Submitting a Statement of Medical Necessity (SMN) for Humatrope® (somatropin for injection)

INFORMATION NEEDED FOR FULL SMN FORM SUBMISSION

☐ PATIENT INFORMATION: Please provide Patient Name and Date of Birth.

☐ PRIMARY CONTACT EMAIL: Humatrope DirectConnect will use this email address to establish initial contact with a patient/caregiver and collect the consents needed to support the case.

☐ INSURANCE INFORMATION: Please attach a complete copy of the patient’s insurance card, both front and back sides.

☐ DIAGNOSIS: Please select the appropriate on-label diagnosis.

☐ PRESCRIPTION OPTIONS: Select Vial or Pen. Specify dose, dose frequency, and number of refills.

☐ PRESCRIBER CERTIFICATION: Please provide prescriber’s printed name, signature, and date.

ADDITIONAL GUIDANCE FOR SUBMISSION

☐ INSURANCE CARD: Provide a copy of both the front and back of the insurance card (legible).

☐ PRESCRIBER CERTIFICATION: The prescriber’s original signature and date are needed to process the SMN.

☐ ADDITIONAL DOCUMENTATION: Recent visit notes, pertinent reports, and/or supporting medical documentation that you feel would assist in obtaining authorization for treatment.

PRESCRIPTION OPTIONS

☐ 6 mg cartridge / HumatroPen® 6 mg
  0.025-1.50 mg dose range
  0.025 mg dose increments
  Cartridge NDC: 0002-8147-01
  Pen NDC: 0002-9560-01

☐ 12 mg cartridge / HumatroPen® 12 mg
  0.05-3.00 mg dose range
  0.05 mg dose increments
  Cartridge NDC: 0002-8148-01
  Pen NDC: 0002-9561-01

☐ 24 mg cartridge / HumatroPen® 24 mg
  0.10-6.00 mg dose range
  0.10 mg dose increments
  Cartridge NDC: 0002-8149-01
  Pen NDC: 0002-9562-01

☐ 5 mg Vial Kit
  5 mg vial, diluent
  NDC: 0002-7335-11

Please see Important Safety Information, and accompanying Full Prescribing Information and Patient Information on pages 4-15 of this file.
## Supporting Material for Humatrope® (somatropin for injection)

Please provide all available and appropriate supporting materials. The chart below includes information generally considered relevant based on the diagnosis.

### ADULT PATIENTS

<table>
<thead>
<tr>
<th>Required Materials</th>
<th>Hypopituitarism</th>
<th>Panhypopituitarism</th>
<th>GH deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical exam</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Karyotype report</td>
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<tr>
<td>Relevant clinical notes</td>
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<td>●</td>
<td>●</td>
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<tr>
<td>Stimulation test results</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Thyroid function test results</td>
<td></td>
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<tr>
<td>IGF-1 results</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>IGFBP-3 results</td>
<td>●</td>
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<tr>
<td>Growth chart</td>
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<tr>
<td>Height velocity</td>
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<tr>
<td>Bone age X-ray report</td>
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</tr>
<tr>
<td>MRI scan report</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>History of head trauma</td>
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<td>Lipid profile results</td>
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<tr>
<td>DEXA scan report</td>
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<tr>
<td>List of hormonal deficiencies and/or replacements</td>
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</tbody>
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### PEDIATRIC PATIENTS

<table>
<thead>
<tr>
<th>Required Materials</th>
<th>ISS: Short stature/Growth failure/Growth retardation</th>
<th>Turner syndrome</th>
<th>SHOX deficiency(^\ddagger^)</th>
<th>Small for gestational age</th>
<th>Panhypopituitarism</th>
<th>GH deficiency</th>
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</thead>
<tbody>
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<td>History and physical exam</td>
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<tr>
<td>Relevant clinical notes</td>
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<tr>
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<td>●</td>
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<td>Growth chart</td>
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<td>●</td>
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<td>MRI scan report</td>
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<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

\(^*\) If available  
\(^\dagger\) 2 failed  
\(^\ddagger\) Include growth chart from years 0-2 including birth weight, length, and gestational age  
SHOX gene deletion or mutation confirmed by genetic testing

Please see Important Safety Information, and accompanying Full Prescribing Information and Patient Information on pages 4-15 of this file.
Statement of Medical Necessity for Humatrope® (somatropin for injection)
Humatrope® DirectConnect Fax: 1-800-642-5442, Phone: 1-84HUMATROPE (1-844-862-8767)

Please check the boxes below to register your patient and/or request one or more services.

- [ ] BENEFITS INVESTIGATION
- [ ] INJECTION TRAINING
- [ ] REGISTRATION ONLY
  (no insurance support or injection training needed)

PATIENT INFORMATION

Translation Services Needed

Interim Medication Request (FastTrack)

Patient is:

(choose one)

New to Humatrope Therapy

Currently Receiving Humatrope Therapy

Currently Receiving Other Brand of GH Therapy

Primary Contact

Relationship to Patient

Email

Primary Phone # — —

Other Phone # — —

INSURANCE INFORMATION

Please attach a complete copy of the patient's insurance card, both front and back sides.

- [ ] No Insurance
- [ ] Prior Authorization Already Submitted

DIAGNOSIS (MORE THAN ONE DIAGNOSIS MAY BE SELECTED IF APPROPRIATE.)

- [ ] Growth Hormone Deficiency (E23.0)
- [ ] Short Stature/Growth Failure/Retardation (R62.52)
- [ ] SHOX Deficiency (E34.3)
- [ ] Small for Gestational Age (P05.10), plus
- [ ] Turner Syndrome (Q96.9)
- [ ] Short Stature/Growth Failure (R62.52)
- [ ] Russell-Silver Syndrome (Q87.1)
- [ ] Hypopituitarism (E23.1/E23.0)
- [ ] Short Stature/Growth Failure (R62.52)
- [ ] Growth Retardation (R62.52)
- [ ] SHOX Deficiency (E34.3)
- [ ] Hypopituitarism (E23.1/E23.0)

MEDICAL ASSESSMENT (PLEASE ATTACH SUPPORTING DOCUMENTATION. COMPLETING THE SECTION BELOW IS OPTIONAL.)

NEEDED FOR BOTH PEDIATRIC AND ADULT PATIENTS

- [ ] IGF-1 Results Dates
- [ ] Thyroid Function Test Results Dates
- [ ] GH Stimulation Test Results
  Agent Peak GH Dates
  Agent Peak GH Dates
- [ ] Start Date of GH Treatment (For Current Patients Only)

REQUIRED FOR PEDIATRIC PATIENTS ONLY

- [ ] Pre-treatment Height Velocity cm/year Date
- [ ] Bone Age years months Date
- [ ] Open Epiphyses
- [ ] Closed Epiphyses
- [ ] Predicted Adult Height cm Date
- [ ] Growth Chart Attached Date

PRESCRIPTION OPTIONS

- [ ] 6 mg cartridge / HumatroPen® 6 mg
  Cartridge NDC: 0002-8147-01 / Pen NDC: 0002-9560-01
  Dose range: 0.025-1.50 mg / 0.025 mg increments
- [ ] 12 mg cartridge / HumatroPen® 12 mg
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  Dose range: 0.05-3.00 mg / 0.05 mg increments
- [ ] 24 mg cartridge / HumatroPen® 24 mg
  Cartridge NDC: 0002-8149-01 / Pen NDC: 0002-9562-01
  Dose range: 0.10-6.00 mg / 0.10 mg increments
- [ ] 5 mg Vial Kit
  NDC: 0002-7335-11
  5 mg vial; diluent amount (1.5-5 mL)
  Needle gauge/length
  Please order syringes and needle gauges for reconstitution and dosing.

