

1 **Nutropin[®]**
2 **[somatotropin (rDNA origin) for injection]**

3 **DESCRIPTION**

4 Nutropin[®] [somatotropin (rDNA origin) for injection] is a human growth hormone (hGH)
5 produced by recombinant DNA technology. Nutropin 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 is a highly purified preparation. Biological potency is determined using a cell
13 proliferation bioassay.

14 Nutropin is a sterile, white, lyophilized powder intended for subcutaneous administration
15 after reconstitution with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved).
16 The reconstituted product is nearly isotonic at a concentration of 5 mg/mL growth hormone
17 (GH) and has a pH of approximately 7.4.

18 Each 5 mg Nutropin vial contains 5 mg (approximately 15 IU) somatotropin, lyophilized with
19 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg sodium phosphate monobasic and 1.3
20 mg sodium phosphate dibasic), and 1.7 mg glycine.

21 Each 10 mg Nutropin vial contains 10 mg (approximately 30 IU) somatotropin, lyophilized
22 with 90 mg mannitol, 3.4 mg sodium phosphates (0.8 mg sodium phosphate monobasic and
23 2.6 mg sodium phosphate dibasic), and 3.4 mg glycine.

24 Bacteriostatic Water for Injection, USP is sterile water containing 0.9 percent benzyl alcohol
25 per mL as an antimicrobial preservative packaged in a multidose vial. The diluent pH is
26 4.5–7.0.

27 **CLINICAL PHARMACOLOGY**

28 **General**

29 In vitro and in vivo preclinical and clinical testing have demonstrated that Nutropin is
30 therapeutically equivalent to pituitary-derived human GH (hGH). Pediatric patients who lack
31 adequate endogenous GH secretion, patients with chronic renal insufficiency, and patients
32 with Turner syndrome that were treated with Nutropin resulted in an increase in growth rate
33 and an increase in insulin-like growth factor-I (IGF-I) levels similar to that seen with
34 pituitary-derived hGH.

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

37 **A. Tissue Growth**

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

51 **B. Protein Metabolism**

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

55 **C. Carbohydrate Metabolism**

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

64 **D. Lipid Metabolism**

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

67 **E. Mineral Metabolism**

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

76 **F. Connective Tissue Metabolism**

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

79 **Pharmacokinetics**

80 Subcutaneous Absorption—The absolute bioavailability of recombinant human growth
81 hormone (rhGH) after subcutaneous administration in healthy adult males has been
82 determined to be $81 \pm 20\%$. The mean terminal $t_{1/2}$ after subcutaneous administration is
83 significantly longer than that seen after intravenous administration

84 (2.1 ± 0.43 hours vs. 19.5 ± 3.1 minutes) indicating that the subcutaneous absorption of the
85 compound is slow and rate-limiting.

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

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

93 Elimination—The mean terminal $t_{1/2}$ after intravenous administration of rhGH in healthy
94 adult males is estimated to be 19.5 ± 3.1 minutes. Clearance of rhGH after intravenous
95 administration in healthy adults and children is reported to be in the range of
96 116–174 mL/hr/kg.

97 Bioequivalence of Formulations—Nutropin has been determined to be bioequivalent to
98 Nutropin AQ[®] [somatotropin (rDNA origin) injection] based on the statistical evaluation of
99 AUC and C_{max} .

100 **SPECIAL POPULATIONS**

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

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

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

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

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

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

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

127 Hepatic Insufficiency—A reduction in rhGH clearance has been noted in patients with severe
128 liver dysfunction. The clinical significance of this decrease is unknown.

