DESCRIPTION

Nutropin AQ® [somatropin (rDNA origin) injection] is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin AQ has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of pituitary-derived human growth hormone. The protein is synthesized by a specific laboratory strain of \textit{E. coli} as a precursor consisting of the rhGH molecule preceded by the secretion signal from an \textit{E. coli} protein. This precursor is directed to the plasma membrane of the cell. The signal sequence is removed and the native protein is secreted into the periplasm so that the protein is folded appropriately as it is synthesized.

Nutropin AQ is a highly purified preparation. Biological potency is determined using a cell proliferation bioassay. Nutropin AQ may contain not more than fifteen percent deamidated growth hormone (GH) at expiration. The deamidated form of GH has been extensively characterized and has been shown to be safe and fully active.

Nutropin AQ is a sterile liquid intended for subcutaneous administration. The product is nearly isotonic at a concentration of 5 mg of GH per mL and has a pH of approximately 6.0.

The Nutropin AQ 2 mL vial contains 10 mg (approximately 30 International Units [IU]) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.

The 10 mg Nutropin AQ 2 mL pen cartridge contains 10 mg (approximately 30 International Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.

The 20 mg Nutropin AQ 2 mL pen cartridge contains 20 mg (approximately 60 International Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.

The Nutropin AQ NuSpin 5 contains 5 mg (approximately 15 International Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.
The Nutropin AQ NuSpin 10 contains 10 mg (approximately 30 International Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.

The Nutropin AQ NuSpin 20 contains 20 mg (approximately 60 International Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.

**CLINICAL PHARMACOLOGY**

**General**

In vitro and in vivo preclinical and clinical testing have demonstrated that Nutropin AQ is therapeutically equivalent to pituitary-derived human GH (hGH). Pediatric patients who lack adequate endogenous GH secretion, patients with chronic renal insufficiency, and patients with Turner syndrome that were treated with Nutropin AQ or Nutropin® [somatropin (rDNA origin) for injection] resulted in an increase in growth rate and an increase in insulin-like growth factor-I (IGF-I) levels similar to that seen with pituitary-derived hGH.

Actions that have been demonstrated for Nutropin AQ, somatropin, somatrem, and/or pituitary-derived hGH include:

**A. Tissue Growth**

1) Skeletal Growth: GH stimulates skeletal growth in pediatric patients with growth failure due to a lack of adequate secretion of endogenous GH or secondary to chronic renal insufficiency and in patients with Turner syndrome. Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by GH and one of its mediators, IGF-I. Serum levels of IGF-I are low in children and adolescents who are GH deficient, but increase during treatment with GH. In pediatric patients, new bone is formed at the epiphyses in response to GH and IGF-I. This results in linear growth until these growth plates fuse at the end of puberty. 2) Cell Growth: Treatment with hGH results in an increase in both the number and the size of skeletal muscle cells. 3) Organ Growth: GH influences the size of internal organs, including kidneys, and increases red cell mass. Treatment of hypophysectomized or genetic dwarf rats
with GH results in organ growth that is proportional to the overall body growth. In normal rats subjected to nephrectomy-induced uremia, GH promoted skeletal and body growth.

B. Protein Metabolism

Linear growth is facilitated in part by GH-stimulated protein synthesis. This is reflected by nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during GH therapy.

C. Carbohydrate Metabolism

GH is a modulator of carbohydrate metabolism. For example, patients with inadequate secretion of GH sometimes experience fasting hypoglycemia that is improved by treatment with GH. GH therapy may decrease insulin sensitivity. Untreated patients with chronic renal insufficiency and Turner syndrome have an increased incidence of glucose intolerance. Administration of hGH to adults or children resulted in increases in serum fasting and postprandial insulin levels, more commonly in overweight or obese individuals. In addition, mean fasting and postprandial glucose and hemoglobin A1c levels remained in the normal range.

D. Lipid Metabolism

In GH-deficient patients, administration of GH resulted in lipid mobilization, reduction in body fat stores, increased plasma fatty acids, and decreased plasma cholesterol levels.

E. Mineral Metabolism

The retention of total body potassium in response to GH administration apparently results from cellular growth. Serum levels of inorganic phosphorus may increase slightly in patients with inadequate secretion of endogenous GH, chronic renal insufficiency, or patients with Turner syndrome during GH therapy due to metabolic activity associated with bone growth as well as increased tubular reabsorption of phosphate by the kidney. Serum calcium is not significantly altered in these patients. Sodium retention also occurs. Adults with childhood-onset GH deficiency show low bone mineral density (BMD). GH therapy results in increases in serum alkaline phosphatase. (See PRECAUTIONS: Laboratory Tests.)
F. Connective Tissue Metabolism

GH stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Subcutaneous Absorption—The absolute bioavailability of recombinant human growth hormone (rhGH) after subcutaneous administration in healthy adult males has been determined to be $81 \pm 20\%$. The mean terminal $t_{1/2}$ after subcutaneous administration is significantly longer than that seen after intravenous administration ($2.1 \pm 0.43$ hours vs. $19.5 \pm 3.1$ minutes) indicating that the subcutaneous absorption of the compound is slow and rate-limiting.

Distribution—Animal studies with rhGH showed that GH localizes to highly perfused organs, particularly the liver and kidney. The volume of distribution at steady state for rhGH in healthy adult males is about 50 mL/kg body weight, approximating the serum volume.

Metabolism—Both the liver and kidney have been shown to be important metabolizing organs for GH. Animal studies suggest that the kidney is the dominant organ of clearance. GH is filtered at the glomerulus and reabsorbed in the proximal tubules. It is then cleaved within renal cells into its constituent amino acids, which return to the systemic circulation.

Elimination—The mean terminal $t_{1/2}$ after intravenous administration of rhGH in healthy adult males is estimated to be $19.5 \pm 3.1$ minutes. Clearance of rhGH after intravenous administration in healthy adults and children is reported to be in the range of $116–174$ mL/hr/kg.

Bioequivalence of Formulations—Nutropin AQ has been determined to be bioequivalent to Nutropin based on the statistical evaluation of AUC and $C_{\text{max}}$.

SPECIAL POPULATIONS

Pediatric—Available literature data suggest that rhGH clearances are similar in adults and children.
Gender—No data are available for exogenously administered rhGH. Available data for methionyl recombinant GH, pituitary-derived GH, and endogenous GH suggest no consistent gender-based differences in GH clearance.

Geriatrics—Limited published data suggest that the plasma clearance and average steady-state plasma concentration of rhGH may not be different between young and elderly patients.

Race—Reported values for half-lives for endogenous GH in normal adult black males are not different from observed values for normal adult white males. No data for other races are available.

Growth Hormone Deficiency (GHD)—Reported values for clearance of rhGH in adults and children with GHD range 138–245 mL/hr/kg and are similar to those observed in healthy adults and children. Mean terminal \( t_{1/2} \) values following intravenous and subcutaneous administration in adult and pediatric GHD patients are also similar to those observed in healthy adult males.

Renal Insufficiency—Children and adults with chronic renal failure (CRF) and end-stage renal disease (ESRD) tend to have decreased clearance compared to normals. In a study with six pediatric patients 7 to 11 years of age, the clearance of Nutropin was reduced by 21.5% and 22.6% after the intravenous infusion and subcutaneous injection, respectively, of 0.05 mg/kg of Nutropin compared to normal healthy adults. Endogenous GH production may also increase in some individuals with ESRD. However, no rhGH accumulation has been reported in children with CRF or ESRD dosed with current regimens.

Turner Syndrome—No pharmacokinetic data are available for exogenously administered rhGH. However, reported half-lives, absorption, and elimination rates for endogenous GH in this population are similar to the ranges observed for normal subjects and GHD populations.

Hepatic Insufficiency—A reduction in rhGH clearance has been noted in patients with severe liver dysfunction. The clinical significance of this decrease is unknown.
## Summary of Nutropin AQ Pharmacokinetic Parameters in Healthy Adult Males

0.1 mg (approximately 0.3 IU\textsuperscript{a})/kg SC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (μg/L)</th>
<th>Median (μg/L)</th>
<th>T\textsubscript{max} (hr)</th>
<th>t\textsubscript{1/2} (hr)</th>
<th>AUC\textsubscript{0-}\textsubscript{∞} (μg•hr/L)</th>
<th>CL/F\textsubscript{sc} (mL/[hr•kg])</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{max}</td>
<td>71.1</td>
<td>67</td>
<td>3.9</td>
<td>2.3</td>
<td>677</td>
<td>150</td>
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<tr>
<td>CV%</td>
<td>17</td>
<td>56</td>
<td>18</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:

- C\textsubscript{max} = maximum concentration
- t\textsubscript{1/2} = half-life
- AUC\textsubscript{0-}\textsubscript{∞} = area under the curve
- CL/F\textsubscript{sc} = systemic clearance
- F\textsubscript{sc} = subcutaneous bioavailability (not determined)
- CV% = coefficient of variation in %; SC = subcutaneous

\textsuperscript{a} Based on current International Standard of 3 IU = 1 mg

\textsuperscript{b} n = 36
**Single Dose Mean Growth Hormone Concentrations in Healthy Adult Males**

![Graph showing single dose mean growth hormone concentrations](image)

**CLINICAL STUDIES**

**Growth Hormone Deficiency (GHD) in Pubertal Patients**

One open label, multicenter, randomized clinical trial of two dosages of Nutropin® [somatropin (rDNA origin) for injection] was performed in pubertal patients with GHD. Ninety-seven patients (mean age 13.9 years, 83 male, 14 female) currently being treated with approximately 0.3 mg/kg/wk of GH were randomized to 0.3 mg/kg/wk or 0.7 mg/kg/wk Nutropin doses. All patients were already in puberty (Tanner stage ≥2) and had bone ages ≤14 years in males or ≤12 years in females. Mean baseline height standard deviation (SD) score was −1.3.