Dose mg sc/day Dose Frequency times/week Days Supply Number of Cartridges (optional)

Number of Refills Suggested Pharmacy (optional): Phone #

Required for both pediatric and adult patients

5 mm x 32G 6 mm x 31G Other:

5 mm x 31G

Preventive Medication (Required for Pediatric Patients Only)

-Control of Tendency to Overeat
  -[ ] Yes
  -[ ] No

AGENT Peak GH Dose Date

(agent peak gh)

Start Date of GH Treatment (For Current Patients Only)

Statement of Medical Necessity for Humatrope® (somatropin for injection)

By signing below, I certify that the therapy is medically necessary and that this information is accurate to the best of my knowledge. I also represent that I am disclosing this information for purposes of treatment, payment and/or healthcare operations and otherwise have consent to disclose this information, as well as other medical information that may be disclosed, including medical records of the patient, to Eli Lilly and Company and Lilly USA, LLC and its agents for the purpose of assessing whether the patient qualifies for any reimbursement benefits through the duration of the patient’s therapy. I also certify that the patient is aware and has consented to my disclosure of their information to Lilly so that Lilly may contact the patient to further enable these services.

Prescriber Name __________________________ NPI # __________________________

DEA License # __________________________ Tax ID # __________________________

Phone # __________________________ Fax # __________________________

Name of Contact Person __________________________ Contact Phone # __________________________

Prescriber Signature __________________________ Date __________________________

Dispense as written. No stamps allowed. Please see Indications for Use and Important Safety Information on the back of this form and accompanying Full Prescribing Information and Patient Information.

See Full Pen User Manual that accompanies the HumatroPen 6 mg, 12 mg, 24 mg.
**Important Safety Information for Humatrope**

**INDICATIONS FOR HUMATROPE**

**Humatrope is indicated for the treatment of:**

- Children who have growth failure or short stature due to growth hormone (GH) deficiency, Turner syndrome, or SHOX deficiency; have idiopathic short stature, defined by height SDS ≤ -2.25, associated with growth rates unlikely to result in adult height in the normal range and in whom other causes of short stature have been excluded, were born small for gestational age and fail to show catch-up growth by 2 to 4 years of age.
- Adults who have GH deficiency, either adult-onset (as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma) or childhood-onset. Patients treated for growth hormone deficiency in childhood who have closed epiphyses should be reevaluated to determine if they should continue growth hormone.

**Contraindications**

- **Acute Critical Illness:** Somatropin should not be used to treat patients with acute critical illness from complications after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure.
- **Prader-Willi Syndrome in Children:** Somatropin should not be used in pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. Humatrope is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.
- **Active Malignancy:** Somatropin is contraindicated in patients with any evidence of active malignancy.
- **Hypersensitivity:** Humatrope is contraindicated in patients with a known hypersensitivity to somatropin or the supplied diluent.
- **Diabetic Retinopathy or Closed Epiphyses:** Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy. It should not be used for growth promotion in pediatric patients with closed epiphyses.

**Warnings and Precautions**

- **Acute Critical Illness:** Increased mortality in patients with acute critical illness from complications after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin.
- **Prader-Willi Syndrome in Children:** There have been reports of fatalities after starting 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 obstruction or sleep apnea, or unidentified respiratory infection. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin.
- **Neoplasms:** An increased risk of a second neoplasm has been reported for childhood cancer survivors treated with somatropin for GH deficiency that developed following radiation to the brain/head. 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. Monitor for progression or recurrence in all patients receiving somatropin therapy who have a history of GH deficiency secondary to an intracranial neoplasm.
- **Glucose Intolerance and Diabetes Mellitus:** Previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. New-onset type 2 diabetes mellitus has been reported. Blood glucose concentrations should be monitored periodically in all patients taking somatropin, especially in those with risk factors for diabetes mellitus and those with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance. The dose of antihyperglycemic drugs may require adjustment when somatropin treatment is instituted.
- **Intracranial Hypertension:** Intracranial hypertension with papilledema, visual changes, headache, nausea, and/or vomiting have been reported in a small number of patients treated with somatropin. If papilledema is observed by funduscopic during treatment with somatropin, treatment should be stopped and the patient’s condition should be reassessed before treatment is resumed.
- **Severe Hypersensitivity:** Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with use of somatropin products.
- **Fluid Retention:** Transient and dose-dependent fluid retention during somatropin replacement in adults may occur frequently.
- **Hypoadrenalism:** Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiencies may be at risk for reduced serum cortisol levels and/or unmasking of central hypoadrenalism. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment.
- **Hypothyroidism:** Patients treated with somatropin should have periodic thyroid function tests, and thyroid hormone replacement therapy should be initiated or adjusted in cases of unmasked or worsening hypothyroidism.
- **Slipped Capital Femoral Epiphysis in Pediatric Patients:** Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders and 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.
- **Progression of Scoliosis in Pediatric Patients:** Progression of scoliosis can occur in patients who experience rapid growth. Patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis.
- **Pancreatitis:** Cases of pancreatitis have been reported rarely in children and adults receiving somatropin. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain.
- **Lipoatrophy:** Tissue atrophy may result when somatropin is administered subcutaneously at the same site over a long period of time. This can be avoided by rotating the injection site.

**Adverse Reactions**

- Common adverse reactions reported in adult and pediatric patients taking somatropin include injection site reactions, hypersensitivity to the diluent, and hypothyroidism. Additional common adverse reactions in adults include edema, arthralgia, myalgia, carpal tunnel syndrome, paresthesias, and hyperglycemia.

HG HCP IS 13JAN2017

See accompanying Full Prescribing Information and Patient Prescribing Information.
HUMATROPE® [somatropin (rDNA ORIGIN)]

for injection, for subcutaneous use

HTR-0003-USPI-20161213

2.3 Dosing for Pediatric Patients

The Humatrope dosage and administration schedule should be individualized for each patient based on the growth response. Failure to increase height velocity, particularly during the first year of treatment, should prompt close assessment of compliance and evaluation of other causes of poor growth, such as hypothyroidism, under-nutrition, advanced bone age and antibodies to recombinant human growth hormone. Response to somatropin treatment tends to decrease with time. Somatropin treatment for stimulation of linear growth should be discontinued once epiphyseal fusion has occurred.

