

Nutropin AQ[®] [somatropin (rDNA origin) injection]

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3 DESCRIPTION

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

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

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

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

21 The 10 mg Nutropin AQ 2 mL pen cartridge contains 10 mg (approximately 30 International
22 Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate
23 20, and 10 mM sodium citrate.

24 The 20 mg Nutropin AQ 2 mL pen cartridge contains 20 mg (approximately 60 International
25 Units) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate
26 20, and 10 mM sodium citrate.

27 The Nutropin AQ[®] NuSpin 5[™] contains 5 mg (approximately 15 International Units)
28 somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and
29 10 mM sodium citrate.

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30 The Nutropin AQ[®] NuSpin 10[™] contains 10 mg (approximately 30 International Units)
31 somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and
32 10 mM sodium citrate.

33 The Nutropin AQ[®] NuSpin 20[™] contains 20 mg (approximately 60 International Units)
34 somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and
35 10 mM sodium citrate.

36 CLINICAL PHARMACOLOGY

37 General

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

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

47 A. Tissue Growth

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

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59 with GH results in organ growth that is proportional to the overall body growth. In normal
60 rats subjected to nephrectomy-induced uremia, GH promoted skeletal and body growth.

61 B. Protein Metabolism

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

65 C. Carbohydrate Metabolism

66 GH is a modulator of carbohydrate metabolism. For example, patients with inadequate
67 secretion of GH sometimes experience fasting hypoglycemia that is improved by treatment
68 with GH. GH therapy may decrease insulin sensitivity. Untreated patients with chronic renal
69 insufficiency and Turner syndrome have an increased incidence of glucose intolerance.
70 Administration of hGH to adults or children resulted in increases in serum fasting and
71 postprandial insulin levels, more commonly in overweight or obese individuals. In addition,
72 mean fasting and postprandial glucose and hemoglobin A_{1c} levels remained in the normal
73 range.

74 D. Lipid Metabolism

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

77 E. Mineral Metabolism

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

86 **F. Connective Tissue Metabolism**

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

89 **Pharmacokinetics**

90 Subcutaneous Absorption—The absolute bioavailability of recombinant human growth
91 hormone (rhGH) after subcutaneous administration in healthy adult males has been
92 determined to be $81 \pm 20\%$. The mean terminal $t_{1/2}$ after subcutaneous administration is
93 significantly longer than that seen after intravenous administration
94 (2.1 ± 0.43 hours vs. 19.5 ± 3.1 minutes) indicating that the subcutaneous absorption of the
95 compound is slow and rate-limiting.

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

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

103 Elimination—The mean terminal $t_{1/2}$ after intravenous administration of rhGH in healthy
104 adult males is estimated to be 19.5 ± 3.1 minutes. Clearance of rhGH after intravenous
105 administration in healthy adults and children is reported to be in the range of
106 116–174 mL/hr/kg.

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

109 **SPECIAL POPULATIONS**

110 Pediatric—Available literature data suggest that rhGH clearances are similar in adults and
111 children.

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112 Gender—No data are available for exogenously administered rhGH. Available data for
113 methionyl recombinant GH, pituitary-derived GH, and endogenous GH suggest no consistent
114 gender-based differences in GH clearance.

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

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

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

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

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

136 Hepatic Insufficiency—A reduction in rhGH clearance has been noted in patients with severe
137 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^a)/kg SC**

	C _{max} (µg/L)	T _{max} (hr)	t _{1/2} (hr)	AUC _{0-∞} (µg • hr/L)	CL/F _{sc} (mL/[hr • kg])
MEAN ^b	71.1	3.9	2.3	677	150
CV%	17	56	18	13	13

Abbreviations:

C_{max} = maximum concentration

t_{1/2} = half-life

AUC_{0-∞} = area under the curve

CL/F_{sc} = systemic clearance

F_{sc} = subcutaneous bioavailability (not determined)

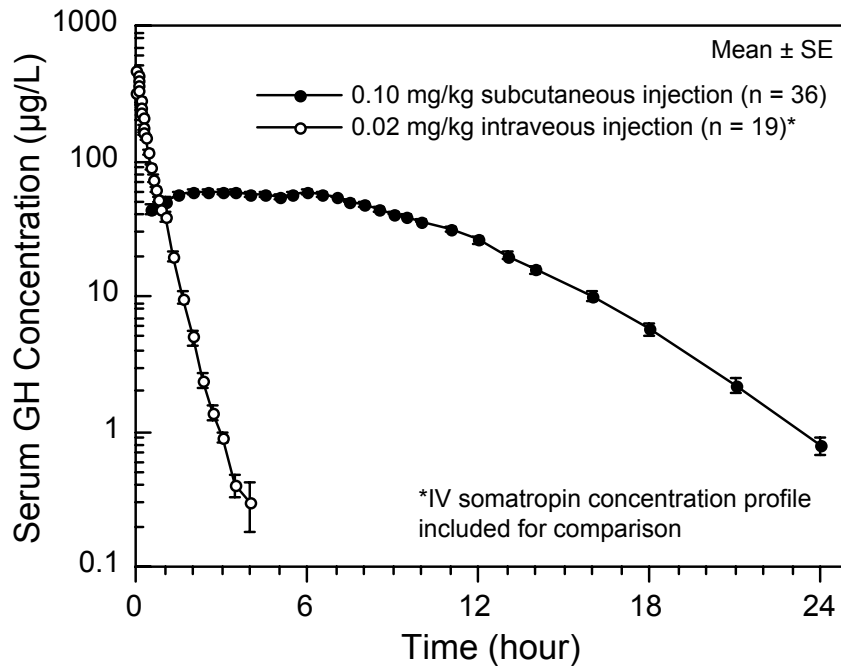
CV% = coefficient of variation in %; SC = subcutaneous

