# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-538**

# LABELING

# Accretropin™ (somatropin) Injection

**[Cangene Corporation]**

## DESCRIPTION

Accretropin™ (recombinant human growth hormone (r-hGH); somatropin) is a protein produced by recombinant DNA technology. It is produced during fermentation in *E. coli* yielding a protein containing 192 amino acids. The N-terminal amino acid, methionine, is later removed to yield a protein that is chemically and physicochemically identical to pituitary derived human growth hormone, consisting of 191 amino acids in a single polypeptide chain.

Accretropin™ is distributed in a liquid solution containing 1 mL of a 5 mg/mL solution of growth hormone (15 IU/mL). The formulation also contains 0.75% NaCl, 0.34% Phenol (as preservative), 0.2% Pluronic F-68 (a non-ionic surfactant) and is designed for subcutaneous administration. Accretropin™ is stabilized to pH 6.0 with 10 mM $NaPO_4$ buffer.

## CLINICAL PHARMACOLOGY

### General

*Linear Growth* — Somatropin stimulates linear growth in pediatric patients who lack adequate normal endogenous growth hormone. *In vitro*, preclinical, and clinical testing have demonstrated that somatropin is therapeutically equivalent to human growth hormone of pituitary origin and achieves equivalent pharmacokinetic profiles in normal adults.

In addition, the following actions have been demonstrated for human growth hormone (somatropin and/or human growth hormone of pituitary origin).

A. *Tissue Growth* – 1. Skeletal Growth: Somatropin stimulates skeletal growth in children with growth failure due to lack of adequate secretion of endogenous GH (i.e. growth hormone deficiency), or in patients with Turner Syndrome. The measurable increase in body length after administration of human growth hormone results from an effect on the epiphysial plates of the long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth hormone-deficient pediatric patients but increase during treatment with somatropin. Elevations in mean serum alkaline phosphatase concentrations may also be seen. 2. Cell Growth: It has been shown that there are fewer skeletal muscle cells in pediatric patients with short stature who lack endogenous growth hormone as compared to the normal pediatric population. Treatment with human growth hormone results in an increase in the size and number of skeletal muscle cells.

B. *Protein Metabolism* — Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with human growth hormone.

C. *Carbohydrate Metabolism* — Growth hormone is a modulator of carbohydrate metabolism. Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. Large doses of human growth hormone may impair glucose tolerance (see PRECAUTIONS, General).

D. *Lipid Metabolism* — In growth hormone-deficient patients, administration of human growth hormone has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

E. *Mineral Metabolism* — Retention of sodium, potassium, and phosphorus is induced by human growth hormone. Serum concentrations of inorganic phosphate increased in patients with growth hormone deficiency after therapy with human growth hormone. Serum calcium is not significantly altered in patients treated with human growth hormone.

## Pharmacokinetics

***Absorption*** —Accretropin™ has been studied following subcutaneous administration in adult volunteers. Bioavailability of Accretropin™ was not determined. However, based on the bioavailability of other r-hGH products, absolute bioavailability has been estimated at approximately 70% when administered subcutaneously (Janssen et al., 1999; Zeisel et al., 1992).

***Distribution*** – The volume of distribution of somatropin was not determined for Accretropin™.

***Metabolism*** — Extensive metabolism studies have not been conducted. Somatropin is metabolized in the liver and kidneys. In the kidneys, hGH is catabolized to its constitutive amino acids, which are then returned to the systemic circulation. Clearance was not determined for Accretropin™. The mean half-life of subcutaneously administered Accretropin™ is 3.63 hours (Table 1).

***Excretion*** — Urinary excretion of intact somatropin has not been measured.

**Table 1: Summary of somatropin pharmacokinetic parameters in the normal population following a 4 mg dose of Accretropin™ administered subcutaneously***

| | $AUC_{(0-t)}$ (ng·h/mL) | $AUC_{(0-inf)}$ (ng·h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| **mean ± SD** | 238.09 ± 44.11 | 255.31 ± 43.03 | 29.49 ± 8.32 | 3.50 (2-6) | 3.63 ± 1.33 |

*Abbreviations: $AUC_{0-t}$=area under the curve until 24 hours after administration; $AUC_{0-inf}$=area under the curve to infinity; $C_{max}$=maximum concentration; $t_{½}$=half-life; $T_{max}$=time to maximum concentration (given as the median value with range); SD=standard deviation.