The mean last measured height in all 97 patients after a mean duration of 2.7±1.2 years, by analysis of covariance (ANCOVA) adjusting for baseline height, is shown below.
**Last Measured Height*** by Sex and Nutropin Dose

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Last Measured Height* (cm)</th>
<th>Height Difference Between Groups (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD (range)</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Male</td>
<td>17.2±1.3 (13.6 to 19.4)</td>
<td>170.9±7.9 (n=42)</td>
</tr>
<tr>
<td>Female</td>
<td>15.8±1.8 (11.9 to 19.3)</td>
<td>154.7±6.3 (n=7)</td>
</tr>
</tbody>
</table>

*Adjusted for baseline height

The mean height SD score at last measured height (n=97) was −0.7 ± 1.0 in the 0.3 mg/kg/wk group and −0.1 ± 1.2 in the 0.7 mg/kg/wk group. For patients completing 3.5 or more years (mean 4.1 years) of Nutropin treatment (15/49 patients in the 0.3 mg/kg/wk group and 16/48 patients in the 0.7 mg/kg/wk group), the mean last measured height was 166.1±8.0 cm in the 0.3 mg/kg/wk group and 171.8±7.1 cm in the 0.7 mg/kg/wk group, adjusting for baseline height and sex.

The mean change in bone age was approximately one year for each year in the study in both dose groups. Patients with baseline height SD scores above −1.0 were able to attain normal adult heights with the 0.3 mg/kg/wk dose of Nutropin (mean height SD score at near-adult height=−0.1, n=15).

Thirty-one patients had bone mineral density (BMD) determined by dual energy x-ray absorptiometry (DEXA) scans at study conclusion. The two dose groups did not differ significantly in mean SD score for total body BMD (−0.9 ± 1.9 in the 0.3 mg/kg/wk group vs. −0.8±1.2 in the 0.7 mg/kg/wk group, n=20) or lumbar spine BMD (−1.0±1.0 in the 0.3 mg/kg/wk group vs. −0.2±1.7 in the 0.7 mg/kg/wk group, n=21).

Over a mean duration of 2.7 years, patients in the 0.7 mg/kg/wk group were more likely to have IGF-I values above the normal range than patients in the 0.3 mg/kg/wk group (27.7% vs. 9.0% of IGF-I measurements for individual patients). The clinical significance of elevated IGF-I values is unknown.
Effects of Nutropin on Growth Failure Due to Chronic Renal Insufficiency (CRI)

Two multicenter, randomized, controlled clinical trials were conducted to determine whether treatment with Nutropin prior to renal transplantation in patients with chronic renal insufficiency could improve their growth rates and height deficits. One study was a double-blind, placebo-controlled trial and the other was an open-label, randomized trial. The dose of Nutropin in both controlled studies was 0.05 mg/kg/day (0.35 mg/kg/week) administered daily by subcutaneous injection. Combining the data from those patients completing two years in the two controlled studies results in 62 patients treated with Nutropin and 28 patients in the control groups (either placebo-treated or untreated). The mean first year growth rate was 10.8 cm/yr for Nutropin-treated patients, compared with a mean growth rate of 6.5 cm/yr for placebo/untreated controls (p < 0.00005). The mean second year growth rate was 7.8 cm/yr for the Nutropin-treated group, compared with 5.5 cm/yr for controls (p < 0.00005). There was a significant increase in mean height standard deviation (SD) score in the Nutropin group (−2.9 at baseline to −1.5 at Month 24, n = 62) but no significant change in the controls (−2.8 at baseline to −2.9 at Month 24, n = 28). The mean third year growth rate of 7.6 cm/yr in the Nutropin-treated patients (n = 27) suggests that Nutropin stimulates growth beyond two years. However, there are no control data for the third year because control patients crossed over to Nutropin treatment after two years of participation. The gains in height were accompanied by appropriate advancement of skeletal age. These data demonstrate that Nutropin therapy improves growth rate and corrects the acquired height deficit associated with chronic renal insufficiency.

Post-Transplant Growth

The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has reported data for growth post-transplant in children who did not receive GH prior to transplantation as well as children who did receive Nutropin during the clinical trials prior to transplantation. The average change in height SD score during the initial two years post-transplant was 0.15 for the 2391 patients who did not receive GH pre-transplant and 0.28 for the 57 patients who did (J Pediatr. 2000;136:376-382). For patients who were followed for 5 years post-transplant, the corresponding changes in height SD score were also similar between groups.

Turner Syndrome

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

In the randomized study GDCT, comparing GH-treated patients to a concurrent control group
who received no GH, the GH-treated patients who received a dose of 0.3 mg/kg/week given
6 times per week from a mean age of 11.7 years for a mean duration of 4.7 years attained a
mean near final height of 146.0 cm (n=27) as compared to the control group who attained a
near final height of 142.1 cm (n=19). By analysis of covariance, the effect of GH therapy
was a mean height increase of 5.4 cm (p=0.001).

In two of the studies (85-023 and 85-044), the effect of long-term GH treatment
(0.375 mg/kg/week given either 3 times per week or daily) on adult height was determined
by comparing adult heights in the treated patients with those of age-matched historical
controls with Turner syndrome who never received any growth-promoting therapy. In
Study 85-023, estrogen treatment was delayed until patients were at least age 14. GH
therapy resulted in a mean adult height gain of 7.4 cm (mean duration of GH therapy of
7.6 years) vs. matched historical controls by analysis of covariance.

In Study 85-044, patients treated with early GH therapy were randomized to receive
estrogen-replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily) at
either age 12 or 15 years. Compared with matched historical controls, early GH therapy
(mean duration of GH therapy 5.6 years) combined with estrogen replacement at age
12 years resulted in an adult height gain of 5.9 cm (n=26), whereas girls who initiated
estrogen at age 15 years (mean duration of GH therapy 6.1 years) had a mean adult height
gain of 8.3 cm (n=29). Patients who initiated GH therapy after age 11 (mean age 12.7 years;
mean duration of GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

Thus, in both studies, 85-023 and 85-044, the greatest improvement in adult height was
observed in patients who received early GH treatment and estrogen after age 14 years.

In a randomized, blinded, dose-response study, GDCI, patients were treated from a mean age
of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or
0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients
receiving growth hormone was 148.7 cm (n=31). This represents a mean gain in adult
height of approximately 5 cm compared with previous observations of untreated Turner syndrome girls.

In these studies, Turner syndrome patients (n=181) treated to final adult height achieved statistically significant average estimated adult height gains ranging from 5.0–8.3 cm.

<table>
<thead>
<tr>
<th>Study/Group</th>
<th>Study Design</th>
<th>N at Adult Height</th>
<th>GH Age (yr)</th>
<th>Estrogen Age (yr)</th>
<th>GH Duration (yr)</th>
<th>Adult Height Gain (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDCT</td>
<td>RCT</td>
<td>27</td>
<td>11.7</td>
<td>13</td>
<td>4.7</td>
<td>5.4</td>
</tr>
<tr>
<td>85-023</td>
<td>MHT</td>
<td>17</td>
<td>9.1</td>
<td>15.2</td>
<td>7.6</td>
<td>7.4</td>
</tr>
<tr>
<td>85-044: A*</td>
<td>MHT</td>
<td>29</td>
<td>9.4</td>
<td>15.0</td>
<td>6.1</td>
<td>8.3</td>
</tr>
<tr>
<td>B*</td>
<td>MHT</td>
<td>26</td>
<td>9.6</td>
<td>12.3</td>
<td>5.6</td>
<td>5.9</td>
</tr>
<tr>
<td>C*</td>
<td>MHT</td>
<td>51</td>
<td>12.7</td>
<td>13.7</td>
<td>3.8</td>
<td>5.0</td>
</tr>
<tr>
<td>GDCI RDT</td>
<td>RDT</td>
<td>31</td>
<td>11.1</td>
<td>8–13.5</td>
<td>5.3</td>
<td>~5^c</td>
</tr>
</tbody>
</table>

^a RCT: randomized controlled trial; MHT: matched historical controlled trial; RDT: randomized dose-response trial
^b Analysis of covariance vs. controls
^c Compared with historical data
* A = GH age < 11 yr, estrogen age 15 yr
  B = GH age < 11 yr, estrogen age 12 yr
  C = GH age > 11 yr, estrogen at Month 12

**Idiopathic Short Stature (ISS)**

A long-term, open-label, multicenter study (86-053) was conducted to examine the safety and efficacy of Nutropin in pediatric patients with idiopathic short stature, also called non-GH deficient short stature. For the first year, 122 pre-pubertal subjects over the age of 5 years with stimulated serum GH ≥ 10 ng/mL were randomized into two treatment groups of approximately equal size; one group was treated with Nutropin 0.3 mg/kg weekly divided into three doses per week (TIW) and the other group served as untreated controls. For the second and subsequent years of the study, all subjects were re-randomized to receive the same total weekly dose of Nutropin (0.3 mg/kg weekly) administered either daily or TIW. Treatment with Nutropin was continued until a subject’s bone age was > 15.0 years (boys) or > 14.0 years (girls) and the growth rate was < 2 cm/yr, after which subjects were followed until adult height was achieved. The mean baseline values were: height SD score −2.8, IGF-I SD score −0.9, age 9.4 years, bone age 7.8 years, growth rate 4.4 cm/yr, mid-parental target height SD score −0.7, and Bayley-Pinneau predicted adult height SD score −2.3. Nearly all subjects had predicted adult height that was less than mid-parental target height.
During the one-year controlled phase of the study, the mean height velocity increased by 0.5±1.8 cm (mean ± SD) in the no-treatment control group and by 3.1±1.7 cm in the Nutropin group (p<0.0001). For the same period of treatment the mean height SD score increased by 0.4±0.2 and remained unchanged (0.0±0.2) in the control group (p<0.001).