The recommended weekly dosages in milligrams (mg) per kilogram (kg) of body weight for pediatric patients are:

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone deficiency</td>
<td>0.025 to 0.043 mg/kg/day (0.18 to 0.30 mg/kg/week)</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>up to 0.054 mg/kg/day (0.375 mg/kg/week)</td>
</tr>
<tr>
<td>Idiopathic short stature</td>
<td>up to 0.053 mg/kg/day (0.37 mg/kg/week)</td>
</tr>
<tr>
<td>SHOX deficiency</td>
<td>0.050 mg/kg/day (0.35 mg/kg/week)</td>
</tr>
</tbody>
</table>
| Small for gestational age | up to 0.067 mg/kg/day (0.47 mg/kg/week)

2.4 Dosing for Patients with Adult Growth Hormone Deficiency

Either of two approaches to Humatrope dosing may be followed: a non-weight-based regimen or a weight-based regimen.

- **Non-weight-based** — based on published consensus guidelines, a starting dose of approximately 0.2 mg/kg/day (range, 0.15-0.30 mg/kg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/kg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor I (IGF-I) concentrations. The dose should be decreased as necessary on the basis of adverse events and/or serum IGF-I concentrations above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person, and between male and female patients.

- **Weight-based** — based on the dosing regimen used in the original adult GH deficiency registration trials, the recommended dosage at the start of treatment is not more than 0.066 mg/kg (6 µg/kg) daily. The dose may be increased according to individual patient requirements to a maximum of 0.0125 mg/kg (12.5 µg/kg) daily. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I concentrations should be used as guidance in dose titration.

3 DOSEAGE AND STRENGTHS

Humatrope is a sterile, white lyophilized powder available in the following vial and cartridge sizes:

- 5 mg vial and a 5-mL vial of Diluent for Humatrope
- 24 mg cartridge (purple) and a prefilled syringe of Diluent for Humatrope
- 12 mg cartridge (teal) and a prefilled syringe of Diluent for Humatrope
- 6 mg cartridge (gold) and a prefilled syringe of Diluent for Humatrope
- 24 mg cartridge (purple) and a prefilled syringe of Diluent for Humatrope

Humatrope cartridges should be used only with the appropriate corresponding pen device.

4 CONTRAINDICATIONS

**Acute Critical Illness** — 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 [see Warnings and Precautions (5.1)].

**Prader-Willi Syndrome in Children** — Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients. Humatrope is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome. [See Warnings and Precautions (5.2)].

**Active Malignancy** — 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 GH 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 [see Warnings and Precautions (5.3)].

**Hypersensitivity** — Humatrope is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products [see Warnings and Precautions (5.6)].

**Diabetic Retinopathy** — Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

**Closed Epiphyses** — Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

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 (4)]. Two placebo-controlled clinical trials in non-GH deficient adult patients (n=522) with these conditions in intensive care
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 patients with Turner syndrome. 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 Patients with Turner Syndrome
Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders, as these patients have an increased risk of ear and hearing disorders. Somatropin treatment 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., hypertension, aortic aneurysm or dissection, stroke) as patients with Turner syndrome are also at increased risk for these conditions.

5.13 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 abdominal pain.

5.14 Lipostrophy
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 (2.2)].

5.15 Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone and IGF-I may increase after somatropin therapy.

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)]
- Pancreatitis [see Warnings and Precautions (5.13)]
- Lipostrophy [see Warnings and Precautions (5.14)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under varying 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.

Pediatric Patients
GH Deficiency
As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. During the first 6 months of Humatrope therapy in 314 naive patients, only 1.6% developed specific antibodies to Humatrope (binding capacity ≥0.02 mg/L). None had antibody concentrations which exceeded 2 mg/L. Throughout 8 years of this same study, two patients (0.6%) had binding capacity ≥2 mg/L. Neither patient demonstrated a decrease in growth velocity at or near the time of increased antibody production. It has been reported that growth attenuation from pituitary-derived GH may occur when antibody concentrations are >1.5 mg/L.

In addition to an evaluation of compliance with the treatment program and of thyroid status, testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy. In studies with GH deficient pediatric patients, injection site pain was reported infrequently. A mild and transient edema, which appeared in 2.5% of patients, was observed early during the course of treatment.

5.16 Neoplasms
In children with certain rare genetic causes of short stature there is 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.

5.17 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. Symptoms usually occurred within the first 8 weeks after the initiation of somatropin treatment. 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, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopic examination during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome may be at increased risk for the development of IH.

5.18 Severe Hypersensitivity
Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing 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)].

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

5.20 Hypoadrenalism
Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In patients with GH deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment.

5.21 Lipostrophy
Lipoatrophy is a rare, usually transient condition that may occur in 2% of patients treated with somatropin. Lipoatrophy may occur at multiple sites. In the head and neck region, lipoatrophy may manifest as nares, cheeks, chin, and temples. Lipoatrophy may occur in patients with Turner syndrome on the upper extremities and in the lower back. In patients treated with somatropin, lipoatrophy may result in a decrease in breast size in girls and a decrease in testicular volume in boys.

5.22 Slipped Capital Femoral Epiphysis in Pediatric Patients
Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric GH deficiency 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.

Table 1: Treatment-Emergent Adverse Reactions of Special Interest by Treatment Group in Turner Syndrome

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Treatment Group</th>
<th>Number of Patients</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipostrophy</td>
<td>Unintreated</td>
<td>62</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Humatropeb</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Total Number of Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>17 (27.4%)</td>
<td>33 (44.6%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Otitis media</td>
<td>16 (25.8%)</td>
<td>32 (43.2%)</td>
<td></td>
</tr>
<tr>
<td>Ear disorders</td>
<td>3 (4.8%)</td>
<td>13 (17.6%)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

a Open-label study.

b Dose=0.3 mg/kg/wk.
In a randomized, placebo-controlled study of Humatrope treatment (0.22 mg/kg/week) to adult height in patients with idiopathic short stature, the adverse events reported in Humatrope-treated patients (Table 2) were similar to those observed in other pediatric populations treated with Humatrope. Mean serum glucose concentration did not change during Humatrope treatment. Mean fasting serum insulin concentration increased 10% in the Humatrope treatment group at the end of treatment relative to baseline, but remained within the normal reference range. For the same duration of treatment, the mean fasting serum insulin concentration decreased by 2% in the placebo group. The occurrence rates of above-average values for glucose, insulin, and HbA₁c were similar in the Humatrope (somatropin)- and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the known mechanism of growth hormone action, Humatrope-treated patients had greater mean increases, relative to baseline, in serum insulin-like growth factor-I (IGF-I) than placebo-treated patients at each study observation. However, there was no significant difference between the Humatrope and placebo treatment groups in the proportion of patients who had at least one serum IGF-I concentration more than 2.0 SD above the age- and gender-appropriate mean (Humatrope: 9 of 35 patients [26%]; placebo: 7 of 28 patients [25%]).