^a Based on current International Standard of 3 IU = 1 mg

^b n = 36

139
140

**Single Dose Mean Growth Hormone Concentrations
in Healthy Adult Males**



141

142 **CLINICAL STUDIES**

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

144 One open label, multicenter, randomized clinical trial of two dosages of Nutropin[®]
145 [somatropin (rDNA origin) for injection] was performed in pubertal patients with GHD.
146 Ninety-seven patients (mean age 13.9 years, 83 male, 14 female) currently being treated with
147 approximately 0.3 mg/kg/wk of GH were randomized to 0.3 mg/kg/wk or 0.7 mg/kg/wk
148 Nutropin doses. All patients were already in puberty (Tanner stage ≥ 2) and had bone ages
149 ≤ 14 years in males or ≤ 12 years in females. Mean baseline height standard deviation (SD)
150 score was -1.3 .

151 The mean last measured height in all 97 patients after a mean duration of 2.7 ± 1.2 years, by
152 analysis of covariance (ANCOVA) adjusting for baseline height, is shown below.

Last Measured Height* by Sex and Nutropin Dose

	Age (yr)	Last Measured Height* (cm)		Height Difference Between Groups (cm)
		0.3 mg/kg/wk	0.7 mg/kg/wk	
	Mean±SD (range)	Mean±SD	Mean±SD	Mean±SE
Male	17.2±1.3 (13.6 to 19.4)	170.9±7.9 (n=42)	174.5±7.9 (n=41)	3.6±1.7
Female	15.8±1.8 (11.9 to 19.3)	154.7±6.3 (n=7)	157.6±6.3 (n=7)	2.9±3.4

*Adjusted for baseline height

153

154 The mean height SD score at last measured height (n=97) was -0.7 ± 1.0 in the
 155 0.3 mg/kg/wk group and -0.1 ± 1.2 in the 0.7 mg/kg/wk group. For patients completing 3.5
 156 or more years (mean 4.1 years) of Nutropin treatment (15/49 patients in the 0.3 mg/kg/wk
 157 group and 16/48 patients in the 0.7 mg/kg/wk group), the mean last measured height was
 158 166.1 ± 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,
 159 adjusting for baseline height and sex.

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

164 Thirty-one patients had bone mineral density (BMD) determined by dual energy x-ray
 165 absorptiometry (DEXA) scans at study conclusion. The two dose groups did not differ
 166 significantly in mean SD score for total body BMD (-0.9 ± 1.9 in the 0.3 mg/kg/wk group
 167 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
 168 0.3 mg/kg/wk group vs. -0.2 ± 1.7 in the 0.7 mg/kg/wk group, n=21).

169 Over a mean duration of 2.7 years, patients in the 0.7 mg/kg/wk group were more likely to
 170 have IGF-I values above the normal range than patients in the 0.3 mg/kg/wk group (27.7%
 171 vs. 9.0% of IGF-I measurements for individual patients). The clinical significance of
 172 elevated IGF-I values is unknown.

173 **Effects of Nutropin on Growth Failure Due to Chronic Renal Insufficiency (CRI)**

174 Two multicenter, randomized, controlled clinical trials were conducted to determine whether
175 treatment with Nutropin prior to renal transplantation in patients with chronic renal
176 insufficiency could improve their growth rates and height deficits. One study was a
177 double-blind, placebo-controlled trial and the other was an open-label, randomized trial. The
178 dose of Nutropin in both controlled studies was 0.05 mg/kg/day (0.35 mg/kg/week)
179 administered daily by subcutaneous injection. Combining the data from those patients
180 completing two years in the two controlled studies results in 62 patients treated with
181 Nutropin and 28 patients in the control groups (either placebo-treated or untreated). The
182 mean first year growth rate was 10.8 cm/yr for Nutropin-treated patients, compared with a
183 mean growth rate of 6.5 cm/yr for placebo/untreated controls ($p < 0.00005$). The mean
184 second year growth rate was 7.8 cm/yr for the Nutropin-treated group, compared with
185 5.5 cm/yr for controls ($p < 0.00005$). There was a significant increase in mean height
186 standard deviation (SD) score in the Nutropin group (-2.9 at baseline to -1.5 at Month 24,
187 $n=62$) but no significant change in the controls (-2.8 at baseline to -2.9 at Month 24, $n=28$).
188 The mean third year growth rate of 7.6 cm/yr in the Nutropin-treated patients ($n=27$)
189 suggests that Nutropin stimulates growth beyond two years. However, there are no control
190 data for the third year because control patients crossed over to Nutropin treatment after two
191 years of participation. The gains in height were accompanied by appropriate advancement of
192 skeletal age. These data demonstrate that Nutropin therapy improves growth rate and
193 corrects the acquired height deficit associated with chronic renal insufficiency.