Of the 118 subjects who were treated with Nutropin in Study 86-053, 83 (70%) reached near-adult height (hereafter called adult height) after 2–10 years of Nutropin therapy. Their last measured height, including post-treatment follow-up, was obtained at a mean age of 18.3 years in males and 17.3 years in females. The mean duration of therapy was 6.2 and 5.5 years, respectively. Adult height was greater than pretreatment predicted adult height in 49 of 60 males (82%) and 19 of 23 females (83%). The mean difference between adult height and pretreatment predicted adult height was 5.2 cm (2.0 inches) in males and 6.0 cm (2.4 inches) in females (p<0.0001 for both). The table (below) summarizes the efficacy data.

### Long-Term Efficacy in Study 86-053 (Mean ±SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Males (n=60)</th>
<th>Females (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult height (cm)</td>
<td>166.3±5.8</td>
<td>153.1±4.8</td>
</tr>
<tr>
<td>Pretreatment predicted adult height (cm)</td>
<td>161.1±5.5</td>
<td>147.1±5.1</td>
</tr>
<tr>
<td>Adult height minus pretreatment predicted adult height (cm)</td>
<td>+5.2±5.0a</td>
<td>+6.0±5.0a</td>
</tr>
<tr>
<td>Adult height SD score</td>
<td>−1.5±0.8</td>
<td>−1.6±0.7</td>
</tr>
<tr>
<td>Pretreatment predicted adult height SD score</td>
<td>−2.2±0.8</td>
<td>−2.5±0.8</td>
</tr>
<tr>
<td>Adult height minus pretreatment predicted adult height SD score</td>
<td>+0.7±0.7a</td>
<td>+0.9±0.8a</td>
</tr>
</tbody>
</table>

*a p<0.0001 versus zero.

Nutropin therapy resulted in an increase in mean IGF-I SD score from −0.9 ± 1.0 to −0.2 ±0.9 in Treatment Year 1. During continued treatment, mean IGF-I levels remained close to the normal mean. IGF-I SD scores above +2 occurred sporadically in 14 subjects.

**Adult Growth Hormone Deficiency (GHD)**

Two multicenter, double-blind, placebo-controlled clinical trials were conducted using Nutropin® [somatropin (rDNA origin) for injection] in GH-deficient adults. One study was conducted in subjects with adult-onset GHD, mean age 48.3 years, n = 166, at doses of 0.0125
or 0.00625 mg/kg/day; doses of 0.025 mg/kg/day were not tolerated in these subjects. A second study was conducted in previously treated subjects with childhood-onset GHD, mean age 23.8 years, n=64, at randomly assigned doses of 0.025 or 0.0125 mg/kg/day. The studies were designed to assess the effects of replacement therapy with GH on body composition.

Significant changes from baseline to Month 12 of treatment in body composition (i.e., total body % fat mass, trunk % fat mass, and total body % lean mass by DEXA scan) were seen in all Nutropin groups in both studies (p<0.0001 for change from baseline and vs. placebo), whereas no statistically significant changes were seen in either of the placebo groups. In the adult-onset study, the Nutropin group improved mean total body fat from 35.0% to 31.5%, mean trunk fat from 33.9% to 29.5%, and mean lean body mass from 62.2% to 65.7%, whereas the placebo group had mean changes of 0.2% or less (p=not significant). Due to the possible effect of GH-induced fluid retention on DEXA measurements of lean body mass, DEXA scans were repeated approximately 3 weeks after completion of therapy; mean % lean body mass in the Nutropin group was 65.0%, a change of 2.8% from baseline, compared with a change of 0.4% in the placebo group (p<0.0001 between groups).

In the childhood-onset study, the high-dose Nutropin group improved mean total body fat from 38.4% to 32.1%, mean trunk fat from 36.7% to 29.0%, and mean lean body mass from 59.1% to 65.5%; the low-dose Nutropin group improved mean total body fat from 37.1% to 31.3%, mean trunk fat from 37.9% to 30.6%, and mean lean body mass from 60.0% to 66.0%; the placebo group had mean changes of 0.6% or less (p=not significant).
Mean Changes from Baseline to Month 12 in Proportion of Fat and Lean by DEXA for Studies M0431g and M0381g (Adult-onset and Childhood-onset GHD, respectively)

<table>
<thead>
<tr>
<th>Proportion</th>
<th>M0431g</th>
<th>M0381g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=62)</td>
<td>Nutropin (n=63)</td>
</tr>
<tr>
<td><strong>Total body percent fat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.8</td>
<td>35.0</td>
</tr>
<tr>
<td>Month 12</td>
<td>36.8</td>
<td>31.5</td>
</tr>
<tr>
<td>Baseline to Month 12 change</td>
<td>−0.1</td>
<td>−3.6</td>
</tr>
<tr>
<td>Post-washout</td>
<td>36.4</td>
<td>32.2</td>
</tr>
<tr>
<td>Baseline to post-washout change</td>
<td>−0.4</td>
<td>−2.8</td>
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<tr>
<td><strong>Trunk percent fat</strong></td>
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<tr>
<td>Baseline</td>
<td>35.3</td>
<td>33.9</td>
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<td>Month 12</td>
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<tr>
<td>Baseline to Month 12 change</td>
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<tr>
<td>Post-washout</td>
<td>34.9</td>
<td>30.5</td>
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<tr>
<td>Baseline to post-washout change</td>
<td>−0.3</td>
<td>−3.4</td>
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<tr>
<td><strong>Total body percent lean</strong></td>
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<tr>
<td>Baseline</td>
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<td>62.2</td>
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<tr>
<td>Month 12</td>
<td>60.5</td>
<td>65.7</td>
</tr>
<tr>
<td>Baseline to Month 12 change</td>
<td>+ 0.2</td>
<td>+ 3.6</td>
</tr>
<tr>
<td>Post-washout</td>
<td>60.9</td>
<td>65.0</td>
</tr>
<tr>
<td>Baseline to post-washout change</td>
<td>+ 0.4</td>
<td>+ 2.8</td>
</tr>
</tbody>
</table>

In the adult-onset study, significant decreases from baseline to Month 12 in LDL cholesterol and LDL:HDL ratio were seen in the Nutropin group compared to the placebo group, p < 0.02; there were no statistically significant between-group differences in change from baseline to Month 12 in total cholesterol, HDL cholesterol, or triglycerides. In the childhood-onset study, significant decreases from baseline to Month 12 in total cholesterol, LDL cholesterol, and LDL:HDL ratio were seen in the high-dose Nutropin group only, compared to the placebo group, p < 0.05. There were no statistically significant between-group differences in HDL cholesterol or triglycerides from baseline to Month 12.
In the childhood-onset study, 55% of the patients had decreased spine bone mineral density (BMD) \((z\text{-score} < -1)\) at baseline. The administration of Nutropin \((n=16)\) \(0.025 \text{ mg/kg/day}\) for two years resulted in increased spine BMD from baseline when compared to placebo \((n=13)\) \((4.6\% \text{ vs. } 1.0\%, \text{ respectively, } p < 0.03)\); a transient decrease in spine BMD was seen at six months in the Nutropin-treated patients. Thirty-five percent of subjects treated with this dose had supraphysiological levels of IGF-I at some point during the study, which may carry unknown risks. No significant improvement in total body BMD was found when compared to placebo. A lower GH dose \((0.0125 \text{ mg/kg/day})\) did not show significant increments in either of these bone parameters when compared to placebo. No statistically significant effects on BMD were seen in the adult-onset study where patients received GH \((0.0125 \text{ mg/kg/day})\) for one year.

Muscle strength, physical endurance, and quality of life measurements were not markedly abnormal at baseline, and no statistically significant effects of Nutropin therapy were observed in the two studies.

A subsequent 32-week, multicenter, open-label, controlled clinical trial (M2378g) was conducted using Nutropin AQ, Nutropin Depot, or no treatment in adults with both adult-onset and childhood-onset GHD. Subjects were randomized into the three groups to evaluate effects on body composition, including change in visceral adipose tissue (VAT) as determined by computed tomography (CT) scan.

For subjects evaluable for change in VAT in the Nutropin AQ \((n=44)\) and untreated \((n=19)\) groups, the mean age was 46.2 years and 78% had adult-onset GHD. Subjects in the Nutropin AQ group were treated at doses up to 0.012 mg/kg per day in women (all of whom received estrogen replacement therapy) and men under age 35 years, and up to 0.006 mg/kg per day in men over age 35 years.

The mean absolute change in VAT from baseline to Week 32 was \(-10.7 \text{ cm}^2\) in the Nutropin AQ group and \(+8.4 \text{ cm}^2\) in the untreated group \((p = 0.013 \text{ between groups})\). There was a 6.7% VAT loss in the Nutropin AQ group (mean percent change from baseline to Week 32) compared with a 7.5% increase in the untreated group \((p = 0.012 \text{ between groups})\). The effect of reducing VAT in adult GHD patients with Nutropin AQ on long-term cardiovascular morbidity and mortality has not been determined.
Visceral Adipose Tissue by Computed Tomography Scan: Percent Change and Absolute Change from Baseline to Week 32 in Study M2378g

<table>
<thead>
<tr>
<th></th>
<th>Nutropin AQ (n = 44)</th>
<th>Untreated (n = 19)</th>
<th>Treatment Difference (adjusted mean)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline VAT (cm²)</td>
<td>126.2</td>
<td>123.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in VAT (cm²)</td>
<td>-10.7</td>
<td>+8.4</td>
<td>-19.1</td>
<td>0.013a</td>
</tr>
<tr>
<td>Percent change in VAT</td>
<td>-6.7</td>
<td>+7.5</td>
<td>-14.2</td>
<td>0.012a</td>
</tr>
</tbody>
</table>

*ANCOVA using baseline VAT as a covariate

INDICATIONS AND USAGE

Pediatric Patients

Nutropin AQ® [somatropin (rDNA origin) injection] is indicated for the long-term treatment of growth failure due to a lack of adequate endogenous GH secretion.

Nutropin AQ® [somatropin (rDNA origin) injection] is also indicated for the treatment of growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Nutropin AQ therapy should be used in conjunction with optimal management of chronic renal insufficiency.