### Table 2: Non-serious Clinically Significant Treatment-Emergent Adverse Reactions by Treatment Group in Idiopathic Short Stature

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>Humatrope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>4 (12.9%)</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>2 (6.5%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1 (3.2%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>1 (3.2%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Hip pain</td>
<td>0</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (3.2%)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>Arthrosis</td>
<td>2 (6.5%)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (12.9%)</td>
<td>9 (24.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1 (2.7%)</td>
</tr>
</tbody>
</table>

The adverse events observed in the dose-response study (239 patients treated for 2 years) did not indicate a pattern suggestive of a somatropin dose effect. Among Humatrope dose groups, mean fasting serum insulin concentration increased 10% in the Humatrope treatment group at the end of treatment relative to baseline, but remained within the normal reference range. For the same duration of treatment, the mean fasting serum insulin concentration decreased by 2% in the placebo group. The occurrence rates of above-average values for glucose, insulin, and HbA₁c, were similar in the Humatrope (somatropin)- and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the known mechanism of growth hormone action, Humatrope-treated patients had greater mean increases, relative to baseline, in serum insulin-like growth factor-I (IGF-I) than placebo-treated patients at each study observation. However, there was no significant difference between the Humatrope and placebo treatment groups in the proportion of patients who had at least one serum IGF-I concentration more than 2.0 SD above the age- and gender-appropriate mean (Humatrope: 9 of 35 patients [26%]; placebo: 7 of 28 patients [25%]).

### Table 3: Clinically Significant Treatment-Emergent Adverse Reactions by Treatment Group in Patients with SHOX Deficiency

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients</td>
<td>Placebo</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>25</td>
</tr>
<tr>
<td>Patients with at least one event</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (8.0%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Excessive number of cutaneous nevi</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

All events were non-serious.

### Table 4: Treatment-Emergent Adverse Reactions with ≥5% Overall Occurrence in Adult-Onset Growth Hormone-Deficient Patients Treated with Humatrope for 18 Months as Compared with 6-Month Placebo and 12-Month Humatrope Exposure

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>18 Months Exposure</th>
<th>18 Months GH Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (6 Months)</td>
<td>[GH (12 Months)]</td>
<td>(N=46)</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Edema</td>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Pain</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Back pain</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joint disorder</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>3</td>
<td>6.5</td>
</tr>
</tbody>
</table>

**Abbreviations: GH = Humatrope; N = number of patients receiving treatment in the period stated; n = number of patients reporting each treatment-emergent adverse event.**

p = 0.04 as compared to placebo (6 months).

### Clinical Studies

**SHOX Deficiency**

Clinically significant adverse events (adverse events previously observed in association with growth hormone treatment in general) were assessed prospectively during the 2-year randomized, open-label study; those observed are presented in Table 3. In both treatment groups, the mean fasting plasma glucose concentration at the end of the first year was similar to the baseline value and remained in the normal range. No patient developed diabetes mellitus or had an above-normal value for fasting plasma glucose at the end of one-year of treatment. During the 2-year study period, the proportion of patients who had at least one IGF-I concentration greater than 2.0 SD above the age- and gender-appropriate mean was 10 of 27 (37.0%) for the Humatrope-treated group vs. 0 of 24 patients (0%) for the untreated group. The proportion of patients who had at least one IGF-BP-3 concentration greater than 2.0 SD above the age and gender appropriate mean was 16 of 27 (59.3%) for the Humatrope treated group vs. 7 of 24 (29.2%) for the untreated group.

**Small for Gestational Age**

**Study 1** — In a 2-year, multicenter, randomized study, 193 non-GH deficient children with short stature born SGA who failed to demonstrate catch-up growth were treated with 2 different Humatrope treatment regimens: a fixed dose of 0.067 mg/kg/day (FHD group) or an individually adjusted dose regimen (IAD group; starting dose 0.035 mg/kg/day which could be increased as early as Month 3 to 0.067 mg/kg/day based on a validated growth prediction model). The most frequently reported adverse events were common childhood infectious diseases. Adverse events possibly/probably related to treatment with Humatrope were reported in either short-term study or were apparent after a review of the post-marketing, observational, safety database.

### Adverse Events

**Adult Patients**

In clinical studies in which high doses of Humatrope were administered to healthy adult volunteers, the following events occurred infrequently: headache, localized muscle pain, weakness, mild hyperglycemia, and glucosuria.

**Adult-Onset GH Deficiency**

In the first 6 months of controlled blinded trials during which patients received either Humatrope or placebo, adult-onset GH deficient adults who received Humatrope experienced a statistically significant increase in edema (Humatrope 17.3% vs. placebo 4.4%, p = 0.043) and peripheral edema (11.5% vs. 5%, respectively, p = 0.017). In patients with adult-onset GH deficiency, edema, muscle pain, joint pain, and joint disorder were reported early in therapy and tended to be transient or resolving by dosage titration. Two of 113 adult-onset patients developed carpal tunnel syndrome after beginning maintenance therapy with a low dose (0.00625 mg/kg/day) lead-in phase. Symptoms abated in these patients after dosage reduction.

All treatment-emergent adverse events with ≥5% overall occurrence rate during 12 or 18 months of replacement therapy with Humatrope are shown in Table 4 (adult-onset patients) and in Table 5 (childhood-onset patients).

Adult patients treated with Humatrope who had been diagnosed with GH deficiency in childhood reported side effects less frequently than those with adult-onset GH deficiency.

**Table 3: Clinically Significant Treatment-Emergent Adverse Reactions by Treatment Group in Patients with SHOX Deficiency**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>Humatrope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Patients with at least one event</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (8.0%)</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>0 (0.0%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>0 (0.0%)</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

**Table 4: Treatment-Emergent Adverse Reactions with ≥5% Overall Occurrence in Adult-Onset Growth Hormone-Deficient Patients Treated with Humatrope for 18 Months as Compared with 6-Month Placebo and 12-Month Humatrope Exposure**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (6 Months)</th>
<th>GH (12 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Edema</td>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Pain</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Back pain</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>10.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joint disorder</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>3</td>
<td>6.5</td>
</tr>
</tbody>
</table>

**Abbreviations:** GH = Humatrope; N = number of patients receiving treatment in the period stated; n = number of patients reporting each treatment-emergent adverse event.
transference were reported significantly more often for Humatrope-treated (12.5%) than placebo-treated patients (0.0%, p<0.031). No other events were reported significantly more often for Humatrope-treated patients during the placebo-controlled phase. The following events were reported for at least 5% of patients in either of the 2 treatment groups over the 18-month duration of the study, listed in descending order of maximum frequency for either group: aspartate aminotransferase increased 13%, headache 11%, edema 9%, pain 9%, alanine aminotransferase increased 6%, asthenia 6%, myalgia 6%, respiratory disorder 6%.

### Table 5: Treatment-Emergent Adverse Reactions with ≥5% Overall Occurrence in Childhood-Onset Growth Hormone-Deficient Patients Treated with Humatrope for 18 Months as Compared with 6-Month Placebo and 12-Month Humatrope Exposure

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>18 Months Exposure [Placebo (6 Months)/GH (12 Months)] (N=35)</th>
<th>18 Months GH Exposure (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>8</td>
<td>22.9</td>
</tr>
<tr>
<td>AST increaseda</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>11.4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Cough increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>Rhiinities</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Gastritis</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5</td>
<td>14.3</td>
</tr>
</tbody>
</table>

* Abbreviations: GH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of patients reporting each treatment-emergent adverse event; ALT=alanine aminotransferase, formerly SGPT; AST=aspartate aminotransferase, formerly SGOT.

### 6.2 Post-Marketing Experience

Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in Sections 6 and 6.1 in children and adults.