194 **Post-Transplant Growth**

195 The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has
196 reported data for growth post-transplant in children who did not receive GH prior to
197 transplantation as well as children who did receive Nutropin during the clinical trials prior to
198 transplantation. The average change in height SD score during the initial two years
199 post-transplant was 0.15 for the 2391 patients who did not receive GH pre-transplant and
200 0.28 for the 57 patients who did (J Pediatr. 2000;136:376-382). For patients who were
201 followed for 5 years post-transplant, the corresponding changes in height SD score were also
202 similar between groups.

203 **Turner Syndrome**

204 One long-term, randomized, open-label, multicenter, concurrently controlled study, two
205 long-term, open-label, multicenter, historically controlled studies, and one long-term,

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206 randomized, dose-response study were conducted to evaluate the efficacy of GH for the
207 treatment of girls with short stature due to Turner syndrome.

208 In the randomized study GDCT, comparing GH-treated patients to a concurrent control group
209 who received no GH, the GH-treated patients who received a dose of 0.3 mg/kg/week given
210 6 times per week from a mean age of 11.7 years for a mean duration of 4.7 years attained a
211 mean near final height of 146.0 cm (n=27) as compared to the control group who attained a
212 near final height of 142.1 cm (n=19). By analysis of covariance, the effect of GH therapy
213 was a mean height increase of 5.4 cm (p=0.001).

214 In two of the studies (85-023 and 85-044), the effect of long-term GH treatment
215 (0.375 mg/kg/week given either 3 times per week or daily) on adult height was determined
216 by comparing adult heights in the treated patients with those of age-matched historical
217 controls with Turner syndrome who never received any growth-promoting therapy. In
218 Study 85-023, estrogen treatment was delayed until patients were at least age 14. GH
219 therapy resulted in a mean adult height gain of 7.4 cm (mean duration of GH therapy of
220 7.6 years) vs. matched historical controls by analysis of covariance.

221 In Study 85-044, patients treated with early GH therapy were randomized to receive
222 estrogen-replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily) at
223 either age 12 or 15 years. Compared with matched historical controls, early GH therapy
224 (mean duration of GH therapy 5.6 years) combined with estrogen replacement at age
225 12 years resulted in an adult height gain of 5.9 cm (n=26), whereas girls who initiated
226 estrogen at age 15 years (mean duration of GH therapy 6.1 years) had a mean adult height
227 gain of 8.3 cm (n=29). Patients who initiated GH therapy after age 11 (mean age 12.7 years;
228 mean duration of GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

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

231 In a randomized, blinded, dose-response study, GDCT, patients were treated from a mean age
232 of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or
233 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients
234 receiving growth hormone was 148.7 cm (n=31). This represents a mean gain in adult

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235 height of approximately 5 cm compared with previous observations of untreated Turner
236 syndrome girls.

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

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

^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

239

240 Idiopathic Short Stature (ISS)

241 A long-term, open-label, multicenter study (86-053) was conducted to examine the safety and
242 efficacy of Nutropin in pediatric patients with idiopathic short stature, also called non-GH
243 deficient short stature. For the first year, 122 pre-pubertal subjects over the age of 5 years
244 with stimulated serum GH ≥ 10 ng/mL were randomized into two treatment groups of
245 approximately equal size; one group was treated with Nutropin 0.3 mg/kg weekly divided
246 into three doses per week (TIW) and the other group served as untreated controls. For the
247 second and subsequent years of the study, all subjects were re-randomized to receive the
248 same total weekly dose of Nutropin (0.3 mg/kg weekly) administered either daily or TIW.
249 Treatment with Nutropin was continued until a subject's bone age was > 15.0 years (boys) or
250 > 14.0 years (girls) and the growth rate was < 2 cm/yr, after which subjects were followed
251 until adult height was achieved. The mean baseline values were: height SD score -2.8, IGF-I
252 SD score -0.9, age 9.4 years, bone age 7.8 years, growth rate 4.4 cm/yr, mid-parental target
253 height SD score -0.7, and Bayley-Pinneau predicted adult height SD score -2.3. Nearly all
254 subjects had predicted adult height that was less than mid-parental target height.

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255 During the one-year controlled phase of the study, the mean height velocity increased by
256 0.5 ± 1.8 cm (mean \pm SD) in the no-treatment control group and by 3.1 ± 1.7 cm in the
257 Nutropin group ($p < 0.0001$). For the same period of treatment the mean height SD score
258 increased by 0.4 ± 0.2 and remained unchanged (0.0 ± 0.2) in the control group ($p < 0.001$).

