-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 11íHSD-1.

8.2 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 hypo-adrenalism and an inhibitory effect on growth.

8.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)- mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

8.4 Oral Estrogen

Because oral estrogens may reduce the serum IGF-1 response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages.

8.5 Insulin and/or Oral/Injectable Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated.

9. Over dosage

Short-Term

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

Long-Term

Long-term over dosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone .

10. Storage

Shelf life

- This product can be used not more than 3 years from the production date (see box)
- After reconstitution, may be stored for a maximum of 14 days in a refrigerator at 2°C - 8°C.
- Store vials in an upright position.
- Store in a refrigerator (2°C - 8°C). Keep in the outer carton in order to protect from light.
- For one month can be stored at room temperature.