Other adverse events that have been reported in somatropin-treated patients include the following:

**Severe Hypersensitivity Reactions** — Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products [see Warnings and Precautions (6.6)].

**Neurologic** — Headaches (common in children and occasional in adults).

**Skin** — In size or number of cutaneous nevi, especially in patients with Turner syndrome and those with SHOX deficiency [see Warnings and Precautions (5.3)].

**Endocrine** — Gynecomastia.

**Gastrointestinal** — 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 abdominal pain [see Warnings and Precautions (5.13)].

**Metabolic** — New-onset type 2 diabetes mellitus in patients.

**Neoplasia** — Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatostatin (methionylated rGH), and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathalogy of GH deficiency itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy per se was responsible for these cases of leukemia. The risk for children with GH deficiency, if any, remains to be established [see Contraindications (4) and Warnings and Precautions (5.3)].

In an ongoing post-marketing observational study of somatropin treatment in 3,102 GH-deficient adults, hypertension, dyspepsia, and sleep apnea were reported by 1% to less than 10% of patients after various durations of treatment.

### 7 DRUG INTERACTIONS

#### 7.1 11β-Hydroxysteroid Dehydrogenase Type 1

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. GH and glucocorticoid replacement for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and glucocorticoid replacement increases in 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 conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and glucocorticoid replacement may alter the clearance of compounds metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Therefore, careful monitoring is advised when somatropin is administered in combination with drugs metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

### 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 (CP450)-mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Therefore, careful monitoring is advised when somatropin is administered in combination with drugs metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

### 7.4 Oral Estrogen

Because oral estrogens may reduce the serum IGF-I response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages [see Dosage and Administration (2.4)].

### 7.5 Insulin and/or Other Hypoglycemic Agents

Patients with diabetes mellitus who receive concomitant treatment with somatropin may require adjustment of their doses of insulin and/or other hypoglycemic agents [see Warnings and Precautions (5.4)].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Pregnancy Category C** — Animal reproduction studies have not been conducted with Humatrope. It is not known whether Humatrope can cause fetal harm when administered to a pregnant woman or can affect reproducive capacity. Humatrope should be given to a pregnant woman only if clearly needed.

#### 8.3 Nursing Mothers

There have been no studies conducted with Humatrope in nursing mothers. It is not known whether this drug is excreted in human milk. Therefore, many drugs are excreted in human milk, caution should be exercised when Humatrope is administered to a nursing woman.

#### 8.5 Geriatric Use

The safety and effectiveness of Humatrope in patients aged 65 years and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to development of adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients [see Dosage and Administration (2.4)].

#### 9 DRUG ABUSE AND DEPENDENCE

Inappropriate use of somatropin by individuals who do not have indications for which somatropin is approved, may result in significant negative health consequences. Somatropin is not a drug of dependence.

#### 10 OVERDOSAGE

**Short-term** — Acute overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia.

**Long-term** — Long-term overdosage could result in signs and symptoms of gigantism or acromegaly consistent with the known effects of excess endogenous human GH.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

GH binds to dimeric GH receptors located within the cell membranes of target tissue cells. This interaction results in intracellular signal transduction and subsequent induction of transcription and translation of GH-dependent proteins including IGF-1, IGF-BP-3 and acid-labile subunit. GH has direct effects as a growth-promoting agent and may also influence the activity of 11βHSD-1 [see Warnings and Precautions (5.8)].

HUMATROPE® [somatropin (rDNA ORIGIN)] for injection, for subcutaneous use

HTR-0003-USPI-20161213
tissue and metabolic effects, including stimulation of chondrocyte differentiation, stimulation of lipolysis and stimulation of hepatic glucose output. In addition, some effects of somatropin are mediated indirectly by IGF-I, including stimulation of protein synthesis and chondrocyte proliferation.

12.2 Pharmacodynamics

In vitro, preclinical, and clinical testing have demonstrated that Humatrope is therapeutically equivalent to human GH of pituitary origin and achieves equivalent pharmacokinetic profiles in healthy adults. The following effects have been reported for human GH of pituitary origin, and/or somatropin.

Cell Growth — Total numbers of muscle cells are reduced in GH deficient children. Somatropin increases the number and size of muscle cells in such children.

Skeletal Growth — Somatropin stimulates skeletal growth in children with GH deficiency as a result of effects on the growth plates (epiphyses) of long bones. Concentrations of IGF-I, which play a role in skeletal growth, are low in the serum of GH deficient children but increase during somatropin treatment in most patients. The stimulation of skeletal growth increases linear growth rate (height velocity) in most somatropin-treated children.

Protein Metabolism — Linear growth is facilitated in part by increased cellular protein synthesis as reflected by nitrogen retention, which can be demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen.

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

Carbohydrate Metabolism — GH has a physiological role in the maintenance of normoglycemia during times of substrate restriction (e.g., fasting), via mechanisms such as stimulation of hepatic gluconeogenesis and suppression of insulin-stimulated glucose uptake by peripheral tissues. Because of these actions GH is considered an insulin antagonist with respect to carbohydrate metabolism. Consequently, the fasting hypoglycemia that may occur in some children with hypopituitarism may be improved by somatropin treatment. As an extension of its physiological actions, supraphysiological GH concentrations may increase glucose production sufficiently to stimulate insulin secretion to maintain normoglycemia. Large doses of somatropin may impair glucose tolerance if compensatory insulin secretion is inadequate. Administration of somatropin to healthy adults and patients with Turner syndrome resulted in increases in mean serum fasting and postprandial insulin concentrations, although mean values remained in the normal range. In addition, mean HbA1c concentrations and mean fasting and postprandial glucose concentrations remained 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 GH deficiency is associated with increased body fat stores, including increased abdominal visceral and subcutaneous adipose tissue. Treatment of GH deficient patients with somatropin results in a general reduction of fat stores, and decreased serum concentrations 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, probably as the result of cell growth. Serum concentrations of inorganic phosphate increase in somatropin-treated GH deficient children because of the metabolic activities associated with bone growth. Although urinary calcium excretion is increased, there is a simultaneous increase in calcium absorption from the intestine. Consequently, serum calcium concentrations generally are not altered, although negative calcium balance may occur occasionally during somatropin treatment. Associated with the changes in mineral metabolism, parathyroid hormone may increase during somatropin treatment.

12.3 Pharmacokinetics

Absorption — Humatrope has been studied following intramuscular, subcutaneous, and intravenous administration in adult volunteers (see Figure 1). The absolute bioavailability of somatropin is 75% and 63% after subcutaneous and intramuscular administration, respectively.

Distribution — The volume of distribution of somatropin after intravenous injection is about 0.07 L/kg (Table B). Metabolism — Extensive metabolism studies have not been conducted. The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products of somatropin is returned to the systemic circulation. In healthy volunteers, mean somatropin clearance is 0.14 L/hr/kg. The mean half-life of intravenous somatropin is 0.36 hours, whereas subcutaneously and intramuscularly administered somatropin have mean half-lives of 3.8 and 4.9 hours, respectively. The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site.

