

## Indications

Humatrope<sup>®</sup> (somatropin [rDNA origin] for injection) is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

1. Adult Onset: 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
2. Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmatory growth hormone stimulation testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.

## Important Safety Information

Patients should be informed of the risks as well as the potential benefits of somatropin therapy, and be given appropriate instructions for use of somatropin.

## Contraindications

- Patients with a known sensitivity to either metacresol or glycerin should not receive Humatrope reconstituted with the supplied diluent for Humatrope.
- Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.
- Somatropin is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.
- Somatropin should not be used or should be discontinued if there is any evidence of active malignancy.
- Because growth hormone deficiency may be an early sign of a pituitary tumor or other intracranial tumor, the presence of such a tumor should be excluded before initiation of somatropin treatment.
- Somatropin should not be used to treat patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure (*see* WARNINGS).
- Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (*see* WARNINGS).

## Warnings

- If sensitivity to the diluent should occur, **vials** of lyophilized Humatrope may be reconstituted with Bacteriostatic Water for Injection (benzyl alcohol preserved), USP or Sterile Water for Injection, USP. When Humatrope is reconstituted with Bacteriostatic Water, the solution should be kept refrigerated at 2° to 8°C (36° to 46°F) and used within 14 days.
- **Benzyl alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns.** Therefore, if Humatrope is to be administered to a newborn, it should be reconstituted with the diluent provided. However, if the infant is known

to be sensitive to the diluent, the Humatrope vial may be reconstituted using Sterile Water for Injection, USP. If the reconstituted solution is not used immediately, it must be refrigerated [2° to 8°C (36° to 46°F)] and used within 24 hours. When Humatrope is reconstituted with Sterile Water for Injection USP, only one Humatrope dose per vial should be administered and the unused solution should be discarded.

- Humatrope **cartridges** should be reconstituted only with the supplied diluent. Humatrope **cartridges** should not be reconstituted with the diluent provided with Humatrope **vials**, or with any other solution. **Humatrope cartridges should not be used if the patient is allergic to metacresol or glycerin.**
- See CONTRAINDICATIONS for information on increased mortality in patients treated with somatropin during acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or with acute respiratory failure. 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 continuing somatropin treatment in patients with acute critical illnesses should be weighed against the potential risk.
- There have been reports of fatalities after initiation of somatropin treatment in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection (*see* CONTRAINDICATIONS).

### **Precautions**

- Patients and their caregivers should be informed that as with any protein, local or systemic allergic reactions to somatropin may occur.
- Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance or diabetes mellitus may be unmasked during somatropin treatment. Therefore, blood glucose concentrations should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy.
- Patients with pre-existing tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process.
- Clinical literature has not revealed a relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial 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. In patients treated with radiation to the head for their first neoplasm, intracranial tumors in particular meningiomas, were the most common of these second neoplasms.
- Somatropin inhibits 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy.
- Careful monitoring is advisable when growth hormone is administered in combination with insulin, other drugs metabolized by CP450 liver enzymes (e.g., hydrocortisone or other corticosteroids, sex steroids, anticonvulsants, cyclosporin), or other hormone replacement therapy.

- Intracranial hypertension with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of pediatric patients treated with somatropin. Therefore, fundoscopic examination is recommended at the initiation of and periodically during growth hormone therapy.
- Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.
- In patients with hypopituitarism (multiple pituitary hormone deficiencies), standard hormone replacement therapy should be monitored closely when somatropin therapy is administered. Any pre-existing skin lesions should be monitored carefully for malignant transformation.
- The somatropin injection site should be rotated frequently to avoid local tissue atrophy.
- Experience with prolonged treatment in adults is limited. 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 adverse reactions.
- It is not known whether somatropin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Accordingly, somatropin should be given to a pregnant woman only if clearly needed.
- Caution should be exercised in administering somatropin to a nursing woman.

## **Adverse Reactions**

### *Adult-Onset Growth Hormone Deficient Patients*

- The most common adverse events reported in patients who received Humatrope therapy for 18 months were: edema (21.2%), arthralgia (17.3%), paresthesia (17.3%), myalgia (13.5%), pain (13.5%), rhinitis (13.5%), peripheral edema (11.5%), back pain (9.6%), headache (7.7%), hypertension (7.7%), and joint disorder (5.8%).
- Events that tended to resolve or become less noticeable with a decrease in Humatrope dose were edema, muscle pain, joint pain, and joint disorder.

### *Childhood-Onset Growth Hormone Deficient Patients*

- The most common adverse events reported in patients who received Humatrope therapy for 18 months were: flu syndrome (15.6%), increased concentrations of liver enzymes (AST 12.5%, ALT 6.3%), headache (9.4%), edema (6.3%), myalgia (6.3%), and pain (6.3%).
- Adult patients diagnosed with hormone deficiency in childhood reported side effects less frequently than patients with adult-onset growth hormone deficiency.