**Summary of Nutropin 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	67.2	6.2	2.1	643	158
CV%	29	37	20	12	12

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

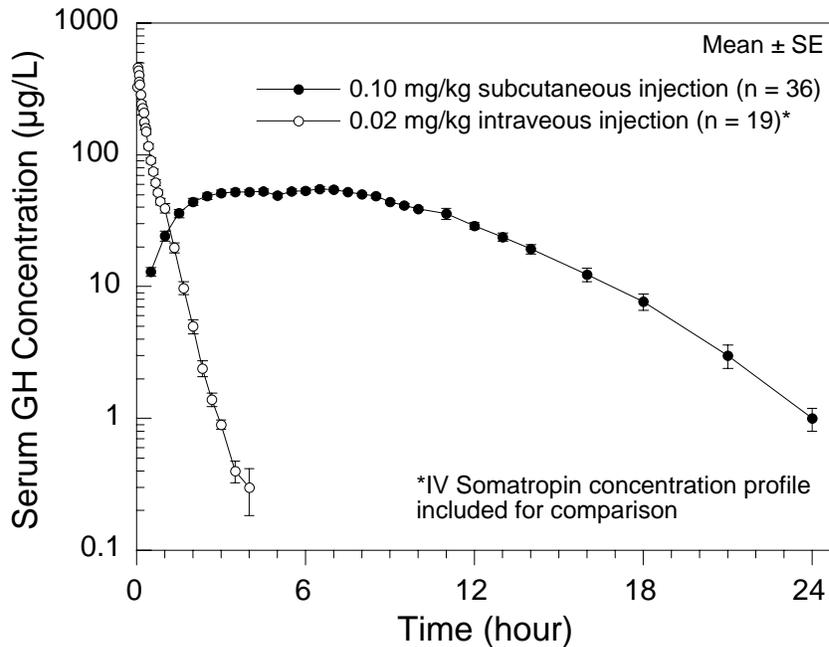
^b n = 36

129

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

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CLINICAL STUDIES

135

Growth Hormone Deficiency (GHD) in Pubertal Patients

136 One open-label, multicenter, randomized clinical trial of two dosages of Nutropin was
137 performed in pubertal patients with GHD. Ninety-seven patients (mean age 13.9 years,
138 83 male, 14 female) currently being treated with approximately 0.3 mg/kg/wk of GH were
139 randomized to 0.3 mg/kg/wk or 0.7 mg/kg/wk Nutropin doses. All patients were already in
140 puberty (Tanner stage ≥ 2) and had bone ages ≤ 14 years in males or ≤ 12 years in females.
141 Mean baseline height standard deviation (SD) score was -1.3 .

142 The mean last measured height in all 97 patients after a mean duration of 2.7 ± 1.2 years, by
143 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 \pm SD (range)	Mean \pm SD	Mean \pm SD	Mean \pm SE
Male	17.2 \pm 1.3 (13.6 to 19.4)	170.9 \pm 7.9 (n=42)	174.5 \pm 7.9 (n=41)	3.6 \pm 1.7
Female	15.8 \pm 1.8 (11.9 to 19.3)	154.7 \pm 6.3 (n=7)	157.6 \pm 6.3 (n=7)	2.9 \pm 3.4

*Adjusted for baseline height

144

145 The mean height SD score at last measured height (n=97) was -0.7 ± 1.0 in the
146 0.3 mg/kg/wk group and -0.1 ± 1.2 in the 0.7 mg/kg/wk group. For patients completing 3.5
147 or more years (mean 4.1 years) of Nutropin treatment (15/49 patients in the 0.3 mg/kg/wk
148 group and 16/48 patients in the 0.7 mg/kg/wk group), the mean last measured height was
149 166.1 ± 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,
150 adjusting for baseline height and sex.

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

155 Thirty-one patients had bone mineral density (BMD) determined by dual energy x-ray
156 absorptiometry (DEXA) scans at study conclusion. The two dose groups did not differ

157 significantly in mean SD score for total body BMD (-0.9 ± 1.9 in the 0.3 mg/kg/wk group
158 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
159 0.3 mg/kg/wk group vs. -0.2 ± 1.7 in the 0.7 mg/kg/wk group, n=21).

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

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

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

185 **Post-Transplant Growth**

186 The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has
187 reported data for growth post-transplant in children who did not receive GH prior to

188 transplantation as well as children who did receive Nutropin during the clinical trials prior to
189 transplantation. The average change in height SD score during the initial two years
190 post-transplant was 0.15 for the 2391 patients who did not receive GH pre-transplant and
191 0.28 for the 57 patients who did (J Pediatr. 2000;136:376-382). For patients who were
192 followed for 5 years post-transplant, the corresponding changes in height SD score were also
193 similar between groups.