Excretion — Urinary excretion of intact Humatrope has not been measured. Small amounts of somatropin have been detected in the urine of pediatric patients following replacement therapy.

Geriatric patients — The pharmacokinetics of Humatrope have not been studied in patients greater than 65 years of age.

Pediatric patients — The pharmacokinetics of Humatrope in pediatric patients are similar to those of adults.

Gender — No gender-specific pharmacokinetic studies have been performed with Humatrope. The available literature indicates that the pharmacokinetics of somatropin are similar in men and women.

Renal, hepatic insufficiency — No studies have been performed with Humatrope.

### Table 6: Summary of Somatropin Parameters in Healthy Adult Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (6 Months)</th>
<th>Humatrope Therapy (6 Months)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>415.7 (75)</td>
<td>532.5 (25.9)</td>
<td>0.14 mg (0.27 IUb)/kg sc Mean (SD)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>0.363 (0.053)</td>
<td>4.93 (2.66)</td>
<td>0.179 (0.028)</td>
</tr>
<tr>
<td>AUCmax (ng*hr/mL)</td>
<td>156 (33)</td>
<td>495 (106)</td>
<td>0.957 (0.301)</td>
</tr>
<tr>
<td>Cis (L/kg*hr)</td>
<td>0.135 (0.029)</td>
<td>0.215 (0.047)</td>
<td>0.55 (0.91)</td>
</tr>
<tr>
<td>VIβ (L/kg)</td>
<td>0.0703 (0.0173)</td>
<td>1.55 (0.91)</td>
<td>0.10 mg (0.27 IUb)/kg, iv Mean (SD)</td>
</tr>
</tbody>
</table>

### Table 7: Changes in Nottingham Health Profile Scores in Adult-Onset Growth Hormone-Deficient Patients

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo</th>
<th>Humatrope Therapy</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical mobility</td>
<td>-3.1</td>
<td>-10.5</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Social isolation</td>
<td>0.5</td>
<td>-4.7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Emotional reactions</td>
<td>-4.5</td>
<td>-5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep</td>
<td>-6.4</td>
<td>-3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Pain</td>
<td>-2.8</td>
<td>-2.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table A: Summary of Somatropin Parameters in Elderly Patients

<table>
<thead>
<tr>
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### Table B: Summary of Somatropin Parameters in Healthy Adult Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (6 Months)</th>
<th>Humatrope Therapy (6 Months)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

### Table C: Summary of Somatropin Parameters in Elderly Patients

<table>
<thead>
<tr>
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<th>Humatrope Therapy (6 Months)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.179 (0.028)</td>
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<tr>
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<tr>
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<td>1.55 (0.91)</td>
<td>0.10 mg (0.27 IUb)/kg, iv Mean (SD)</td>
</tr>
</tbody>
</table>
Two studies evaluating the effect of Humatrope on bone mineralization were conducted subsequently. In a 2-year, randomized, double-blind, placebo-controlled trial, 67 patients with previously untreated adult-onset GH deficiency received placebo or Humatrope injections titrated to maintain serum IGF-I within the age-adjusted normal range. In one, but not the other, lumbar spine bone mineral density (BMD) increased with Humatrope treatment compared to placebo, with a treatment difference of approximately 4% (p=0.001). There was no significant change in hip BMD with Humatrope treatment in men or women, when compared to placebo.

In a 2-year, open-label, randomized trial, 149 patients with childhood-onset GH deficiency who had completed somatropin therapy, had attained final height (height velocity <1 cm/yr) and were confirmed to be GH-deficient as young adults (commonly referred to as transition patients), were randomized to receive Humatrope 0.0125 mg/kg/day (12.5 µg/kg/day), Humatrope 0.025 mg/kg/day (25 µg/kg/day), or no injections (control). Patients who were randomized to treatment with Humatrope at 12.5 µg/kg/day achieved a 2.9% greater increase from baseline than control patients in total body bone mineral content (BCM) (8.1 ± 3.9% vs. 5.2 ± 8.2%, p=0.02), whereas patients treated with Humatrope at 25 µg/kg/day had no significant change in BCM. These results include data from patients who received less than 2 years of treatment. A greater treatment effect was observed for patients who completed 2 years of treatment. Increases in lumbar spine BMD and BCM were also statistically significant compared to control with the 12.5 µg/kg/day dose but not the 25 µg/kg/day dose. Hip BMD and BCM did not change significantly compared to control with either dose. The effect of GH treatment on BMC and BCM in transition patients at doses lower than 12.5 µg/kg/day was not studied. The effect of Humatrope on the occurrence of osteoporotic fractures has not been studied.

14.2 Pediatric Patients with Turner Syndrome

One long-term, randomized, open-label, Canadian multicenter, concurrently controlled study, two long-term, open-label multicenter, historically controlled US studies and one long-term, randomized, US dose-response study were conducted to evaluate the efficacy of somatropin treatment of short stature due to Turner syndrome.

The Canadian randomized study compared near-adult height outcomes for Humatrope-treated patients to those of a concurrent control group who received no injections. The Humatrope-treated patients received a dosage of 0.3 mg/kg/week from a mean age of 11.7 years for a mean duration of 4.7 years. Puberty was induced with a standardized estrogen regimen initiated at 13 years of age for both treatment groups. The Humatrope-treated group (n=27) attained a mean (± SD) near-final height of 146.0 ± 6.2 cm; the untreated control group (n=19) attained a near-final height of 142.1 ± 4.8 cm. By analysis of covariance (with adjustments for baseline height and mid-parental height), the effect of somatropin treatment was a mean height increase of 5.4 cm (p=0.001).

In two of the US studies, the effect of long-term somatropin treatment (0.375 mg/kg/week given in divided doses every 3 or 6 times per week) on mean gain in adult height was determined by comparing adult heights in the treated patients with those of age-matched historical controls with Turner syndrome who received no growth-promoting therapy. Puberty was induced with a standardized estrogen regimen initiated after 14 years of age in one study; in the second study patients treated with early somatropin (before 11 years of age) were randomized to begin pubertal induction at either age 12 (n=26) or 15 (n=29) years (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily); those whose somatropin was initiated after 11 years of age began estrogen replacement after 1 year of somatropin. Mean height gains from baseline to adult (or near-adult) height ranged from 5.0 to 8.3 cm, depending on age at initiation of somatropin treatment and estrogen replacement (Table 8).

In the third US study, a randomized, blinded dose-response study, patients were treated from a mean age of 11.1 years for a mean duration of 5.3 years with a Humatrope weekly dosage of either 0.27 mg/kg or 0.36 mg/kg administered in divided doses 3 or 6 times weekly. The mean near-final height of Humatrope-treated patients was 148.7 ± 6.5 cm (n=31). When compared to historical control data, the mean gain in adult height was approximately 5 cm.

In summary, patients with Turner syndrome (total n=181 from the 4 studies above) treated to adult height attained a mean gain in adult height was approximately 5 cm. Patients who received the Humatrope dosage of 0.37 mg/kg/kg had a significantly greater increase in mean height velocity during the first 2 years of therapy in a dose-dependent manner. Additionally, after completing the initial 2-year-dose-response phase of the study, 50% of patients were followed to final height.