259 Of the 118 subjects who were treated with Nutropin in Study 86-053, 83 (70%) reached
260 near-adult height (hereafter called adult height) after 2–10 years of Nutropin therapy. Their
261 last measured height, including post-treatment follow-up, was obtained at a mean age of
262 18.3 years in males and 17.3 years in females. The mean duration of therapy was 6.2 and
263 5.5 years, respectively. Adult height was greater than pretreatment predicted adult height in
264 49 of 60 males (82%) and 19 of 23 females (83%). The mean difference between adult
265 height and pretreatment predicted adult height was 5.2 cm (2.0 inches) in males and 6.0 cm
266 (2.4 inches) in females ($p < 0.0001$ for both). The table (below) summarizes the efficacy
267 data.

Long-Term Efficacy in
Study 86-053 (Mean \pm SD)

Characteristic	Males (n=60)	Females (n=23)
Adult height (cm)	166.3 ± 5.8	153.1 ± 4.8
Pretreatment predicted adult height (cm)	161.1 ± 5.5	147.1 ± 5.1
Adult height minus pretreatment predicted adult height (cm)	$+5.2 \pm 5.0^a$	$+6.0 \pm 5.0^a$
Adult height SD score	-1.5 ± 0.8	-1.6 ± 0.7
Pretreatment predicted adult height SD score	-2.2 ± 0.8	-2.5 ± 0.8
Adult height minus pretreatment predicted adult height SD score	$+0.7 \pm 0.7^a$	$+0.9 \pm 0.8^a$

^a $p < 0.0001$ versus zero.

268

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

272 **Adult Growth Hormone Deficiency (GHD)**

273 Two multicenter, double-blind, placebo-controlled clinical trials were conducted using
274 Nutropin[®] [somatropin (rDNA origin) for injection] in GH-deficient adults. One study was
275 conducted in subjects with adult-onset GHD, mean age 48.3 years, n=166, at doses of 0.0125

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276 or 0.00625 mg/kg/day; doses of 0.025 mg/kg/day were not tolerated in these subjects. A
277 second study was conducted in previously treated subjects with childhood-onset GHD, mean
278 age 23.8 years, n=64, at randomly assigned doses of 0.025 or 0.0125 mg/kg/day. The
279 studies were designed to assess the effects of replacement therapy with GH on body
280 composition.

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

292 In the childhood-onset study, the high-dose Nutropin group improved mean total body fat
293 from 38.4% to 32.1%, mean trunk fat from 36.7% to 29.0%, and mean lean body mass from
294 59.1% to 65.5%; the low-dose Nutropin group improved mean total body fat from 37.1% to
295 31.3%, mean trunk fat from 37.9% to 30.6%, and mean lean body mass from 60.0% to
296 66.0%; the placebo group had mean changes of 0.6% or less ($p = \text{not significant}$).

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)

Proportion	M0431g			M0381g			Placebo vs. Pooled Nutropin t-test p-value
	Placebo (n=62)	Nutropin (n=63)	Between-Groups t-test p-value	Placebo (n=13)	Nutropin 0.0125 mg/kg/day (n=15)	Nutropin 0.025 mg/kg/day (n=15)	
Total body percent fat							
Baseline	36.8	35.0	0.38	35.0	37.1	38.4	0.45
Month 12	36.8	31.5		35.2	31.3	32.1	
Baseline to Month 12 change	-0.1	-3.6	< 0.0001	+ 0.2	-5.8	-6.3	< 0.0001
Post-washout	36.4	32.2		NA	NA	NA	
Baseline to post-washout change	-0.4	-2.8	< 0.0001	NA	NA	NA	
Trunk percent fat							
Baseline	35.3	33.9	0.50	32.5	37.9	36.7	0.23
Month 12	35.4	29.5		33.1	30.6	29.0	
Baseline to Month 12 change	0.0	-4.3	< 0.0001	+ 0.6	-7.3	-7.6	< 0.0001
Post-washout	34.9	30.5		NA	NA	NA	
Baseline to post-washout change	-0.3	-3.4		NA	NA	NA	
Total body percent lean							
Baseline	60.4	62.2	0.37	62.0	60.0	59.1	0.48
Month 12	60.5	65.7		61.8	66.0	65.5	
Baseline to Month 12 change	+ 0.2	+ 3.6	< 0.0001	-0.2	+ 6.0	+ 6.4	< 0.0001
Post-washout	60.9	65.0		NA	NA	NA	
Baseline to post-washout change	+ 0.4	+ 2.8	< 0.0001	NA	NA	NA	

297

298 In the adult-onset study, significant decreases from baseline to Month 12 in LDL cholesterol
 299 and LDL:HDL ratio were seen in the Nutropin group compared to the placebo group,
 300 p<0.02; there were no statistically significant between-group differences in change from
 301 baseline to Month 12 in total cholesterol, HDL cholesterol, or triglycerides. In the
 302 childhood-onset study, significant decreases from baseline to Month 12 in total cholesterol,
 303 LDL cholesterol, and LDL:HDL ratio were seen in the high-dose Nutropin group only,
 304 compared to the placebo group, p<0.05. There were no statistically significant
 305 between-group differences in HDL cholesterol or triglycerides from baseline to Month 12.