Nutropin AQ® [somatropin (rDNA origin) injection] is also indicated for the long-term treatment of short stature associated with Turner syndrome.

Nutropin AQ® [somatropin (rDNA origin) injection] is also indicated for the long-term treatment of idiopathic short stature, also called non-growth hormone-deficient short stature, defined by height SDS ≤−2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.
Adult Patients

Nutropin AQ® [somatropin (rDNA origin) injection] is indicated for 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 pre-existing 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). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Nutropin AQ is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

**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).

Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Nutropin AQ is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

**PRECAUTIONS**

**General:**
Nutropin AQ® [somatropin (rDNA origin) injection]

Nutropin AQ 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). No studies have been completed evaluating Nutropin AQ therapy in patients who have received renal transplants. Currently, treatment of patients with functioning renal allografts is not indicated.

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.

In subjects treated in a long-term study of Nutropin for idiopathic short stature, mean fasting and postprandial insulin levels increased, while mean fasting and postprandial glucose levels remained unchanged. Mean hemoglobin A1c levels rose slightly from baseline as expected during adolescence; sporadic values outside normal limits occurred transiently.

Nutropin therapy in adults with GH deficiency of adult onset was associated with an increase of median fasting insulin level in the Nutropin 0.0125 mg/kg/day group from 9.0 μU/mL at baseline to 13.0 μU/mL at Month 12 with a return to the baseline median level after a 3-week post-washout period of GH therapy. In the placebo group there was no change from 8.0 μU/mL at baseline to Month 12, and after the post-washout period, the median level was 9.0 μU/mL. The between-treatment groups difference on the change from baseline to Month 12 in median fasting insulin level was significant, p<0.0001. In childhood-onset subjects, there was an increase of median fasting insulin level in the Nutropin 0.025 mg/kg/day group from 11.0 μU/mL at baseline to 20.0 μU/mL at Month 12, in the Nutropin 0.0125 mg/kg/day group from 8.5 μU/mL to 11.0 μU/mL, and in the placebo group from 7.0 μU/mL to 8.0 μU/mL. The between-treatment groups differences for these changes were significant, p=0.0007.
In subjects with adult onset GH deficiency, there were no between-treatment group differences on change from baseline to Month 12 in mean HbA1c level, p=0.08. In childhood-onset GH deficiency, the mean HbA1c level increased in the Nutropin 0.025 mg/kg/day group from 5.2% at baseline to 5.5% at Month 12, and did not change in the Nutropin 0.0125 mg/kg/day group from 5.1% at baseline or in the placebo group from 5.3% at baseline. The between-treatment group differences were significant, p=0.009.

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, 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.

Children with growth failure secondary to CRI should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy, and it is uncertain whether these problems are affected by somatropin therapy. X-rays of the hip should be obtained prior to initiating somatropin therapy in CRI patients. Physicians and parents should be alert to the development of a limp or complaints of hip or knee pain in CRI patients treated with Nutropin AQ.

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 Nutropin AQ (and/or their parents) should be informed about the potential benefits and risks associated with Nutropin AQ 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 Nutropin AQ should receive appropriate training and instruction on the proper use of Nutropin AQ 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, and parathyroid hormone (PTH) may increase during somatropin therapy.
**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.

The use of Nutropin AQ in patients with CRI requiring glucocorticoid therapy has not been evaluated. Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Nutropin AQ. Therefore, if glucocorticoid replacement is required for CRI, the glucocorticoid dose should be carefully adjusted to avoid an inhibitory effect on growth.
There was no evidence in the controlled studies of Nutropin’s interaction with drugs commonly used in chronic renal insufficiency patients. 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, cyclosporin). 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 Nutropin AQ.

Pregnancy:

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

Nursing Mothers:

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

Geriatric Usage:

Clinical studies of Nutropin AQ 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 clinical studies of pediatric patients that were treated with Nutropin® [somatropin (rDNA origin) for injection] for the first time, 0/107 growth hormone–deficient (GHD) patients, 0/125 CRI patients, 0/112 Turner syndrome, and 0/117 ISS patients screened for antibody production developed antibodies with binding capacities ≥2 mg/L at six months. In a clinical study of patients that were treated with Nutropin AQ for the first time, 0/38 GHD patients screened for antibody production for up to 15 months developed antibodies with binding capacities ≥2 mg/L.

Additional short-term immunologic and renal function studies were carried out in a group of patients with CRI after approximately one year of treatment to detect other potential adverse effects of antibodies to GH. Testing included measurements of C1q, C3, C4, rheumatoid factor, creatinine, creatinine clearance, and BUN. No adverse effects of GH antibodies were noted.

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.

In a post-marketing surveillance study, the National Cooperative Growth Study, the pattern of adverse events in over 8000 patients with idiopathic short stature was consistent with the known safety profile of GH, and no new safety signals attributable to GH were identified. The frequency of protocol-defined targeted adverse events is described in the table, below.
### Protocol-Defined Targeted Adverse Events in the ISS NCGS Cohort

<table>
<thead>
<tr>
<th>Reported Events</th>
<th>NCGS (N=8018)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>103 (1.3%)</td>
</tr>
<tr>
<td><strong>Targeted adverse event</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>103 (1.3%)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>28 (0.3%)</td>
</tr>
<tr>
<td>New onset or progression of scoliosis</td>
<td>16 (0.2%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>12 (0.1%)</td>
</tr>
<tr>
<td>Any new onset or recurring tumor (benign)</td>
<td>12 (0.1%)</td>
</tr>
<tr>
<td>Arthralgia or arthritis</td>
<td>10 (0.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (0.1%)</td>
</tr>
<tr>
<td>Edema</td>
<td>5 (0.1%)</td>
</tr>
<tr>
<td>Cancer, neoplasm (new onset or recurrence)</td>
<td>4 (0.0%)</td>
</tr>
<tr>
<td>Fracture</td>
<td>4 (0.0%)</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>4 (0.0%)</td>
</tr>
<tr>
<td>Abnormal bone or other growth</td>
<td>3 (0.0%)</td>
</tr>
<tr>
<td>Central nervous system tumor</td>
<td>2 (0.0%)</td>
</tr>
<tr>
<td>New or recurrent SCFE or AVN</td>
<td>2 (0.0%)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>1 (0.0%)</td>
</tr>
</tbody>
</table>

AVN=avascular necrosis; SCFE=slipped capital femoral epiphysis.

Data obtained with several rhGH products (Nutropin, Nutropin AQ, Nutropin Depot and Protropin).

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Injection site discomfort has been reported. This is more commonly observed in children switched from another GH product to Nutropin AQ. Experience with Nutropin AQ in adults is limited.

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. The risk to GHD, CRI, or Turner syndrome patients, if any, remains to be established.
Other adverse drug reactions that have been reported in GH-treated patients include the following: 1) Metabolic: mild, transient peripheral edema. In GHD adults, edema or peripheral edema was reported in 41% of GH-treated patients and 25% of placebo-treated patients; 2) Musculoskeletal: arthralgias; carpal tunnel syndrome. In GHD adults, arthralgias and other joint disorders were reported in 27% of GH-treated patients and 15% of placebo-treated patients; 3) Skin: rare increased growth of pre-existing nevi; patients should be monitored for malignant transformation; and 4) Endocrine: gynecomastia. Rare pancreatitis.

**OVERDOSAGE**

Acute overdosage could lead to hyperglycemia. Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess GH. (See recommended and maximal dosage instructions given below.)

**DOSAGE AND ADMINISTRATION**

The Nutropin AQ® [somatropin (rDNA origin) injection] dosage and administration schedule should be individualized for each patient. Response to GH therapy in pediatric patients tends to decrease with time. However, in pediatric patients whose failure to increase growth rate, particularly during the first year of therapy, suggests the need for close assessment of compliance and evaluation of other causes of growth failure, such as hypothyroidism, under-nutrition, and advanced bone age.

**Dosage**

**Pediatric Growth Hormone Deficiency (GHD)**

A weekly dosage of up to 0.3 mg/kg of body weight divided into daily subcutaneous injection is recommended. In pubertal patients, a weekly dosage of up to 0.7 mg/kg divided daily may be used.

**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 more 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.

**Chronic Renal Insufficiency (CRI)**

A weekly dosage of up to 0.35 mg/kg of body weight divided into daily subcutaneous injection is recommended.

Nutropin AQ therapy may be continued up to the time of renal transplantation.

In order to optimize therapy for patients who require dialysis, the following guidelines for injection schedule are recommended:

1. Hemodialysis patients should receive their injection at night just prior to going to sleep or at least 3-4 hours after their hemodialysis to prevent hematoma formation due to the heparin.

2. Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in the morning after they have completed dialysis.

3. Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection in the evening at the time of the overnight exchange.

**Turner Syndrome**

A weekly dosage of up to 0.375 mg/kg of body weight divided into equal doses 3 to 7 times per week by subcutaneous injection is recommended.
Idiopathic Short Stature (ISS)

A weekly dosage of up to 0.3 mg/kg of body weight divided into daily subcutaneous injection has been shown to be safe and efficacious, and is recommended.

Administration

The solution should be clear immediately after removal from the refrigerator. Occasionally, after refrigeration, you may notice that small colorless particles of protein are present in the solution. This is not unusual for solutions containing proteins. Allow the vial or pen cartridge to come to room temperature and gently swirl. If the solution is cloudy, the contents MUST NOT be injected.

For Nutropin AQ® Vial

Before needle insertion, wipe the septum of the Nutropin AQ vial with rubbing alcohol or an antiseptic solution to prevent contamination of the contents by microorganisms that may be introduced by repeated needle insertions. It is recommended that Nutropin AQ be administered using sterile, disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

For Nutropin AQ Pen® 10 mg Cartridge

The Nutropin AQ Pen® 10 mg Cartridge must be used with its corresponding color-coded Nutropin AQ Pen® 10. The Nutropin AQ Pen® 10 mg Cartridge must not be inserted into a pen with a different color code.