194 **Turner Syndrome**

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

199 In the randomized study GDCT, comparing GH-treated patients to a concurrent control group
200 who received no GH, the GH-treated patients who received a dose of 0.3 mg/kg/week given
201 6 times per week from a mean age of 11.7 years for a mean duration of 4.7 years attained a
202 mean near final height of 146.0 cm (n=27) as compared to the control group who attained a
203 near final height of 142.1 cm (n=19). By analysis of covariance, the effect of GH therapy
204 was a mean height increase of 5.4 cm (p=0.001).

205 In two of the studies (85-023 and 85-044), the effect of long-term GH treatment
206 (0.375 mg/kg/week given either 3 times per week or daily) on adult height was determined
207 by comparing adult heights in the treated patients with those of age-matched historical
208 controls with Turner syndrome who never received any growth-promoting therapy. In
209 Study 85-023, estrogen treatment was delayed until patients were at least age 14. GH
210 therapy resulted in a mean adult height gain of 7.4 cm (mean duration of GH therapy of
211 7.6 years) vs. matched historical controls by analysis of covariance.

212 In Study 85-044, patients treated with early GH therapy were randomized to receive
213 estrogen-replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily) at
214 either age 12 or 15 years. Compared with matched historical controls, early GH therapy
215 (mean duration of GH therapy 5.6 years) combined with estrogen replacement at age
216 12 years resulted in an adult height gain of 5.9 cm (n=26), whereas girls who initiated
217 estrogen at age 15 years (mean duration of GH therapy 6.1 years) had a mean adult height

218 gain of 8.3 cm (n=29). Patients who initiated GH therapy after age 11 (mean age 12.7 years;
219 mean duration of GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

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

222 In a randomized, blinded, dose-response study, GDCI, patients were treated from a mean age
223 of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or
224 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients
225 receiving growth hormone was 148.7 cm (n=31). This represents a mean gain in adult
226 height of approximately 5 cm compared with previous observations of untreated Turner
227 syndrome girls.

228 In these studies, Turner syndrome patients (n=181) treated to final adult height achieved
229 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
GDCI	RCT	27	11.7	13	4.7	5.4
85-023	MHT	17	9.1	15.2	7.6	7.4
85-044: A*	MHT	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

230

231 Idiopathic Short Stature (ISS)

232 A long-term, open-label, multicenter study (86-053) was conducted to examine the safety and
233 efficacy of Nutropin in pediatric patients with idiopathic short stature, also called non-GH
234 deficient short stature. For the first year, 122 pre-pubertal subjects over the age of 5 years
235 with stimulated serum GH ≥ 10 ng/mL were randomized into two treatment groups of
236 approximately equal size; one group was treated with Nutropin 0.3 mg/kg weekly divided

237 into three doses per week (TIW) and the other group served as untreated controls. For the
238 second and subsequent years of the study, all subjects were re-randomized to receive the
239 same total weekly dose of Nutropin (0.3 mg/kg weekly) administered either daily or TIW.
240 Treatment with Nutropin was continued until a subject's bone age was > 15.0 years (boys) or
241 > 14.0 years (girls) and the growth rate was < 2 cm/yr, after which subjects were followed
242 until adult height was achieved. The mean baseline values were: height SD score -2.8, IGF-I
243 SD score -0.9, age 9.4 years, bone age 7.8 years, growth rate 4.4 cm/yr, mid-parental target
244 height SD score -0.7, and Bayley-Pinneau predicted adult height SD score -2.3. Nearly all
245 subjects had predicted adult height that was less than mid-parental target height.

246 During the one-year controlled phase of the study, the mean height velocity increased by
247 0.5 ± 1.8 cm (mean \pm SD) in the no-treatment control group and by 3.1 ± 1.7 cm in the
248 Nutropin group ($p < 0.0001$). For the same period of treatment the mean height SD score
249 increased by 0.4 ± 0.2 and remained unchanged (0.0 ± 0.2) in the control group ($p < 0.001$).

250 Of the 118 subjects who were treated with Nutropin in Study 86-053, 83 (70%) reached
251 near-adult height (hereafter called adult height) after 2–10 years of Nutropin therapy. Their
252 last measured height, including post-treatment follow-up, was obtained at a mean age of
253 18.3 years in males and 17.3 years in females. The mean duration of therapy was 6.2 and
254 5.5 years, respectively. Adult height was greater than pretreatment predicted adult height in
255 49 of 60 males (82%) and 19 of 23 females (83%). The mean difference between adult
256 height and pretreatment predicted adult height was 5.2 cm (2.0 inches) in males and 6.0 cm
257 (2.4 inches) in females ($p < 0.0001$ for both). The table (below) summarizes the efficacy
258 data.