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306 In the childhood-onset study, 55% of the patients had decreased spine bone mineral density
307 (BMD) ($z\text{-score} < -1$) at baseline. The administration of Nutropin ($n = 16$) (0.025 mg/kg/day)
308 for two years resulted in increased spine BMD from baseline when compared to placebo
309 ($n = 13$) (4.6% vs. 1.0%, respectively, $p < 0.03$); a transient decrease in spine BMD was seen
310 at six months in the Nutropin-treated patients. Thirty-five percent of subjects treated with
311 this dose had supraphysiological levels of IGF-I at some point during the study, which may
312 carry unknown risks. No significant improvement in total body BMD was found when
313 compared to placebo. A lower GH dose (0.0125 mg/kg/day) did not show significant
314 increments in either of these bone parameters when compared to placebo. No statistically
315 significant effects on BMD were seen in the adult-onset study where patients received GH
316 (0.0125 mg/kg/day) for one year.

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

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

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

330 The mean absolute change in VAT from baseline to Week 32 was -10.7 cm^2 in the Nutropin
331 AQ group and $+8.4 \text{ cm}^2$ in the untreated group ($p = 0.013$ between groups). There was a
332 6.7% VAT loss in the Nutropin AQ group (mean percent change from baseline to Week 32)
333 compared with a 7.5% increase in the untreated group ($p = 0.012$ between groups). The
334 effect of reducing VAT in adult GHD patients with Nutropin AQ on long-term
335 cardiovascular morbidity and mortality has not been determined.

336

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Visceral Adipose Tissue by Computed Tomography Scan:
Percent Change and Absolute Change
from Baseline to Week 32 in Study M2378g

	Nutropin AQ (n = 44)	Untreated (n = 19)	Treatment Difference (adjusted mean)	p-value
Baseline VAT (cm ²) (mean)	126.2	123.3		
Change in VAT (cm ²) (adjusted mean)	-10.7	+8.4	-19.1	0.013 ^a
Percent change in VAT (adjusted mean)	-6.7	+7.5	-14.2	0.012 ^a

^aANCOVA using baseline VAT as a covariate

337

338 **INDICATIONS AND USAGE**

339 **Pediatric Patients**

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

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

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

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

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354 Adult Patients

355 Nutropin AQ[®] [somatropin (rDNA origin) injection] is indicated for replacement of
356 endogenous growth hormone in adults with growth hormone deficiency who meet either of
357 the following two criteria:

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

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

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

368 CONTRAINDICATIONS

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

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

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

380 Somatropin should not be used to treat patients with acute critical illness due to
381 complications following open heart surgery, abdominal surgery or multiple accidental
382 trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-
383 growth hormone deficient adult patients (n=522) with these conditions in intensive care units

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384 revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated
385 patients (doses 5.3–8 mg/day) compared to those receiving placebo (see [WARNINGS](#)).

386 Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese
387 or have severe respiratory impairment (see [WARNINGS](#)). Unless patients with Prader-Willi
388 syndrome also have a diagnosis of growth hormone deficiency, Nutropin AQ is not indicated
389 for the long-term treatment of pediatric patients who have growth failure due to genetically
390 confirmed Prader-Willi syndrome.

391 WARNINGS

392 See CONTRAINDICATIONS for information on increased mortality in patients with acute
393 critical illness due to complications following open heart surgery, abdominal surgery or
394 multiple accidental trauma, or those with acute respiratory failure. The safety of continuing
395 somatropin treatment in patients receiving replacement doses for approved indications who
396 concurrently develop these illnesses has not been established. Therefore, the potential
397 benefit of treatment continuation with somatropin in patients having acute critical illnesses
398 should be weighed against the potential risk.

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

413 PRECAUTIONS

414 General:

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415 Nutropin AQ should be prescribed by physicians experienced in the diagnosis and
416 management of patients with GH deficiency, idiopathic short stature, Turner syndrome, or
417 chronic renal insufficiency (CRI). No studies have been completed evaluating Nutropin AQ
418 therapy in patients who have received renal transplants. Currently, treatment of patients with
419 functioning renal allografts is not indicated.

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

430 In subjects treated in a long-term study of Nutropin for idiopathic short stature, mean fasting
431 and postprandial insulin levels increased, while mean fasting and postprandial glucose levels
432 remained unchanged. Mean hemoglobin A_{1c} levels rose slightly from baseline as expected
433 during adolescence; sporadic values outside normal limits occurred transiently.