The dose-response study included 239 pediatric patients (158 males, 81 females), 5 to 15 years old, (mean age 9.8 ± 2.3 years). Mean ± SD baseline characteristics included: height SDS -3.21 ± 0.70, predicted adult height SDS -2.63 ± 1.08, and height velocity SDS -1.09 ± 1.15. All but 3 patients were prepubertal. Patients were randomized to one of three Humatrope treatment groups: 0.24 mg/kg/week (equivalent to 34 µg/kg/day); 0.24/0.37 mg/kg/week for year 1, followed by 0.37 mg/kg/week (equivalent to 53 µg/kg/day); and 0.37 mg/kg/week. The primary hypothesis of this study was that treatment with Humatrope would increase height velocity during the first 2 years of therapy in a dose-dependent manner. Additionally, after completing the initial 2-year-dose-response phase of the study, 50% of patients were followed to final height.

Patients who received the Humatrope dosage of 0.37 mg/kg/kg had a significantly greater increase in mean height velocity after 2 years of treatment than patients who received 0.24 mg/kg/week (4.04 ± 2.27 cm/year, p=0.003). The mean difference between height and baseline predicted height was 7.2 cm for patients who received Humatrope 0.37 mg/kg/week and 5.4 cm for patients who received 0.24 mg/kg/week (Table 10). While no patient had height above the 95th percentile in any dosage group at baseline, 82% of the patients who received 0.37 mg/kg/week and 47% of the patients who received 0.24 mg/kg/week achieved final heights above the 5th percentile of the general population height standards (p<NS).

In summary, patients with Turner syndrome had significantly greater first- and second-year height gain than untreated patients (8.7 cm/year vs. 5.2 cm/year, p<0.001, primary efficacy analysis) and similar first-year height velocity to Humatrope-treated patients with Turner syndrome (8.7 cm/year vs. 8.9 cm/year). In addition, patients who received Humatrope had significantly greater second year height velocity, and first- and second-year height gain (cm and SDS) than untreated patients (Table 11).

Table 9: Baseline Height Characteristics and Effect of Humatrope on Final Height in Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Humatrope</th>
<th>Treatment Effect Mean (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height SDS</td>
<td>-2.75 (0.6)</td>
<td>-2.7 (0.6)</td>
<td>NA 0.77</td>
</tr>
<tr>
<td>BPH SDS</td>
<td>-2.3 (0.8)</td>
<td>-2.1 (0.7)</td>
<td>NA 0.53</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>-2.3 (0.6)</td>
<td>-1.8 (0.8)</td>
<td>0.51 (0.10; 0.92) 0.017</td>
</tr>
<tr>
<td>FH SDS - baseline height SDS</td>
<td>0.4 (0.2)</td>
<td>0.9 (0.7)</td>
<td>0.51 (0.04; 0.97) 0.034</td>
</tr>
<tr>
<td>FH SDS - BPH SDS</td>
<td>-0.1 (0.6)</td>
<td>0.3 (0.6)</td>
<td>0.46 (0.02; 0.89) 0.493</td>
</tr>
</tbody>
</table>

Table 10: Idiopathic Short Stature Trials: Final Height Minus Baseline Predicted Height

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Humatrope 0.22 mg/kg/week (n=22)</th>
<th>Humatrope 0.24 mg/kg/week (n=13)</th>
<th>Humatrope 0.24/0.37 mg/kg/week (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH - Baseline PH Mean (95% CI), cm</td>
<td>-0.7 (-3.6, 2.3)</td>
<td>+2.2 (0.4, 3.9)</td>
<td>+5.4 (2.8, 7.9)</td>
<td>+6.7 (4.1; 9.2) +7.2 (4.6; 9.8)</td>
</tr>
</tbody>
</table>

Abbreviations: FH = final height; PH = predicted height; CI = confidence interval; cm = centimeters.

14.4 Pediatric Patients with SHOX Deficiency

SHOX deficiency may result from a deletion of one copy of the short stature homeobox-containing (SHOX) gene or from a mutation within or outside one copy of the SHOX gene that impairs the production or function of SHOX protein.

In this two-year, three-arm, open-label, randomized trial, two-year, randomized, placebo-controlled trial, three-arm, open-label study was conducted to evaluate the efficacy of Humatrope treatment of short stature in pediatric patients with SHOX deficiency who were not GH–deficient. 52 patients (24 male, 28 female) with SHOX deficiency, 3.0 to 12.3 years of age, were randomized to either a Humatrope-treated arm (27 patients; mean age 7.3 ± 2.1 years) or an untreated control arm (25 patients; mean age 7.5 ± 2.7 years). To determine the comparability of treatment effect between patients with SHOX deficiency and patients with Turner syndrome, the third study arm enrolled 26 patients with Turner syndrome, 4.5 to 11.8 years of age (mean age 7.5 ± 1.8 years), to Humatrope treatment. All patients in the Humatrope-treated group (27 patients) received daily subcutaneous injections of 0.05 mg/kg (50 µg/kg) of Humatrope, equivalent to 0.35 mg/kg/day. Patients in the untreated group received no injections.

Patients with SHOX deficiency who received Humatrope had significantly greater first-year height velocity than untreated patients (8.7 cm/year vs. 5.2 cm/year, p<0.001, primary efficacy analysis) and similar first-year height velocity to Humatrope-treated patients with Turner syndrome (8.7 cm/year vs. 8.9 cm/year). In addition, patients who received Humatrope had significantly greater second year height velocity, and first- and second-year height gain (cm and SDS) than untreated patients (Table 11).

HUMATROPE® [somatropin (rDNA ORIGIN)]

for injection, for subcutaneous use

HTR-0003-USPI-20161213

1 Abbreviations: BFS = baseline height SDS; FH = final height SDS; CI = confidence interval; cm = centimeters.

2 Abbreviations: BFS = baseline height SDS; FH = final height SDS; CI = confidence interval; cm = centimeters.

3 Abbreviations: BFS = baseline height SDS; FH = final height SDS; CI = confidence interval; cm = centimeters.
14.5 Pediatric Patients Born Small for Gestational Age (SGA) Who Fail to Demonstrate Catch-up Growth by Age 2 - 4 Years

Data from 2 clinical trials demonstrate the effectiveness of Humatrope in promoting linear growth in short children born SGA who fail to demonstrate catch-up growth.

The primary objective of Study 1 was to demonstrate that the increase from baseline in height SDS after 1 year of treatment would be similar when Humatrope is administered according to an individually adjusted dose (IAD) regimen or a fixed high dose (FHD) regimen. The height increases would be considered similar if the lower bound of the 95% confidence interval (CI) for the mean difference between the groups (IAD – FHD) was greater than -0.5 height SDS. This 2-year, open-label, multicenter, European study enrolled 193 prepubertal, non-GH deficient children with mean chronological age 6.8 ± 2.4 years (range: 3 to 12.3). Additional study entry criteria included birth length SDS <-2 or <3rd percentile for gestational age, and height SDS for chronological age 6.8 ± 2.4 years (range: 3 to 12.3). Additional study entry criteria included birth length SDS <-2 or <3rd percentile for gestational age, and height SDS for chronological age 6.8 ± 2.4 years (range: 3 to 12.3). Additional study entry criteria included birth length SDS <-2 or <3rd percentile for gestational age, and height SDS for chronological age 6.8 ± 2.4 years (range: 3 to 12.3).