Wipe the septum of the Nutropin AQ pen cartridge with rubbing alcohol or an antiseptic solution to prevent contamination of the contents by microorganisms that may be introduced by repeated needle insertions. It is recommended that Nutropin AQ be administered using sterile, disposable needles. Follow the directions provided in the Nutropin AQ Pen® Instructions for Use.

The Nutropin AQ Pen® 10 allows for administration of a minimum dose of 0.1 mg to a maximum dose of 4.0 mg, in 0.1 mg increments.

For Nutropin AQ® NuSpin™ 5
The Nutropin AQ NuSpin 5 is a multi-dose, dial-a-dose injection device pen prefilled with Nutropin AQ® [somatropin (rDNA origin) injection] in a 5 mg/2mL cartridge for subcutaneous use. It is recommended that Nutropin AQ be administered using sterile, disposable needles. Follow the directions provided in the Nutropin AQ® NuSpin™ 5 Instructions for Use.

The Nutropin AQ NuSpin 5 allows for administration of a minimum dose of 0.05 mg to a maximum dose of 1.75 mg, in increments of 0.05 mg.

For Nutropin AQ® NuSpin™ 10

The Nutropin AQ NuSpin 10 is a multi-dose, dial-a-dose injection device prefilled with Nutropin AQ® [somatropin (rDNA origin) injection] in a 10 mg/2mL cartridge for subcutaneous use. It is recommended that Nutropin AQ be administered using sterile, disposable needles. Follow the directions provided in the Nutropin AQ® NuSpin™ 10 Instructions for Use.

The Nutropin AQ NuSpin 10 allows for administration of a minimum dose of 0.1 mg to a maximum dose of 3.5 mg, in increments of 0.1 mg.

For Nutropin AQ® NuSpin™ 20

The Nutropin AQ NuSpin 20 is a multi-dose, dial-a-dose injection device pen prefilled with Nutropin AQ® [somatropin (rDNA origin) injection] in a 20 mg/2mL cartridge for subcutaneous use. It is recommended that Nutropin AQ be administered using sterile, disposable needles. Follow the directions provided in the Nutropin AQ® NuSpin™ 20 Instructions for Use.

The Nutropin AQ NuSpin allows for administration of a minimum dose of 0.2 mg to a maximum dose of 7.0 mg, in increments of 0.2 mg.

For Nutropin AQ Pen® 20 mg Cartridge

The Nutropin AQ Pen® 20 mg Cartridge must be used with its corresponding color-coded Nutropin AQ Pen® 20. The Nutropin AQ Pen® 20 mg Cartridge must not be inserted into a pen with a different color code.
Wipe the septum of the Nutropin AQ pen cartridge with rubbing alcohol or an antiseptic solution to prevent contamination of the contents by microorganisms that may be introduced by repeated needle insertions. It is recommended that Nutropin AQ be administered using sterile, disposable needles. Follow the directions provided in the Nutropin AQ Pen 

The Nutropin AQ Pen 20 allows for administration of a minimum dose of 0.2 mg to a maximum dose of 8.0 mg, in 0.2 mg increments.

**STABILITY AND STORAGE**
Vial, cartridge, and Nutropin AQ NuSpin contents are stable for 28 days after initial use when stored at 2–8°C/36–46°F (under refrigeration). Avoid freezing Nutropin AQ in the vial, cartridge, or NuSpin injection device. Nutropin AQ is light sensitive and the vial, cartridges, and Nutropin AQ NuSpin should be protected from light. Store the vial, cartridge, and Nutropin AQ NuSpin refrigerated in a dark place when they are not in use.

**HOW SUPPLIED**
Nutropin AQ® [somatropin (rDNA origin) injection] is supplied as either 10 mg (approximately 30 International Units) of sterile liquid somatropin per vial, a 10 mg (approximately 30 International Units) of sterile liquid somatropin per pen cartridge, or a 20 mg (approximately 60 International Units) of sterile liquid somatropin per pen cartridge, or as 5 mg (approximately 15 International Units) of sterile liquid somatropin per Nutropin AQ NuSpin 5, or as 10 mg (approximately 30 International Units) of sterile liquid somatropin per Nutropin AQ NuSpin 10, or as 20 mg (approximately 60 International Units) of sterile liquid somatropin per Nutropin AQ NuSpin 20.

Each vial carton contains one single vial containing 2 mL of Nutropin AQ® [somatropin (rDNA origin) injection] 10 mg/2 mL (5 mg/mL). NDC 50242-022-20.

Each 10 mg pen cartridge carton contains one single pen cartridge containing 2 mL of Nutropin AQ® [somatropin (rDNA origin) injection] 10 mg/2 mL (5 mg/mL).

NDC 50242-043-14.
Each 20 mg pen cartridge carton contains one single pen cartridge containing 2 mL of Nutropin AQ® [somatropin (rDNA origin) injection] 20 mg/2 mL (10 mg/mL).

NDC 50242-073-01.

Each Nutropin AQ NuSpin 5 carton contains one single Nutropin AQ NuSpin injection device prefilled with a cartridge containing 2 mL of Nutropin AQ® [somatropin (rDNA origin) injection] 5 mg/2 mL (2.5 mg/mL).

NDC 50242-075-01.

Each Nutropin AQ NuSpin 10 carton contains one single Nutropin AQ NuSpin injection device prefilled with a cartridge containing 2 mL of Nutropin AQ® [somatropin (rDNA origin) injection] 10 mg/2 mL (5 mg/mL).

NDC 50242-074-01.

Each Nutropin AQ NuSpin 20 carton contains one single Nutropin AQ NuSpin injection device prefilled with a cartridge containing 2 mL of Nutropin AQ® [somatropin (rDNA origin) injection] 20 mg/2 mL (10 mg/mL).

NDC 50242-076-01.

Nutropin AQ® [somatropin (rDNA origin) injection]
Manufactured by: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080–4990
NDA 20-522/S-026 Labeling
Pen Case Label

Nutropin AQ Pen 20
Storage: With a Nutropin AQ Pen 20 mg Cartridge inserted, refrigerate at 2-8°C (36-46°F). Do not freeze. Protect from light.
Genentech
4832500
Part IV: Commonly Asked Questions

Q: Do I need to change the needle every time I use my Nutropin AQ Pen?
A: Yes. We recommend that a new needle be used for every injection. The needle is only sterile on the first use.

Q: Where should I store my Nutropin AQ Pen?
A: Your Nutropin AQ Pen should be stored in the glass container provided in the refrigerator at 2-8°C (35-46°F) for up to 30 days in unopened blister packs. The glass container can be used in the refrigerator or a cooler while traveling. Always place your pen case in a cooler. DO NOT FREEZE. KEEP DRY.

Q: Why do I keep my medication in the refrigerator?
A: To maintain the potency of Nutropin AQ.

Q: Can I store my Nutropin AQ Pen in the freezer?
A: No. Freezing will damage the pen and drug.

Q: How long can I keep my Nutropin AQ Pen and Cartridge outside the refrigerator?
A: We recommend no longer than one hour. Your healthcare provider will advise you regarding pen storage.

Q: What is the maximum dose of Nutropin AQ that can deliver in one injection?
A: The maximum dose that may be delivered in one injection depends on the strength of the Nutropin AQ Pen and Cartridge that you are using. The maximum dose that may be delivered in one injection is 40 clicks, which equals 4 mg for the Nutropin AQ Pen 10 mg or Nutropin AQ Pen 20 mg.

Q: Is it possible to turn the black dose knob back if I click too many times?
A: Yes. You can turn the black dose knob backwards until the correct amount appears in the LCD.

Q: What should I do if there is not enough medication left in the cartridge to meet my dosing requirements?
A: Your healthcare provider will advise you on the procedure for the last dose in the cartridge.

Q: Why do I have to rewind the black dose knob on my Nutropin AQ Pen every time I replace the cartridge?
A: This ensures that the plunger push rod completely resets itself back to the starting position. If this is not done, liquid will come out of the needle when a new cartridge is placed into the pen.

Q: Can I use my Nutropin AQ Pen without the shields?
A: Yes. Your Nutropin AQ Pen is fully functional without the shields. The shields are optional to help you administer your injection.

Q: Where is the best place to inject my medication?
A: Consult your healthcare provider for proper injection sites.

Q: What should I do if I drop my Nutropin AQ Pen?
A: If you drop the Nutropin AQ Pen, check to see if the cartridge is damaged. You should also check the pen to see if the black dose knob is moving up and down properly and that the LCD counter is working. If you discover damage to your cartridge or pen, notify your healthcare provider/distributor for a replacement.

Q: How long can I use my Nutropin AQ Pen?
A: The Nutropin AQ Pen is designed to last approximately 24 months from the time you first use your pen.

Q: What does “bt” (blinking or steady) mean in the LCD?
A: The battery in your Nutropin AQ Pen is losing its charge. Please contact your healthcare provider/distributor for a replacement pen. Batteries typically last 24 months and have a 4-week life from the time the “bt” first appears.

Q: How do I replace my Nutropin AQ Pen?
A: Contact your healthcare provider/distributor if you need a replacement part or if you need to replace your entire pen.

Q: How do I use the dose recall function?
A: If you would like to use the dose recall function for subsequent injections, wait at least 2 minutes after your previous injection before pressing the white reset button.

Q: Is the Nutropin AQ Pen waterproof?
A: No. Exposure to moisture may cause the Nutropin AQ Pen’s LCD display to malfunction. Do not immerse the Nutropin AQ Pen in water. If the Nutropin AQ Pen is accidentally immersed, remove it from the water and dry it immediately.

Q: What does it mean when either three or six bars flash or appear steady on the digital display?
A: When this occurs, it means this pen has been used for 2 years and should be replaced. Your pen has 4 weeks of life remaining from the time that the flashing bars first appear. Ask your healthcare provider for a replacement Nutropin AQ Pen.