434 Nutropin therapy in adults with GH deficiency of adult onset was associated with an increase
435 of median fasting insulin level in the Nutropin 0.0125 mg/kg/day group from 9.0 µU/mL at
436 baseline to 13.0 µU/mL at Month 12 with a return to the baseline median level after a 3-week
437 post-washout period of GH therapy. In the placebo group there was no change from
438 8.0 µU/mL at baseline to Month 12, and after the post-washout period, the median level was
439 9.0 µU/mL. The between-treatment groups difference on the change from baseline to
440 Month 12 in median fasting insulin level was significant, $p < 0.0001$. In childhood-onset
441 subjects, there was an increase of median fasting insulin level in the Nutropin
442 0.025 mg/kg/day group from 11.0 µU/mL at baseline to 20.0 µU/mL at Month 12, in the
443 Nutropin 0.0125 mg/kg/day group from 8.5 µU/mL to 11.0 µU/mL, and in the placebo group
444 from 7.0 µU/mL to 8.0 µU/mL. The between-treatment groups differences for these changes
445 were significant, $p = 0.0007$.

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446 In subjects with adult onset GH deficiency, there were no between-treatment group
447 differences on change from baseline to Month 12 in mean HbA_{1c} level, p=0.08. In
448 childhood-onset GH deficiency, the mean HbA_{1c} level increased in the Nutropin
449 0.025 mg/kg/day group from 5.2% at baseline to 5.5% at Month 12, and did not change in the
450 Nutropin 0.0125 mg/kg/day group from 5.1% at baseline or in the placebo group from 5.3%
451 at baseline. The between-treatment group differences were significant, p=0.009.

452 Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial
453 lesion should be examined routinely for progression or recurrence of the underlying disease
454 process. In pediatric patients, clinical literature has revealed no relationship between
455 somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new
456 extracranial tumors. However, in childhood cancer survivors, an increased risk of a second
457 neoplasm has been reported in patients treated with somatropin after their first
458 neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to
459 the head for their first neoplasm, were the most common of these second neoplasms. In
460 adults, it is unknown whether there is any relationship between somatropin replacement
461 therapy and CNS tumor recurrence.

462 Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or
463 vomiting has been reported in a small number of patients treated with somatropin products.
464 Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin
465 therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after
466 cessation of therapy or a reduction of the somatropin dose. Funduscopy examination should
467 be performed routinely before initiating treatment with somatropin to exclude preexisting
468 papilledema, and periodically during the course of somatropin therapy. If papilledema is
469 observed by funduscopy during somatropin treatment, treatment should be stopped. If
470 somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower
471 dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome,
472 CRI, and Prader-Willi syndrome may be at increased risk for the development of IH.

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

475 Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in
476 particular, the growth response in children. Patients with Turner syndrome have an inherently

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477 increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In
478 patients with growth hormone deficiency, central (secondary) hypothyroidism may first
479 become evident or worsen during somatropin treatment. Therefore, patients treated with
480 somatropin should have periodic thyroid function tests and thyroid hormone replacement
481 therapy should be initiated or appropriately adjusted when indicated.

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

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

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

488 **Pediatric Patients (see [PRECAUTIONS, General](#)):**

489 Slipped capital femoral epiphysis may occur more frequently in patients with endocrine
490 disorders (including GH deficiency and Turner syndrome) or in patients undergoing rapid
491 growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain
492 during somatropin therapy should be carefully evaluated.

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

500 Progression of scoliosis can occur in patients who experience rapid growth. Because
501 somatropin increases growth rate, patients with a history of scoliosis who are treated with
502 somatropin should be monitored for progression of scoliosis. However, somatropin has not
503 been shown to increase the occurrence of scoliosis. Skeletal abnormalities including
504 scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also
505 commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert
506 to these abnormalities, which may manifest during somatropin therapy.

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507 Patients with Turner syndrome should be evaluated carefully for otitis media and other ear
508 disorders since these patients have an increased risk of ear and hearing disorders. In a
509 randomized, controlled trial, there was a statistically significant increase, as compared to
510 untreated controls, in otitis media (43% vs. 26%) and ear disorders (18% vs. 5%) in patients
511 receiving somatropin. In addition, patients with Turner syndrome should be monitored
512 closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as
513 these patients are also at risk for these conditions.

514 **Adult Patients (see [PRECAUTIONS, General](#)):**

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

521 Experience with prolonged somatropin treatment in adults is limited.

522 **Information for Patients:**

523 Patients being treated with Nutropin AQ (and/or their parents) should be informed about the
524 potential benefits and risks associated with Nutropin AQ treatment, including a review of the
525 contents of the Patient Information Insert. This information is intended to better educate
526 patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

527 Patients and caregivers who will administer Nutropin AQ should receive appropriate training
528 and instruction on the proper use of Nutropin AQ from the physician or other suitably
529 qualified health care professional. A puncture-resistant container for the disposal of used
530 syringes and needles should be strongly recommended. Patients and/or parents should be
531 thoroughly instructed in the importance of proper disposal, and cautioned against any reuse
532 of needles and syringes. This information is intended to aid in the safe and effective
533 administration of the medication (see [Patient Information Insert](#)).