## Special Populations

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

***Pediatric*** — No formal pharmacokinetic studies of r-hGH in pediatric patients have been conducted using Accretropin™.

***Gender*** — No studies have been performed to evaluate the effect of gender on the pharmacokinetics of Accretropin™.

***Race*** — No data are available.

***Renal, Hepatic insufficiency*** — No studies have been performed with Accretropin™ in patients with renal or hepatic insufficiency.

**Figure 1. Mean serum hGH levels over time following single dose administration.**

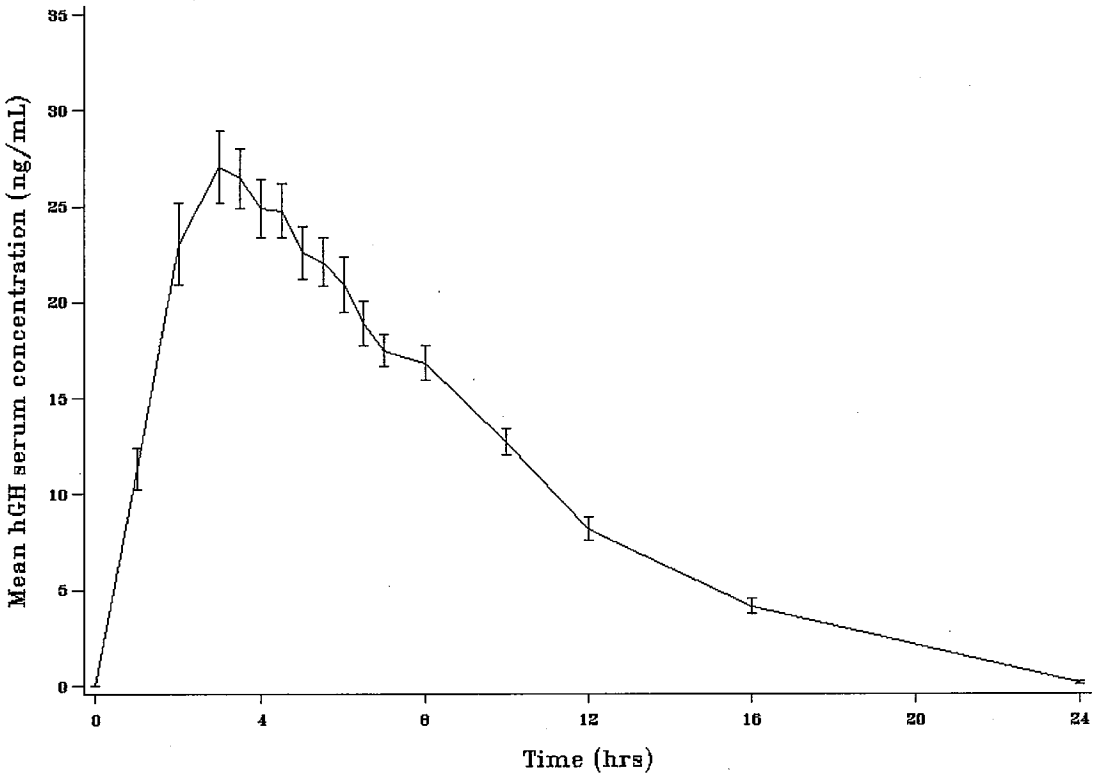


Figure 1 shows changes in mean hGH serum concentrations over time following single dose administration of Accretropin™ (N= 20, data represent means ± Standard Error).

## CLINICAL TRIALS

### Pediatric Patients with GHD

The safety and efficacy of Accretropin™ in the treatment of pediatric patients with GHD was studied in a single-arm, open-label, multicenter trial conducted in 44 patients with GHD who were treated for up to 3 years with an Accretropin™ dose of 0.03 to 0.05 mg/kg/day (0.18 to 0.30 mg/kg/week) subcutaneously. The efficacy of Accretropin™ is displayed in Table 2.