In the unlikely event your Nutropin AQ Pen comes with the following:
- Alcohol wipes
- Pen needles
- Active shield
- Passive shield

Your Nutropin AQ Pen Cartridges are supplied separately.

To guard against the spread of infection, follow these safety measures:
- Wash your hands before using your pen.
- Clean the cartridge rubber seal with an alcohol swab.
- Avoid touching the cartridge rubber seal at all times.
- If you unintentionally touch the rubber seal, clean it with an alcohol swab.
- Use needles only once.
- Do not use the same needle for more than one person.
Part I: Preparing and Injecting

Follow the instructions in this section if you are using the pen for the first time or are replacing an empty cartridge.

Prior to use, always check to make sure that you are using your prescribed strength Nutropin AQ Pen® Cartridge (somatropin (rDNA origin) injection) (10 mg or 20 mg) and the corresponding Nutropin AQ Pen for that cartridge. Inspect all new cartridges prior to use. If the solution is cloudy or contains any solid matter, the cartridge should not be used.

1. Remove the green pen cap and unscrew the cartridge holder from the pen. If necessary, remove the empty cartridge and discard it properly.

2. Press the white reset button.

3. Turn the black dose knob counterclockwise back to its starting position until it no longer turns. (See illustration.) Then turn the dose knob clockwise until the first click position is reached (approximately 1/8 turn). This ensures that the plunger push rod is reset to the starting position. If this is not done when the dosage knob is first depressed, Nutropin AQ will be wasted or the cartridge may crack.

4. Make sure that your cartridge and your Nutropin AQ Pen are the same strength (10 mg cartridge and 10 mg pen or 20 mg cartridge and 20 mg pen). Insert cartridge into the cartridge holder, then screw the cartridge holder back onto the pen. (Be careful not to touch the rubber seal.)

5. Remove the paper seal from a new needle assembly and screw it onto the cartridge holder.

6. Carefully remove both protective caps from the needle by pulling gently. Do not throw the larger cap away as it will be used later for proper needle removal and disposal.

7. Holding the pen with the needle pointing upward, gently tap the cartridge holder to move any air bubbles to the top. While still holding the pen in the upright position, push in the black dose knob until it locks into position. You should see a drop of medicine appear. Be patient. If medicine doesn’t appear within a few seconds, you may need to press the reset button again.

8. If no drop of medicine appears, push the white reset button again. Now turn the black dose knob clockwise (see illustration) by one click, which equals:
0.1 mg for the Nutropin AQ Pen 10 mg
0.2 mg for the Nutropin AQ Pen 20 mg
If you accidently turn it too far, go back one click.

9. While still holding the pen in the upright position, push in the black dose knob again and watch the needle tip for a drop of medicine to appear. Repeat steps 8 and 9 until it appears.

10. Press the white reset button.

11. Set the required dose by turning the black dose knob. If you cannot dial the full dose, either start a new cartridge (as described in Part I), or administer the partial dose. Then, start a new cartridge (as described in Part I) to administer the remaining portion of your medication. Your healthcare provider will advise you on the procedure for administering the last dose in the cartridge.

Prepare the injection site by wiping with an alcohol wipe. Injection sites include the upper arms, abdomen, and upper thighs. Rotate the injection sites to avoid discomfort.

12. If you are using the passive shield (or no shield), proceed to step 13. If you are using the active shield, slide the shield onto the pen, and push the 2 black lock knobs on the needle shield toward the tip.

13. Set the tip of the pen on the prepared injection site, and press the needle into the skin by pushing the pen downward until the shield is totally depressed. Your healthcare provider will show you how to do this. Now you are ready to administer the dose. Press down on the black dose knob until it locks in place. Wait 5 seconds then withdraw the needle from the skin.

14. Pull the needle shield off the pen (if applicable) and place the larger needle cap on a flat surface. Slide the needle in to pick it up and push the cap completely down over the needle. Twist off the needle and discard it properly.

15. Attach the pen cap and return it to its case with the black dose knob pressed in. You should always store the pen in a refrigerator. Do not remove cartridge between injections. DO NOT FREEZE.

Part II: Storage and Maintenance

Follow these tips to ensure proper care of your Nutropin AQ Pen:

• Do not immerse the Nutropin AQ Pen in water or expose to moisture.

• If your pen requires cleaning, do not place underwater. Use a damp cloth to wipe away dirt. Do not use alcohol.

• Always keep your Nutropin AQ Pen and Cartridge refrigerated and protected from light when not in use.

• You may remove the pen and cartridge from the refrigerator up to 45 minutes prior to use.

• Do not let your Nutropin AQ Pen and/or Cartridge freeze. Contact your healthcare provider/distributor for a replacement if either the pen or cartridge malfunctions.

• Avoid excessive temperatures. Cartridge contents are stable for 28 days after first use when stored at 2–8°C/36–46°F.

• When priming a new cartridge, you may need to repeat Part I, steps 8 and 9, up to a total of 6 times to remove air bubbles. Small bubbles may remain and will not affect the dose.

• The pen should contain the Nutropin AQ Pen Cartridge that is being used. Do not remove cartridge between injections.

• Do not store the Nutropin AQ Pen with needle attached.

Part III: Needles for the Nutropin AQ Pen

Your healthcare provider will recommend a needle that is appropriate for you. The following needle is provided by Genentech, Inc. in your Nutropin AQ Pen kit:

<table>
<thead>
<tr>
<th>Name</th>
<th>Gauge</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD Ultra-Fine™ (Original)</td>
<td>29 g</td>
<td>12.7 mm</td>
</tr>
</tbody>
</table>

Needles from other regions or countries may not fit on your Nutropin AQ Pen. If you travel outside the United States, make sure you take enough needles for the duration of your stay.

Nutropin AQ Pen Components:

Listed below are the components necessary for giving an injection. Gather all of these components prior to use.

- Pen cap
- Black lock knob
- Digital dose display
- Active needle shield (if applicable)
- Passive needle shield (if applicable)
- Cartridge holder
- Black dose knob
- Needle assembly
- Nutropin AQ Pen Cartridge

For subsequent injections with the Nutropin AQ Pen, attach a new needle, push the white reset button, and dial your dose. If you would like to use the dose recall function for subsequent injections, wait at least 2 minutes after your previous injection before pressing the white reset button.
NDA 20-522/S-036 Labeling
Nutropin Aq® NuSpin 10
[somatropin (rDNA origin) injection]
10 mg/2 mL (5 mg/mL)

DO NOT FREEZE. Store at 2–8°C (36–46°F). PROTECT FROM LIGHT. For subcutaneous use. Rx only

Genentech, Inc.  So. San Francisco, CA 94080-4990
INSTRUCTIONS FOR USE

Description: The Nutropin AQ NuSpin 10 is a multi-dose, dial-a-dose injection device prefilled with Nutropin AQ [somatropin (rDNA origin) injection] for subcutaneous use. It features automatic injection of the drug and is disposable. The Nutropin AQ NuSpin 10 (Teal Color, 10 mg/2 mL) delivers doses from 0.1 to 3.5 mg in increments of 0.1 mg.

Intended Use: The Nutropin AQ NuSpin 10 is intended to be used by a healthcare professional or patient to deliver Nutropin AQ [somatropin (rDNA origin) injection] from an injection device. The device can be used in any setting, including the home, and is disposable.

IMPORTANT NOTES

• Always follow the directions of your healthcare professional and the instructions provided on the back. Contact your healthcare professional if you have any questions.
• Check the label on the NuSpin 10 to make sure the medicine matches your prescription and it has not expired.
• Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject. Return the NuSpin 10 to your healthcare professional.
• Store your NuSpin 10 inside the refrigerator at 2–8°C (36–46°F). Protect from light.
• The product can be used for 28 days after it has been primed and kept under proper storage conditions.
• For the first use of each NuSpin 10, always follow the New NuSpin 10 Set Up Instructions to ensure that air is expelled from the cartridge.
• Do not store with the needle attached. The needle should be removed and safely disposed of immediately after use.

FREQUENTLY ASKED QUESTIONS

1. What type of needles should be used?
   Your healthcare professional will recommend a needle that is appropriate for you. If you use the optional needle shield with your NuSpin 10, we recommend needles 8 mm (5/16”) or longer to provide adequate needle length during usage. Needles from other countries may not fit on your NuSpin 10. If you travel outside the United States, make sure you take enough needles for the duration of your stay.

2. Do I need to change the needle every time I use my Nutropin AQ NuSpin?
   Yes. A new needle must be used for every injection. The needle is sterile only for one single injection.

3. Do I need to prime the Nutropin AQ NuSpin each time?
   No. The NuSpin 10 only needs to be primed once, at first use. After the first use of each NuSpin 10, follow the instructions and skip Step 2.

4. When and how do I dispose of my Nutropin AQ NuSpin?
   Your NuSpin 10 is prefilled and the cartridge cannot be replaced. When your NuSpin 10 is empty, dispose of the entire NuSpin 10 as instructed by your healthcare professional. If the empty NuSpin 10 is disposed of with the needle attached, discard the entire device using the same procedure as for needle disposal.

5. Where should I store my Nutropin AQ NuSpin?
   When not in use, your NuSpin 10 should be stored inside a refrigerator at 2–8°C (36–46°F) to maintain the potency of Nutropin AQ [somatropin (rDNA origin) injection]. During use, we recommend that you have your NuSpin 10 outside of the refrigerator for no longer than one hour per day. When traveling, place your NuSpin 10 in a water-resistant container before placing in a cooler. DO NOT FREEZE. KEEP DRY.

6. What should I do if my Nutropin AQ NuSpin is dropped or damaged?
   If you drop the NuSpin 10, check to see if it is damaged. You should also check to see that the black dose knob and the Activator are moving properly. If you notice the NuSpin 10 is damaged, contact your healthcare professional or call 1-866-NUTROPIN for advice.