Long-Term Efficacy in
Study 86-053 (Mean ±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±5.0 ^a	+6.0±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±0.7 ^a	+0.9±0.8 ^a

^a p<0.0001 versus zero.

259

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

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

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

272 Significant changes from baseline to Month 12 of treatment in body composition (i.e., total
273 body % fat mass, trunk % fat mass, and total body % lean mass by DEXA scan) were seen in
274 all Nutropin groups in both studies (p<0.0001 for change from baseline and vs. placebo),
275 whereas no statistically significant changes were seen in either of the placebo groups. In the
276 adult-onset study, the Nutropin group improved mean total body fat from 35.0% to 31.5%,
277 mean trunk fat from 33.9% to 29.5%, and mean lean body mass from 62.2% to 65.7%,
278 whereas the placebo group had mean changes of 0.2% or less (p=not significant). Due to the
279 possible effect of GH-induced fluid retention on DEXA measurements of lean body mass,

280 DEXA scans were repeated approximately 3 weeks after completion of therapy; mean % lean
281 body mass in the Nutropin group was 65.0%, a change of 2.8% from baseline, compared with
282 a change of 0.4% in the placebo group ($p < 0.0001$ between groups).

283 In the childhood-onset study, the high-dose Nutropin group improved mean total body fat
284 from 38.4% to 32.1%, mean trunk fat from 36.7% to 29.0%, and mean lean body mass from
285 59.1% to 65.5%; the low-dose Nutropin group improved mean total body fat from 37.1% to
286 31.3%, mean trunk fat from 37.9% to 30.6%, and mean lean body mass from 60.0% to
287 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)

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		N/A	N/A	N/A	
Baseline to post-washout change	-0.4	-2.8	< 0.0001	N/A	N/A	N/A	
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		N/A	N/A	N/A	
Baseline to post-washout change	-0.3	-3.4		N/A	N/A	N/A	
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		N/A	N/A	N/A	
Baseline to post-washout change	+ 0.4	+ 2.8	< 0.0001	N/A	N/A	N/A	

288

289 In the adult-onset study, significant decreases from baseline to Month 12 in LDL cholesterol
 290 and LDL:HDL ratio were seen in the Nutropin group compared to the placebo group,
 291 $p < 0.02$; there were no statistically significant between-group differences in change from
 292 baseline to Month 12 in total cholesterol, HDL cholesterol, or triglycerides. In the
 293 childhood-onset study, significant decreases from baseline to Month 12 in total cholesterol,
 294 LDL cholesterol, and LDL:HDL ratio were seen in the high-dose Nutropin group only,

295 compared to the placebo group, $p < 0.05$. There were no statistically significant
296 between-group differences in HDL cholesterol or triglycerides from baseline to Month 12.

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

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

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

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

321 The mean absolute change in VAT from baseline to Week 32 was -10.7 cm^2 in the Nutropin
322 AQ group and $+8.4 \text{ cm}^2$ in the untreated group ($p = 0.013$ between groups). There was a
323 6.7% VAT loss in the Nutropin AQ group (mean percent change from baseline to Week 32)
324 compared with a 7.5% increase in the untreated group ($p = 0.012$ between groups). The
325 effect of reducing VAT in adult GHD patients with Nutropin AQ on long-term
326 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

	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

327

328 **INDICATIONS AND USAGE**

329 **Pediatric Patients**

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

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

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

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

344 **Adult Patients**

345 Nutropin® [somatotropin (rDNA origin) for injection] is indicated for the replacement of
346 endogenous growth hormone in adults with growth hormone deficiency who meet either of
347 the following two criteria:

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

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

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

358 **CONTRAINDICATIONS**

359 Somatotropin should not be used for growth promotion in pediatric patients with closed
360 epiphyses.

361 Somatotropin is contraindicated in patients with active proliferative or severe non-proliferative
362 diabetic retinopathy.