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Study 2 was an open-label, multicenter, single arm study conducted in France, during which 35 prepubertal, non-GH deficient children were treated for 2 years with Humatrope 0.067 mg/kg/day (0.47 mg/kg/week). Mean chronological age at baseline was 9.3 ± 0.9 years (range: 6.7 to 10.8). Additional study entry criteria included birth length SDS <-2 or <3rd percentile for gestational age, and height SDS for chronological age <-2. Exclusion criteria included syndromal conditions (e.g., Turner syndrome), chronic disease (e.g., diabetes mellitus), and any active disease. All 35 patients completed the study. Mean height SDS increased from a baseline value of -2.7 (SD 0.5) to -1.5 (SD 0.6) after 2 years of Humatrope treatment.
HUMATROPE CARTRIDGES ARE ONLY TO BE USED WITH HUMATROPEN® OR HUMATROPEN® 3 INJECTION DEVICES.

Important Things to Know
It is important to learn the names of the parts of the Humatrope Cartridge Kit and how these parts work before injecting yourself or your child. Make sure you have been properly trained by your nurse, pharmacist or doctor before you mix the drug (add the diluent liquid to the dry Humatrope powder) or inject it. Wash your hands and be careful to follow the instructions given to you by your nurse, pharmacist or doctor. After mixing, throw away the diluent syringe in a puncture-resistant container such as the type your nurse, pharmacist or doctor has told you to use.

Storage
Humatrope must be kept refrigerated (36° to 46°F [2° to 8°C]) before and after it is mixed. Do not freeze. Once Humatrope has been mixed and is in liquid form, it must be used within 28 days. Throw away any mixed Humatrope left over after 28 days. Before giving an injection, check the date on the cartridge. Do not use the cartridge if it has expired.

WARNING
HUMATROPE CARTRIDGES SHOULD NOT BE USED IF THE PATIENT IS ALLERGIC TO METACRESOL OR GLYCERIN.

Contents
• one cartridge with 6, 12, or 24 mg of dried Humatrope
• one prefilled syringe with diluent (the liquid used to mix the dried Humatrope)

NOTE: There are three kinds of Humatrope cartridges that have different amounts of Humatrope (6, 12, or 24 mg). Make sure that you have the cartridge that your doctor prescribed.

Mixing the Humatrope in the Cartridge
Use only the prefilled diluent syringe to mix the Humatrope in the cartridge. DO NOT use the diluent that comes in the Humatrope vial box, or any other liquid.

Preparing Your New Cartridge

1a
Remove ALL contents from the tray.
Note: This product is designed for left or right handed use so you may use whichever hand is most comfortable for you.

1b
Grasp the gray Needle Cover, at the bottom of the Diluent Syringe.

1c
Remove the Needle Cover and discard. DO NOT depress the Plunger yet. It is okay if a drop of fluid is lost. It is not necessary to release air from the Diluent Syringe.

2
Hold the cartridge, with the Black Triangles toward the Diluent Syringe. Align the cartridge and Diluent Syringe in a straight line. DO NOT insert the cartridge at an angle.

*Note: The liquid is colorless. It is shown here as blue for illustration purposes only.
Inspect the solution. The Humatrope solution should be clear. If the solution is clear, your cartridge is now prepared and ready to be attached to your pen injection device (see the User Manual for your pen injection device).

If the solution is cloudy or contains particles, gently invert the cartridge 10 additional times. Let the cartridge sit for 5 more minutes. If the solution remains cloudy or contains particles, DO NOT USE THE CARTRIDGE.

Contact your healthcare professional or Lilly.

If you have questions about preparing your Humatrope cartridge, you should contact your Humatrope provider or your healthcare professional.

Injections can be given in the following areas:
- Abdomen (above, below, or either side of the navel)
- Front of the upper thighs
- Upper, outer buttocks
- Back of the arms above the elbow and below the shoulder

Discuss use of the pen injection device, the right places to inject, and site rotation with your nurse or doctor.
INFORMATION FOR THE PATIENT

Always start by washing your hands.

1. Remove and discard plastic caps from tops of vials of diluent and Humatrope. Wipe tops of both vials with an alcohol swab (Figure 1). Remove needle cover and save. Pull back on syringe plunger to draw up an amount of air equal to the amount of diluent your doctor has prescribed. Insert needle in stopper of diluent vial, and inject air into vial.

2. Hold vial upside down and, making sure needle tip remains in solution, withdraw the amount of diluent your doctor has prescribed (Figure 2). After making sure that no air bubbles are in the syringe, turn vial upright and, holding barrel, remove syringe.

3. Insert same needle into vial of Humatrope and gently aim needle tip toward wall of vial. Slowly inject the diluent by aiming the stream of liquid against the wall of vial (Figure 3). Do not aim it at the white powder at the bottom of the vial. To equalize the pressure, withdraw a volume of air equal to the amount of diluent added before removing the syringe from the vial. If the needle can be removed from the barrel of the syringe, remove, destroy, and discard the needle. If the needle and syringe are made as 1 unit, another unit should be used for the injection.

4. Swirl the vial with a gentle rotary motion until contents are completely dissolved (Figure 4). Do not shake.

5. Insert needle into vial of reconstituted Humatrope and inject the air into the vial. Turn the vial upside down, and, making sure needle tip is in solution, withdraw your correct dose (see Figure 2). Make sure that no air bubbles are in the syringe.

6. Remove syringe and replace needle cover. Write date of reconstitution on vial label, and discard unused diluent.

7. Return unused portion of reconstituted Humatrope to refrigerator and use within 14 days.

8. Destroy needle or the needle and syringe after use.

Preparing the Injection

1. Do not use reconstituted Humatrope if it is cloudy or contains particles.
2. If the needle can be removed from the type of syringe you are using, a new needle should be placed on the syringe before the injection. If the syringe and needle are made as 1 unit, another unit should be used for the injection.
3. Before and after injection, the rubber stopper of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions.
4. Remove the needle cover and draw an amount of air into the syringe equal to your dose of Humatrope.
5. Insert needle into vial of reconstituted Humatrope and inject the air into the vial. Turn the vial upside down, and, making sure needle tip is in solution, withdraw your correct dose (see Figure 2). Make sure that no air bubbles are in the syringe.
6. Remove syringe and replace needle cover. Write date of reconstitution on vial label, and discard unused diluent.
7. Return unused portion of reconstituted Humatrope to refrigerator and use within 14 days.
8. Destroy needle or the needle and syringe after use.

Intramuscular Injection:

With the thumb and first 2 fingers, press the skin down firmly against a large muscle mass, such as the thigh.

• Holding the syringe at a 90-degree angle to injection site, quickly insert the needle all the way into the skin.
• Slowly inject the solution.
• Remove the needle quickly, and apply pressure over the injection site with a dry gauze pad or cotton ball. Rub for several seconds.
• Destroy needle or needle and syringe after use.

If you have any questions, consult your doctor.

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