**Table 2: Height Velocity (cm/yr) and Height Velocity SDS in patients with GHD***

| | Height Velocity (cm/yr)<br>N= number of patients<br>Mean (cm/yr) ± SD | Height Velocity SDS<br>N= number of patients<br>Mean (SDS) ± SD |
|---|---|---|

| | | |
|---|---|---|
| Year 1 | N=41<br>8.88 ± 2.29 | N=41<br>3.60 ± 3.58 |
| Year 2 | N=34<br>7.64 ± 1.41 | N=33<br>1.95 ± 2.32 |
| Year 3 | N=26<br>6.98 ± 1.62 | N=26<br>1.76 ± 2.87 |

*Patients who entered puberty during the clinical trial were discontinued as per protocol specifications.

Height SD score calculated relative to population of normally growing children increased on Accretropin™ treatment from -3.04 at baseline to -2.46 at one year, -2.12 at two years, and -1.78 at three years.

### Pediatric Patients with Turner Syndrome

The safety and efficacy of Accretropin™ in the treatment of children with short stature due to Turner Syndrome was evaluated in a single-arm, open-label, single-center trial conducted in 37 patients treated with an Accretropin™ dose of 0.06 mg/kg/day subcutaneously (0.36 mg/kg/week). The efficacy of Accretropin™ is shown in Table 3.

**Table 3: Height Velocity (cm/yr) and Height Velocity SDS in patients with Turner Syndrome**

| | Height Velocity (cm/yr)<br>N= number of patients<br>Mean (cm/yr) ± SD | Height Velocity SDS<br>N= number of patients<br>Mean (SDS) ± SD |
|---|---|---|
| Year 1 | N=37<br>8.56 ± 1.71 | N=37<br>3.08 ± 2.56 |
| Year 2 | N=36<br>6.85 ± 1.21 | N=36<br>1.50 ± 1.90 |
| Year 3 | N=35<br>5.84 ± 1.86 | N=33<br>0.48 ± 3.28 |

Height SD score calculated relative to population of Turner Syndrome patients increased on Accretropin™ treatment from -3.17 at baseline to -2.67 at one year, -2.43 at two years, and -2.28 at three years.

## INDICATIONS AND USAGE

Accretropin™ (somatropin) is indicated for:

- treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone.
- treatment of short stature associated with Turner Syndrome in pediatric patients whose epiphyses are not closed.

## CONTRAINDICATIONS

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.

In general, somatropin is contraindicated in the presence of active malignancy. Any pre-existing malignancy should be inactive and its treatment complete prior to initiation of therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

Somatropin should not be used to treat patients who have acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

Somatropin is contraindicated in patients with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment (see WARNINGS).

## WARNINGS

See CONTRAINDICATIONS for information on 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. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients experiencing acute critical illnesses should be weighed against the potential risk.

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

## PRECAUTIONS

### General

Treatment with Accretropin™ as with other growth hormone preparations, should be directed by physicians who are experienced in the diagnosis and management of pediatric patients with GHD and Turner Syndrome (TS).

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi Syndrome), Turner Syndrome, or a family history of diabetes mellitus. Patients with preexisting type-1 or type-2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no 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. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. 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 funduscopy 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, Prader-Willi Syndrome, and chronic renal insufficiency may be at increased risk for the development of IH.

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

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner Syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

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

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

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

**Pediatric Patients (see PRECAUTIONS, General)**

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD 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.

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 Turner Syndrome patients. 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.

Patients with Turner Syndrome should be evaluated carefully for otitis media and other ear disorders since 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., stroke, aortic aneurysm/dissection, hypertension).

## Adult Patients

The safety and effectiveness of Accretropin™ in adult patients have not been evaluated in clinical studies.

## Geriatric Use

The safety and effectiveness of somatropin in patients aged 65 and over have not been evaluated in clinical studies.

## Drug Interactions

Somatropin inhibits 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-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. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; 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 the 11βHSD-1 enzyme.