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

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

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

376 Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese
377 or have severe respiratory impairment (see WARNINGS). Unless patients with Prader-Willi
378 syndrome also have a diagnosis of growth hormone deficiency, Nutropin is not indicated for
379 the long-term treatment of pediatric patients who have growth failure due to genetically
380 confirmed Prader-Willi syndrome.

381 Nutropin, when reconstituted with Bacteriostatic Water for Injection, USP (benzyl alcohol
382 preserved), should not be used in patients with a known sensitivity to benzyl alcohol. For use
383 in newborns see WARNINGS.

384 **WARNINGS**

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

392 There have been reports of fatalities after initiating therapy with somatropin in pediatric
393 patients with Prader-Willi syndrome who had one or more of the following risk factors:
394 severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory
395 infection. Male patients with one or more of these factors may be at greater risk than
396 females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway
397 obstruction and sleep apnea before initiation of treatment with somatropin. If, during
398 treatment with somatropin, patients show signs of upper airway obstruction (including onset
399 of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All
400 patients with Prader-Willi syndrome treated with somatropin should also have effective
401 weight control and be monitored for signs of respiratory infection, which should be
402 diagnosed as early as possible and treated aggressively (see CONTRAINDICATIONS).
403 Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone

404 deficiency, Nutropin is not indicated for the long-term treatment of pediatric patients who
405 have growth failure due to genetically confirmed Prader-Willi syndrome.

406 Benzyl alcohol as a preservative in Bacteriostatic Water for Injection, USP, has been
407 associated with toxicity in newborns. When administering Nutropin to newborns,
408 reconstitute with Sterile Water for Injection, USP. USE ONLY ONE DOSE PER
409 NUTROPIN VIAL AND DISCARD THE UNUSED PORTION.

410 **PRECAUTIONS**

411 **General:**

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

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

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

431 Nutropin therapy in adults with GH deficiency of adult onset was associated with an increase
432 of median fasting insulin level in the Nutropin 0.0125 mg/kg/day group from 9.0 µU/mL at

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

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

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

459 Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or
460 vomiting has been reported in a small number of patients treated with somatotropin products.
461 Symptoms usually occurred within the first eight (8) weeks after the initiation of somatotropin
462 therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after
463 cessation of therapy or a reduction of the somatotropin dose. Fundoscopic examination should
464 be performed routinely before initiating treatment with somatotropin to exclude preexisting

465 papilledema, and periodically during the course of somatropin therapy. If papilledema is
466 observed by funduscopy during somatropin treatment, treatment should be stopped. If
467 somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower
468 dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome,
469 CRI, and Prader-Willi syndrome may be at increased risk for the development of IH.

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

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

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

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

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

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

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

490 Children with growth failure secondary to CRI should be examined periodically for evidence
491 of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular
492 necrosis of the femoral head may be seen in children with advanced renal osteodystrophy,
493 and it is uncertain whether these problems are affected by somatropin therapy. X-rays of the
494 hip should be obtained prior to initiating somatropin therapy in CRI patients. Physicians and

495 parents should be alert to the development of a limp or complaints of hip or knee pain in CRI
496 patients treated with Nutropin.

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

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

511 **Adult Patients (see PRECAUTIONS, General):**

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

518 Experience with prolonged somatropin treatment in adults is limited.

519 **Information for Patients:**

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

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

531 See WARNINGS for use of Bacteriostatic Water for Injection, USP, (benzyl alcohol
532 preserved), in newborns.

533 **Laboratory Tests:**

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

536 **Drug Interactions:**

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

541 In addition, patients treated with glucocorticoid replacement therapy for previously
542 diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this
543 may be especially true for patients treated with cortisone acetate and prednisone since
544 conversion of these drugs to their biologically active metabolites is dependent on the activity
545 of the 11 β HSD-1 enzyme.

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

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

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

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

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

567 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

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

570 **Pregnancy:**

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

575 **Nursing Mothers:**

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

579 **Geriatric Usage:**

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

585 **ADVERSE REACTIONS**

586 As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to
587 the protein. GH antibody binding capacities below 2 mg/L have not been associated with
588 growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth
589 attenuation has been observed. In clinical studies of pediatric patients that were treated with
590 Nutropin for the first time, 0/107 growth hormone–deficient (GHD) patients, 0/125 CRI
591 patients, 0/112 Turner syndrome, and 0/117 ISS patients screened for antibody production
592 developed antibodies with binding capacities ≥ 2 mg/L at six months.