534 **Laboratory Tests:**

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

537 **Drug Interactions:**

538 Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in
539 adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone.
540 As a consequence, in patients treated with somatropin, previously undiagnosed central
541 (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy.
542 In addition, patients treated with glucocorticoid replacement therapy for previously
543 diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this
544 may be especially true for patients treated with cortisone acetate and prednisone since
545 conversion of these drugs to their biologically active metabolites is dependent on the activity
546 of the 11 β HSD-1 enzyme.

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

551 The use of Nutropin AQ in patients with CRI requiring glucocorticoid therapy has not been
552 evaluated. Concomitant glucocorticoid therapy may inhibit the growth promoting effect of
553 Nutropin AQ. Therefore, if glucocorticoid replacement is required for CRI, the
554 glucocorticoid dose should be carefully adjusted to avoid an inhibitory effect on growth.

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555 There was no evidence in the controlled studies of Nutropin's interaction with drugs
556 commonly used in chronic renal insufficiency patients. Limited published data indicate that
557 somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in
558 man. These data suggest that somatropin administration may alter the clearance of
559 compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex
560 steroids, anticonvulsants, cyclosporin). Careful monitoring is advisable when somatropin is
561 administered in combination with other drugs known to be metabolized by CP450 liver
562 enzymes. However, formal drug interaction studies have not been conducted.

563 In adult women on oral estrogen replacement, a larger dose of somatropin may be required to
564 achieve the defined treatment goal (see [DOSAGE AND ADMINISTRATION](#)).

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

568 Carcinogenesis, Mutagenesis, Impairment of Fertility:

569 Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with
570 Nutropin AQ.

571 Pregnancy:

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

576 Nursing Mothers:

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

580 Geriatric Usage:

581 Clinical studies of Nutropin AQ did not include sufficient numbers of subjects aged 65 and
582 over to determine whether they respond differently from younger subjects. Elderly patients

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583 may be more sensitive to the action of somatropin, and therefore may be more prone to
584 develop adverse reactions. A lower starting dose and smaller dose increments should be
585 considered for older patients (see [DOSING AND ADMINISTRATION](#)).

586

587 **ADVERSE REACTIONS**

588 As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to
589 the protein. GH antibody binding capacities below 2 mg/L have not been associated with
590 growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth
591 attenuation has been observed. In clinical studies of pediatric patients that were treated with
592 Nutropin[®] [somatropin (rDNA origin) for injection] for the first time, 0/107 growth
593 hormone-deficient (GHD) patients, 0/125 CRI patients, 0/112 Turner syndrome, and 0/117
594 ISS patients screened for antibody production developed antibodies with binding capacities
595 ≥ 2 mg/L at six months. In a clinical study of patients that were treated with Nutropin AQ for
596 the first time, 0/38 GHD patients screened for antibody production for up to 15 months
597 developed antibodies with binding capacities ≥ 2 mg/L.

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

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

606 In a post-marketing surveillance study, the National Cooperative Growth Study, the pattern
607 of adverse events in over 8000 patients with idiopathic short stature was consistent with the
608 known safety profile of GH, and no new safety signals attributable to GH were identified.
609 The frequency of protocol-defined targeted adverse events is described in the table, below.

610

Protocol-Defined Targeted Adverse Events in the ISS NCGS Cohort

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

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

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

611

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

615 Leukemia has been reported in a small number of GHD patients treated with GH. It is
616 uncertain whether this increased risk is related to the pathology of GH deficiency itself, GH
617 therapy, or other associated treatments such as radiation therapy for intracranial tumors. On
618 the basis of current evidence, experts cannot conclude that GH therapy is responsible for
619 these occurrences. The risk to GHD, CRI, or Turner syndrome patients, if any, remains to be
620 established.

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

628 OVERDOSAGE

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

632 DOSAGE AND ADMINISTRATION

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

639 *Dosage*

640 Pediatric Growth Hormone Deficiency (GHD)

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

644 Adult Growth Hormone Deficiency (GHD)

645 Based on the weight-based dosing utilized in the original pivotal studies described herein, the
646 recommended dosage at the start of therapy is not more than 0.006 mg/kg given as a daily
647 subcutaneous injection. The dose may be increased according to individual patient
648 requirements to a maximum of 0.025 mg/kg daily in patients under 35 years old and to a
649 maximum of 0.0125 mg/kg daily in patients over 35 years old. Clinical response, side effects,

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650 and determination of age- and gender-adjusted serum IGF-I levels may be used as guidance
651 in dose titration.

652 Alternatively, taking into account more recent literature, a starting dose of approximately 0.2
653 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This
654 dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2
655 mg/day, according to individual patient requirements based on the clinical response and
656 serum IGF-I concentrations. During therapy, the dose should be decreased if required by the
657 occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific
658 normal range. Maintenance dosages vary considerably from person to person.