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

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

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies for carcinogenicity, mutagenicity and impairment of fertility with Accretropin™ have not been performed.

### Pregnancy

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

### Nursing Mothers

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

## ADVERSE REACTIONS

As with all protein pharmaceuticals, some patients may develop antibodies to the protein. Over 3 years of Accretropin™ therapy, no patient with growth hormone deficiency or Turner syndrome developed anti-GH antibodies with binding capacities greater than 0.67 mg/L, which is below the threshold at which attenuation of growth velocity has been observed. Anti-GH antibody titers peaked by 6-12 months and remained stable or declined subsequently. Anti-E.coli antibody titers increased slightly during Accretropin™ treatment. No growth attenuation was noted in any patient who developed anti-hGH or anti-E. coli antibodies.

### Pediatric Growth Hormone-Deficient Patients

In the clinical study conducted in children with GHD injection site reactions were the most frequent treatment-related adverse event reported in 50% of patients (includes the following descriptions: bruising, erythema, hemorrhage, edema, pain, pruritis, rash, swelling). Other treatment-related adverse events (as assessed by the investigators) with a frequency $\geq 3\%$ were nausea, headache, fatigue, and scoliosis. One patient with pre-existing type-1 diabetes required adjustment of the insulin dose under observation. See also growth hormone associated adverse events under PRECAUTIONS and WARNINGS.

### Turner Syndrome Patients

In the clinical study conducted in pediatric patients with Turner Syndrome the only treatment-related adverse event (as assessed by the investigators) that occurred in ≥ 3% of patients was injection site reaction which occurred in 32% of patients (includes the following descriptions: erythema, edema, pain, pruritis). See also growth hormone associated adverse events under PRECAUTIONS and WARNINGS.

## OVERDOSAGE

Acute overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Long-term overdosage could result in signs and symptoms of gigantism/acromegaly consistent with the known effects of excess human growth hormone.

## DOSAGE AND ADMINISTRATION

The dose regimen for Accretropin™ [(somatropin) for injection] should be individualized for each patient. Therapy should not be continued if epiphyseal fusion has occurred. Response to growth hormone therapy tends to decrease with time. However, failure to increase growth rate, particularly during the first year of therapy, should prompt close assessment of compliance and evaluation of other causes of growth failure such as hypothyroidism, under-nutrition and advanced bone age.

***Growth hormone deficiency*** – The recommended weekly dose is 0.18 mg/kg body weight to 0.3 mg/kg (0.90 IU/kg) body weight. The dose should be divided into equal daily doses given 6 or 7 times per week subcutaneously.

***Turner Syndrome*** – The recommended weekly dose is 0.36 mg/kg of body weight. The dose should be divided into equal daily doses given 6 or 7 times per week subcutaneously.

**Accretropin™ should not be injected intravenously.**

***Administration*** – the vial should be swirled with a GENTLE rotary motion. DO NOT SHAKE. The solution should be inspected for clarity. It should be clear. If the solution is cloudy or contains particles, the contents MUST NOT be injected.

## STORAGE

Vials of Accretropin™ Injection should be stored in the refrigerator [2° to 8°C (36° to 46°F)]. Avoid freezing and shaking. Expiration dates are stated on the vial and carton

labels. Do not use after expiration date. Once opened, Accretropin™ may be stored up to 14 days when refrigerated [2° to 8°C (36° to 46°F)]. Discard 14 days after first use. Protect from light.

Rx only.

## HOW SUPPLIED

| NDC Number | Contents |
|---|---|
| 60492-0162-1 | A single vial carton containing one multidose vial and a package insert. |

## REFERENCES

Janssen YJ, Frolich M, Roelfsema F. The absorption profile and availability of a physiological subcutaneously administered dose of recombinant human growth hormone (GH) in adults with GH deficiency. Br J Clin Pharmacol 1999 Mar;47(3):273-8.

Zeisel HJ, Lutz A, von Petrykowski W. Immunogenicity of a mammalian cell-derived recombinant human growth hormone preparation during long-term treatment. Horm Res 1992;37 Suppl 2:47-55.

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