

Changes in Recombinant Human Growth Hormone (rhGH) Prescribing Information

Paulo Ferrez Collett-Solberg, MD and Anna Petryk, MD on behalf of the Members of the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society.

In June of 2007, during the LWPES meeting in Toronto, the Drugs and Therapeutics Committee was informed of changes in the prescribing information for the different forms of rhGH. Each manufacturing company implemented changes specific to their product, but more importantly, a decision was made to harmonize all growth hormone product package inserts.

The old and new labels can be found at the following website:
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

This document briefly highlights the recent changes in rhGH prescribing information.

The main points pertain to the following sections:

- Indications section: the wording for what is required for documentation of GHD in adults was changed.
- Contraindications and Warning section: this section states as a contraindication, or cautions against the use of rhGH to promote growth in short patients with closed epiphyses, diabetic patients with retinopathy, patients with active malignancy, patients with acute critical illnesses. Somatotropin is contraindicated in patients with the Prader Willi syndrome who are severely obese or have severe respiratory impairment.
- Precautions section: this section is now divided into General, Pediatric and Adult subsections.
 - General: recommends that rhGH be prescribed by physicians experienced in rhGH administration, and the following issues are discussed: effects of rhGH on glucose metabolism, management of intracranial hypertension, management of patients with other endocrinopathies, the need to monitor skin lesions, rotate injection sites and to inform patients about possible allergic reactions. A word of caution regarding secondary malignancy in children was added.
 - Pediatric patients: discusses the risks of slipped capital femoral epiphysis, scoliosis, otitis media and cardiovascular disorders in patients with Turner syndrome.
 - Adult patients: discusses transition of pediatric patients to adult GH replacement, the issues of fluid retention, and introduces a word of caution regarding the limited experience with prolonged treatment in adults.
- Information for patients: divided into subsections that include General, Laboratory tests, Drug interactions, “Carcinogenesis, mutagenesis, impairment of fertility”, Pregnancy, Nursing mothers and Geriatric usage.
 - General: discusses the need to inform patients about the contents of the information insert and also discusses the disposal of needles and syringes.
 - Laboratory tests: points out possible biochemical changes during rhGH therapy.
 - Drug interaction section: discusses glucocorticoid metabolism and replacement, cytochrome P450 activity in patients using rhGH, and the use of rhGH in patients with diabetes mellitus.
 - Carcinogenesis, mutagenesis, impairment of fertility: states that these studies have not been conducted.
 - Pregnancy: some of the rhGH products are labeled class B whereas others are labeled class C.
 - Nursing mothers: gives a word of caution
 - Geriatric usage: states that there are not enough studies although elderly patients may be more sensitive to rhGH.
- Adverse reactions: discusses anti rhGH antibodies and leukemia.
- Dosage and Administration section: adult dosing recommendations were changed.

In the precautions section a word of caution was added with regards to the risk for secondary malignancy following use of rhGH in cancer survivors. This was based on data from a study by Ergun-Longmire et al (J Clin Endocrinol Metab 2006; 91: 3494–3498) in which the authors reported a 2.15 rate ratio of developing a secondary neoplasm in childhood cancer survivors who received rhGH compared to non-rhGH treated survivors. The data presented in this paper suggested that treatment with rhGH may accelerate the development of secondary neoplasms. However, this risk appears to decrease with increasing length of follow up and the overall risk appears small.

Some of the rhGH products have specific indications and consequently specific changes: Nutropin had changes related to patients with renal insufficiency and after renal transplantation. Humatrope is now indicated to treat patients with SHOX deficiency and Norditropin is indicated in Noonan syndrome.

We transcribed the new wording common to all of the packaging inserts.

INDICATIONS AND USAGE

Adult Patients

Somatropin is indicated for the replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

Adult onset: patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or

Childhood onset: patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

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

CONTRAINDICATIONS

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

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 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 with 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 having 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).

PRECAUTIONS

Somatropin should be prescribed by physicians experienced in the diagnosis and management of patients with GH deficiency, idiopathic short stature, Turner syndrome, or chronic renal insufficiency (CRI).

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. Funduscopy 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, CRI, and Prader-Willi syndrome 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 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.

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. In a randomized, controlled trial, there was a statistically significant increase, as compared to untreated controls, in otitis media (43% vs. 26%) and ear disorders (18% vs. 5%) in patients receiving somatropin. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

Adult Patients (see PRECAUTIONS, General):

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults. Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent (see ADVERSE REACTIONS).

Experience with prolonged somatropin treatment in adults is limited.

Information for Patients:

Patients being treated with somatropin should be informed about the potential benefits and risks associated with somatropin treatment, including a review of the contents of the Patient Information Insert. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects. Patients and caregivers who will administer somatropin should receive appropriate training and instruction on the proper use of somatropin from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication (see Patient Information Insert).

Laboratory Tests:

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and IGF-1 may increase during somatropin therapy.

Drug Interactions:

Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. 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 11 β HSD-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.

The use of somatropin in patients with CRI requiring glucocorticoid therapy has not been evaluated. Concomitant glucocorticoid therapy may inhibit the growth promoting effects of somatropin. Therefore, if glucocorticoid therapy is required for CRI, the glucocorticoid dose should be carefully adjusted to avoid 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 adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal (see DOSAGE AND ADMINISTRATION).

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:

Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with somatropin.

Pregnancy:

Note from the authors: Some of the products are labeled class B while others are labeled class C.

Nursing Mothers:

It is not known whether somatropin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when somatropin is administered to a nursing mother.

Geriatric Usage:

Clinical studies with somatropin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients (see DOSING AND ADMINISTRATION).

ADVERSE REACTIONS

As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. GH antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been observed.

In addition to an evaluation of compliance with the prescribed treatment program and thyroid status, testing for antibodies to GH should be carried out in any patient who fails to respond to therapy.

Leukemia has been reported in a small number of GHD patients treated with GH. It is uncertain whether this increased risk is related to the pathology of GH deficiency itself, GH therapy, or other associated treatments such as radiation therapy for intracranial tumors. On the basis of current evidence, experts cannot conclude that GH therapy is responsible for these occurrences.

DOSAGE AND ADMINISTRATION

Adult Growth Hormone Deficiency (GHD)

Based on the weight-based dosing utilized in the original pivotal studies described herein, the recommended dosage at the start of therapy is not more than 0.006 mg/kg given as a daily subcutaneous injection. The dose may be increased according to individual patient requirements to a maximum of 0.025 mg/kg daily in patients under 35 years old and to a maximum of 0.0125 mg/kg daily in patients over 35 years old. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/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/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person. A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