7. What should I do if my Nutropin AQ NuSpin needs cleaning?
   Use a damp cloth to wipe away dirt. Do not place underwater. Do not use alcohol.

Please see other side for additional instructions.
NEW NuSpin 10 SET UP: STEP-BY-STEP INSTRUCTIONS FOR THE FIRST USE OF EACH NEW NUTROPIN AQ NuSpin

STEP 1: Attach the needle
Before you begin, wash your hands. Twist gently and pull to remove the NuSpin 10 cap. Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject. Open a new needle by peeling off the tab from the needle package.

STEP 2: Prime the Nutropin AQ NuSpin
If your dose is “between” two numbers in the dose window, the – between those two numbers indicates your dose. Turn the dose knob to – . The position indicates a 0.7 mg dose on your NuSpin 10. If you turn the dose knob too far, simply turn it back to the correct dose. (Example above shows a dose of 0.1 mg, represented by – .)

STEP 3: Set the dose
If your dose is “between” two numbers in the dose window, the – between those two numbers indicates your dose. Turn the dose knob to – . The position indicates a 0.7 mg dose on your NuSpin 10. If you turn the dose knob too far, simply turn it back to the correct dose. (Example above shows a dose of 0.1 mg, represented by – .)

STEP 4: Give the injection
If your dose is “between” two numbers in the dose window, the – between those two numbers indicates your dose. Turn the dose knob to – . The position indicates a 0.7 mg dose on your NuSpin 10. If you turn the dose knob too far, simply turn it back to the correct dose. (Example above shows a dose of 0.1 mg, represented by – .)

Checking dose given
If the dose knob stops before it returns to 0.0 , your Nutropin AQ NuSpin 10 is empty and you have not received your full dose. The number shown in the dose window is the amount needed to obtain a full dose. Your healthcare professional will advise you on the procedure for using the last dose in the NuSpin 10.

REMOVAL AND DISPOSAL OF THE NEEDLE
Carefully place the outer cover of the needle package over the needle, unscrew, and dispose of it as instructed by your healthcare professional. If you are using the needle shield, refer to the detailed instructions included with the shield for removing and disposing of the needle. KEEP YOUR SHIELD FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.

STORAGE AND NEXT USE
Replace the cap and store your NuSpin 10 inside the refrigerator at 2–8°C (36–46°F). Protect from light. For the next use, it is already primed. Follow the instructions and skip Step 2.
Contents:

One Nutropin AQ® ZOOM™ 10, Instructions for Use, and Package Insert. Each Nutropin AQ® ZOOM™ 10 contains 10 mg (approximately 30 IU) of Nutropin AQ® [somatropin (rDNA origin) injection] formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate in 2 mL (5 mg/mL).

Usage and Administration:

For subcutaneous use. See enclosed Full Prescribing Information and Instructions for Use.

Storage:

Refrigerate at 2–8ºC (36–46ºF). DO NOT FREEZE. PROTECT FROM LIGHT.

Components:

- Needle Holder
- Cartridge Holder
- Dose Window
- Dose Knob
- Activator
- Cap
NDA 20-522/S-037 Labeling
DO NOT FREEZE. Store at 2–8°C (36–46°F).
PROTECT FROM LIGHT.

Nutropin NuSpin™
5 mg/2 mL (2.5 mg/mL)

Genentech, Inc.
So. San Francisco, CA 94080-4990

Rx only
INSTRUCTIONS FOR USE

Description: The Nutropin AQ NuSpin 5 is a multi-dose, dial-a-dose injection device prefilled with Nutropin AQ [somatropin (rDNA origin) injection] for subcutaneous use. It features automatic injection of the drug and is disposable. The Nutropin AQ NuSpin 5 (Clear Color, 5 mg/2 mL) delivers doses from 0.05 to 1.75 mg in increments of 0.05 mg.

Intended Use: The Nutropin AQ NuSpin 5 is intended to be used by a healthcare professional or patient to deliver Nutropin AQ [somatropin (rDNA origin) injection] from an injection device. The device can be used in any setting, including the home, and is disposable.

IMPORTANT NOTES

- Always follow the directions of your healthcare professional and the instructions provided on the back. Contact your healthcare professional if you have any questions.
- Check the label on the NuSpin 5 to make sure the medicine matches your prescription and it has not expired.
- Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject. Return the NuSpin 5 to your healthcare professional.
- Store your NuSpin 5 inside the refrigerator at 2–8°C (36–46°F). Protect from light.
- The product can be used for 28 days after it has been primed and kept under proper storage conditions.
- For the first use of each NuSpin 5, always follow the New NuSpin 5 Set Up Instructions to ensure that air is expelled from the cartridge.
- Do not store with the needle attached. The needle should be removed and safely disposed of immediately after use.

FREQUENTLY ASKED QUESTIONS

1. What type of needles should be used?
   Your healthcare professional will recommend a needle that is appropriate for you. If you use the optional needle shield with your NuSpin 5, we recommend needles 8 mm (5/16") or longer to provide adequate needle length during usage. Needles from other countries may not fit on your NuSpin 5. If you travel outside the United States, make sure you take enough needles for the duration of your stay.

2. Do I need to change the needle every time I use my Nutropin AQ NuSpin?
   Yes. A new needle must be used for every injection. The needle is sterile only for one single injection.

3. Do I need to prime the Nutropin AQ NuSpin each time?
   No. The NuSpin 5 only needs to be primed once, at first use. After the first use of each NuSpin 5, follow the instructions and skip Step 2.

4. When and how do I dispose of my Nutropin AQ NuSpin?
   Your NuSpin 5 is prefilled and the cartridge cannot be replaced. When your NuSpin 5 is empty, dispose of the entire NuSpin 5 as instructed by your healthcare professional. If the empty NuSpin 5 is disposed of with the needle attached, discard the entire device using the same procedure as for needle disposal.

5. Where should I store my Nutropin AQ NuSpin?
   When not in use, your NuSpin 5 should be stored inside a refrigerator at 2–8°C (36–46°F) to maintain the potency of Nutropin AQ [somatropin (rDNA origin) injection]. During use, we recommend that you have your NuSpin 5 outside of the refrigerator for no longer than one hour per day. When traveling, place your NuSpin 5 in a water-resistant container before placing in a cooler. 
   DO NOT FREEZE. KEEP DRY.

6. What should I do if my Nutropin AQ NuSpin is dropped or damaged?
   If you drop the NuSpin 5, check to see if it is damaged. You should also check to see that the black dose knob and the Activator are moving properly. If you notice the NuSpin 5 is damaged, contact your healthcare professional or call 1-866-NUTROPIN for advice.

7. What should I do if my Nutropin AQ NuSpin needs cleaning?
   Use a damp cloth to wipe away dirt. Do not place underwater. Do not use alcohol.

Genentech, Inc.
1 DNA Way, South San Francisco, CA 94080-4990
Revision Date MMM/YYYY
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Please see other side for additional instructions.
NEW NuSpin 5 SET UP: STEP-BY-STEP INSTRUCTIONS FOR THE FIRST USE OF EACH NEW NUTROPIN AQ NuSpin 5

STEP 1: Attach the needle

Before you begin, wash your hands. Twist gently and pull to remove the NuSpin 5 cap. Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject. Open a new needle by peeling off the paper tab from the needle package.

STEP 2: Prime the Nutropin AQ NuSpin

Attach the needle by carefully screwing the needle onto the needle holder. Do not overtighten. Remove both protective covers from the needle and save the outer cover. Turn the dose knob to the \( P \) position in the dose window. It may take multiple clicks to get to \( P \). Hold the NuSpin 5 with the needle pointing upwards. Gently tap the cartridge holder to move any air bubbles to the NuSpin 5 tip.

STEP 3: Set the dose

Make sure the dose window reads \( 0.0 \). Turn the dose knob until the dose prescribed by your healthcare professional appears in the dose window.

STEP 4: Give the injection

Select and prepare your injection site as instructed by your healthcare professional. Position your hand so you can easily slide the Activator. Push the needle into the skin. If you are using the needle shield, refer to the instructions provided with the shield.

Check dose given

If your dose is “between” two numbers in the dose window, the \( \bullet \) between those two numbers indicates your dose. Turn the dose knob to \( \bullet \). The \( \bullet \) position indicates a 0.35 mg dose on your NuSpin 5. If you turn the dose knob too far, simply turn it back to the correct dose. (Example above shows a dose of 0.05 mg, represented by \( \bullet \).)

If the dose knob stops before it returns to \( 0.0 \), your Nutropin AQ NuSpin 5 is empty and you have not received your full dose. The number shown in the dose window is the amount needed to obtain a full dose. If you do not see fluid at the needle tip, redial to \( P \) and slide the Activator forward again. Repeat until you see fluid.

If the dose knob returns to \( 0.0 \), you have received your full dose.

Optional step: Attach the needle shield

Use of the needle shield is optional. It may be obtained from your healthcare professional. Refer to the detailed instructions provided with the shield and attach it now.

Removal and disposal of the needle

Carefully place the outer cover of the needle package over the needle, unscrew, and dispose of it as instructed by your healthcare professional. If you are using the needle shield, refer to the detailed instructions included with the shield for removing and disposing of the needle. KEEP YOUR SHIELD FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.

Storage and next use

Replace the cap and store your NuSpin 5 inside the refrigerator at 2–8°C (36–46°F). Protect from light. For the next use, it is already primed. Follow the instructions and skip Step 2.
Contents: One Nutropin AQ® NuSpin™ 5, Instructions for Use, and Package Insert. Each Nutropin AQ® NuSpin™ 5 contains 5 mg (approximately 15 IU) of Nutropin AQ® (somatropin (rDNA origin) injection) formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate in 2 mL (2.5 mg/mL).

Usage and Administration: For subcutaneous use. Your healthcare professional will recommend a needle that is appropriate for you (needles not included). See enclosed Package Insert and Instructions for Use.