659 A lower starting dose and smaller dose increments should be considered for older patients,
660 who are more prone to the adverse effects of somatropin than younger individuals. In
661 addition, obese individuals are more likely to manifest adverse effects when treated with a
662 weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women
663 may need higher doses than men. Oral estrogen administration may increase the dose
664 requirements in women.

665 Chronic Renal Insufficiency (CRI)

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

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

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

- 671 1. Hemodialysis patients should receive their injection at night just prior to going to sleep
672 or at least 3-4 hours after their hemodialysis to prevent hematoma formation due to the
673 heparin.
- 674 2. Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in
675 the morning after they have completed dialysis.
- 676 3. Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection
677 in the evening at the time of the overnight exchange.

678 Turner Syndrome

679 A weekly dosage of up to 0.375 mg/kg of body weight divided into equal doses 3 to 7 times
680 per week by subcutaneous injection is recommended.

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681 **Idiopathic Short Stature (ISS)**

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

684 ***Administration***

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

690 **For Nutropin AQ[®] Vial**

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

697 **For Nutropin AQ Pen[®] 10 mg Cartridge**

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

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

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

Nutropin AQ[®] [somatropin (rDNA origin) injection]

708 **For Nutropin AQ Pen[®] 20 mg Cartridge**

709 The Nutropin AQ Pen[®] 20 mg Cartridge must be used with its corresponding color-coded
710 Nutropin AQ Pen[®] 20. The Nutropin AQ Pen[®] 20 mg Cartridge must not be inserted into a
711 pen with a different color code.

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

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

719 **For Nutropin AQ[®] NuSpin[™] 5**

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

725 The Nutropin AQ[®] NuSpin[™] 5 allows for administration of a minimum dose of 0.05 mg to a
726 maximum dose of 1.75 mg, in increments of 0.05 mg.

727 **For Nutropin AQ[®] NuSpin[™] 10**

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

733 The Nutropin AQ[®] NuSpin[™] 10 allows for administration of a minimum dose of 0.1 mg to a
734 maximum dose of 3.5 mg, in increments of 0.1 mg.

Nutropin AQ[®] [somatropin (rDNA origin) injection]

735 For Nutropin AQ[®] NuSpin[™] 20

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

741 The Nutropin AQ[®] NuSpin[™] 20 allows for administration of a minimum dose of 0.2 mg to a
742 maximum dose of 7.0 mg, in increments of 0.2 mg.

743 STABILITY AND STORAGE

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

750 HOW SUPPLIED

751 Nutropin AQ[®] [somatropin (rDNA origin) injection] is supplied as: 10 mg (approximately
752 30 International Units) of sterile liquid somatropin per vial; 10 mg
753 (approximately 30 International Units) of sterile liquid somatropin per pen cartridge; 20 mg
754 (approximately 60 International Units) of sterile liquid somatropin per pen cartridge; 5 mg
755 (approximately 15 International Units) of sterile liquid somatropin per Nutropin AQ[®] NuSpin[™]
756 [™] 5; 10 mg (approximately 30 International Units) of sterile liquid somatropin per Nutropin
757 AQ[®] NuSpin[™] 10; and 20 mg (approximately 60 International Units) of sterile liquid
758 somatropin per Nutropin AQ[®] NuSpin[™] 20.

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

761 Each 10 mg pen cartridge carton contains one single pen cartridge containing 2 mL of
762 Nutropin AQ[®] [somatropin (rDNA origin) injection] 10 mg/2 mL (5 mg/mL).
763 NDC 50242-043-14.

Nutropin AQ[®] [somatropin (rDNA origin) injection]

764 Each 20 mg pen cartridge carton contains one single pen cartridge containing 2 mL of
765 Nutropin AQ[®] [somatropin (rDNA origin) injection] 20 mg/2 mL (10 mg/mL).
766 NDC 50242-073-01.

767 Each Nutropin AQ[®] NuSpin[™] 5 carton contains one single Nutropin AQ NuSpin injection
768 device prefilled with a cartridge containing 2 mL of Nutropin AQ[®]
769 [somatropin (rDNA origin) injection] 5 mg/2 mL (2.5 mg/mL).
770 NDC 50242-075-01.

771 Each Nutropin AQ[®] NuSpin[™] 10 carton contains one single Nutropin AQ NuSpin injection
772 device prefilled with a cartridge containing 2 mL of Nutropin AQ[®]
773 [somatropin (rDNA origin) injection] 10 mg/2 mL (5 mg/mL).
774 NDC 50242-074-01.

775 Each Nutropin AQ[®] NuSpin[™] 20 carton contains one single Nutropin AQ NuSpin injection
776 device prefilled with a cartridge containing 2 mL of Nutropin AQ[®]
777 [somatropin (rDNA origin) injection] 20 mg/2 mL (10 mg/mL).
778 NDC 50242-076-01.

Nutropin AQ[®]
[somatropin (rDNA origin) injection]
Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

(4834603)
FDA Approval Date January 2008
Code Revision Date January 2008
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