Storage: Refrigerate at 2–8°C (36–46°F). DO NOT FREEZE. PROTECT FROM LIGHT.
Nutropin AQ® NuSpin™ 20
[somatropin (rDNA origin) injection] 20 mg/2 mL

100%

300%
Nutropin AQ® NuSpin™ 20
[somatropin (rDNA origin) injection]
20 mg/2 mL (10 mg/mL)

DO NOT FREEZE. Store at 2–8°C (36–46°F).
PROTECT FROM LIGHT. For subcutaneous use.  Rx only

Genentech, Inc.  So. San Francisco, CA 94080-4990
INSTRUCTIONS FOR USE

Description: The Nutropin AQ NuSpin 20 is a multi-dose, dial-a-dose injection device prefilled with Nutropin AQ (somatropin (rDNA origin) injection) for subcutaneous use. It features automatic injection of the drug and is disposable. The Nutropin AQ NuSpin 20 (Blue Color, 20 mg/2 mL) delivers doses from 0.2 to 7.0 mg in increments of 0.2 mg.

Intended Use: The Nutropin AQ NuSpin 20 is intended to be used by a healthcare professional or patient to deliver Nutropin AQ (somatropin (rDNA origin) injection) from an injection device. The device can be used in any setting, including the home, and is disposable.

IMPORTANT NOTES

- Always follow the directions of your healthcare professional and the instructions provided on the back. Contact your healthcare professional if you have any questions.
- Check the label on the NuSpin 20 to make sure the medicine matches your prescription and it has not expired.
- Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject. Return the NuSpin 20 to your healthcare professional.
- Store your NuSpin 20 inside the refrigerator at 2–8°C (36–46°F). Protect from light.
- The product can be used for 28 days after it has been primed and kept under proper storage conditions.
- For the first use of each NuSpin 20, always follow the New NuSpin 20 Set Up Instructions to ensure that air is expelled from the cartridge.
- Do not store with the needle attached.
- The needle should be removed and safely disposed of immediately after use.

FREQUENTLY ASKED QUESTIONS

1. What type of needles should be used?
   Your healthcare professional will recommend a needle that is appropriate for you. If you use the optional needle shield with your NuSpin 20, we recommend needles 8 mm (5/16”) or longer to provide adequate needle length during usage. Needles from other countries may not fit on your NuSpin 20. If you travel outside the United States, make sure you take enough needles for the duration of your stay.

2. Do I need to change the needle every time I use my Nutropin AQ NuSpin?
   Yes. A new needle must be used for every injection. The needle is sterile only for one single injection.

3. Do I need to prime the Nutropin AQ NuSpin each time?
   No. The NuSpin 20 only needs to be primed once, at first use. After the first use of each NuSpin 20, follow the instructions and skip Step 2.

4. When and how do I dispose of my Nutropin AQ NuSpin?
   Your NuSpin 20 is prefilled and the cartridge cannot be replaced. When your NuSpin 20 is empty, dispose of the entire NuSpin 20 as instructed by your healthcare professional. If the empty NuSpin 20 is disposed of with the needle attached, discard the entire device using the same procedure as for needle disposal.

5. Where should I store my Nutropin AQ NuSpin?
   When not in use, your NuSpin 20 should be stored inside a refrigerator at 2–8°C (36–46°F) to maintain the potency of Nutropin AQ (somatropin (rDNA origin) injection). During use, we recommend that you have your NuSpin 20 outside of the refrigerator for no longer than one hour per day. When traveling, place your NuSpin 20 in a water-resistant container before placing in a cooler. DO NOT FREEZE. KEEP DRY.

6. What should I do if my Nutropin AQ NuSpin is dropped or damaged?
   If you drop the NuSpin 20, check to see if it is damaged. You should also check to see that the black dose knob and the Activator are moving properly. If you notice the NuSpin 20 is damaged, contact your healthcare professional or call 1-866-NUTROPIN for advice.

7. What should I do if my Nutropin AQ NuSpin needs cleaning?
   Use a damp cloth to wipe away dirt. Do not place underwater. Do not use alcohol.

Please see other side for additional instructions.
NEW NuSpin 20 SET UP: STEP-BY-STEP INSTRUCTIONS FOR THE FIRST USE OF EACH NEW NUTROPIN AQ NuSpin 20

STEP 1: Attach the needle

Before you begin, wash your hands. Twist gently and pull to remove the NuSpin 20 cap. Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject. Open a new needle by peeling off the paper tab from the needle package.

STEP 2: Prime the Nutropin AQ NuSpin

If your dose is “between” two numbers in the dose window, the – • between those two numbers indicates your dose. Turn the dose knob to – •. The • position indicates a 1.4 mg dose on your NuSpin 20. If you turn the dose knob too far, simply turn it back to the correct dose. (Example above shows a dose of 0.2 mg, represented by • – •.)

STEP 3: Set the dose

Make sure the dose window reads • 0.0 •. Turn the dose knob until the dose prescribed by your healthcare professional appears in the dose window.

STEP 4: Give the injection

Select and prepare your injection site as instructed by your healthcare professional. Position your hand so you can easily slide the Activator. Push the needle into the skin. If you are using the needle shield, refer to the instructions provided with the shield.

If the dose knob stops before it returns to • 0.0 •, your Nutropin AQ NuSpin 20 is empty and you have not received your full dose. The number shown in the dose window is the amount needed to obtain a full dose. Your healthcare professional will advise you on the procedure for using the last dose in the NuSpin 20.

REMOVAL AND DISPOSAL OF THE NEEDLE

Carefully place the outer cover of the needle package over the needle, unscrew, and dispose of it as instructed by your healthcare professional. If you are using the needle shield, refer to the detailed instructions included with the shield for removing and disposing of the needle. **KEEP YOUR SHIELD FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.**

STORAGE AND NEXT USE

Replace the cap and store your NuSpin 20 inside the refrigerator at 2–8°C (36–46°F). Protect from light. For the next use, it is already primed. Follow the instructions and skip Step 2.
Contents: Each Nutropin AQ® NuSpin™ 20 contains 20 mg (approximately 60 IU) of Nutropin AQ® (somatropin (rDNA origin) injection) formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate in 2 mL (10 mg/mL).

Usage and Administration: For subcutaneous use. Your healthcare professional will recommend a needle that is appropriate for you (needles not included). See enclosed Package Insert and Instructions for Use.

Storage: Refrigerate at 2–8ºC (36–46ºF). DO NOT FREEZE. PROTECT FROM LIGHT.
Needle Shield for use with Nutropin® NuSpin™
[somatropin (rDNA origin) injection]

See enclosed Instructions for Use

Contents: 1 Needle Shield and Instructions for Use
Recommended: Use needle shield with needles
8 mm (5/16") or longer
AC/0424/14/0000/01

List# NNNNNN Lot# NNNN EXP Date
**STEP 3: Attach the needle shield**

Make sure the shield is in the locked position with the slide lock in line with the arrow. Align the shield so the slide lock is in line with the Activator. Attach the shield by pushing it directly onto the NuSpin, without twisting. The shield will be in the locked position with the needle cover completely visible. It will need to be unlocked prior to injection.

**STEP 4: Set the dose**

Make sure the dose window reads 0.0. Turn the dose knob to the dose prescribed by your healthcare professional until it appears in the dose window.

If your dose is “between” two numbers in the dose window, the number between those two numbers indicates your dose. Turn the dose knob to the number. If you turn the dose knob too far, simply turn it back to the correct dose.

**STEP 5: Give the injection**

Select and prepare your injection site as instructed by your healthcare professional. Hold the needle shield in place with your dominant hand. Set the tip of the needle cover flat on the prepared injection site. Without touching the Activator or slide lock, position your hand so you can easily reach the Activator. Push the needle into the skin by pushing the NuSpin downward until the needle cover is fully depressed and the needle is in the skin. SLIDE the Activator toward the needle. Continue to hold the Activator down until the dose knob returns to 0.0 and hold in place for another 5 seconds. Withdraw the NuSpin until the needle is removed from the skin.

**STEP 5 (cont’d): Check dose given**

If the dose knob returns to 0.0, you have received your full dose. If the dose knob stops before it returns to 0.0, your NuSpin is empty and you have not received your full dose.

The number shown in the dose window is the amount needed to obtain a full dose. Your healthcare professional will advise you on the procedure for the last dose in the NuSpin.

Place the outer cover of the needle package on a flat surface. Hold the shield by grasping the finger grips firmly in one hand. Carefully pull the shield away from the NuSpin body, as pictured.

**Removing the Shield from the NuSpin**

Carefully place the outer cover of the needle package over the needle, unscrew, and dispose of it as instructed by your healthcare professional.

**KEEPS YOUR SHIELD AND THESE INSTRUCTIONS FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.**

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**IMPORTANT INFORMATION ABOUT THE NEEDLE SHIELD**

The shield hides the needle and has a locking mechanism that protects against needle damage. The use of the shield is optional. Please refer to the package insert for Nutropin AQ NuSpin Instructions For Use and full prescribing information.

- The NuSpin can be used with or without the shield.
- When using the optional needle shield, we recommend needles 8 mm (5/16”) or longer to provide adequate needle length during usage.
- Read the instructions below for using the shield and keep these instructions for future reference.
- Remove both protective covers from the needle and save the outer cover before attaching the shield to your NuSpin.
- Make sure the needle cover is fully depressed and the needle is in the skin before sliding the Activator forward.
- The shield is reusable. Do not discard it. Your shield may be cleaned with a cloth dampened with water.

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**GIVE NUTROPIN AQ NuSpin INJECTION USING THE NEEDLE SHIELD**

Before attaching the needle shield onto your Nutropin AQ NuSpin, inspect the cartridge, and attach a new needle. Additionally, prime the NuSpin if you are using a new NuSpin for the first time. The detailed instructions for these steps are in STEP 1 and STEP 2 in the NEW NuSpin SET UP section of the Nutropin AQ NuSpin Instructions For Use, which is inside each box of Nutropin AQ NuSpin.