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

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

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

605

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).

606

607 In studies in patients treated with Nutropin, injection site pain was reported infrequently.

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

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

621 **OVERDOSAGE**

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

625 **DOSAGE AND ADMINISTRATION**

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

632 *Dosage*

633 **Pediatric Growth Hormone Deficiency (GHD)**

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

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

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

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

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

658 **Chronic Renal Insufficiency (CRI)**

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

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

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

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

- 667 2. Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in
668 the morning after they have completed dialysis.
- 669 3. Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection
670 in the evening at the time of the overnight exchange.

671 **Turner Syndrome**

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

674 **Idiopathic Short Stature (ISS)**

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

677 **Administration**

678 After the dose has been determined, reconstitute as follows: each 5 mg vial should be
679 reconstituted with 1–5 mL of Bacteriostatic Water for Injection, USP (benzyl alcohol
680 preserved); or each 10 mg vial should be reconstituted with 1–10 mL of Bacteriostatic Water
681 for Injection, USP (benzyl alcohol preserved), only. For use in newborns, see WARNINGS.
682 The pH of Nutropin after reconstitution with Bacteriostatic Water for Injection, USP (benzyl
683 alcohol preserved), is approximately 7.4.

684 To prepare the Nutropin solution, inject the Bacteriostatic Water for Injection, USP (benzyl
685 alcohol preserved) into the Nutropin vial, aiming the stream of liquid against the glass wall.
686 Then swirl the product vial with a **GENTLE** rotary motion until the contents are completely
687 dissolved. **DO NOT SHAKE**. Because Nutropin is a protein, shaking can result in a cloudy
688 solution. The Nutropin solution should be clear immediately after reconstitution.
689 Occasionally, after refrigeration, you may notice that small colorless particles of protein are
690 present in the Nutropin solution. This is not unusual for solutions containing proteins. If the
691 solution is cloudy immediately after reconstitution or refrigeration, the contents **MUST NOT**
692 be injected.

693 Before needle insertion, wipe the septum of both the Nutropin and diluent vials with rubbing
694 alcohol or an antiseptic solution to prevent contamination of the contents by microorganisms
695 that may be introduced by repeated needle insertions. It is recommended that Nutropin be
696 administered using sterile, disposable syringes and needles. The syringes should be of small

Nutropin® [somatropin (rDNA origin) for injection]
Clean Version

697 enough volume that the prescribed dose can be drawn from the vial with reasonable
698 accuracy.

699 **STABILITY AND STORAGE**

700 Before Reconstitution—Nutropin and Bacteriostatic Water for Injection, USP (benzyl
701 alcohol preserved), must be stored at 2–8°C/36–46°F (under refrigeration). **Avoid freezing**
702 **the vials of Nutropin and Bacteriostatic Water for Injection, USP (benzyl alcohol**
703 **preserved)**. Expiration dates are stated on the labels.

704 After Reconstitution— Vial contents are stable for 14 days when reconstituted with
705 Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), and stored at
706 2–8°C/36–46°F (under refrigeration). **Avoid freezing the reconstituted vial of Nutropin**
707 **and the Bacteriostatic Water for Injection, USP (benzyl alcohol preserved)**.

708 **HOW SUPPLIED**

709 Nutropin® [somatropin (rDNA origin) for injection] is supplied as 5 mg (approximately
710 15 IU) or 10 mg (approximately 30 IU) of lyophilized, sterile somatropin per vial.

711 Each 5 mg carton contains one vial of Nutropin® [somatropin (rDNA origin) for injection]
712 (5 mg per vial) and one 10 mL multiple dose vial of Bacteriostatic Water for Injection, USP
713 (benzyl alcohol preserved). NDC 50242-072-03.

714 Each 10 mg carton contains one vial of Nutropin® [somatropin (rDNA origin) for injection]
715 (10 mg per vial) and one 10 mL multiple dose vial of Bacteriostatic Water for Injection, USP
716 (benzyl alcohol preserved). NDC 50242-018-21.

Nutropin®	7123911
[somatropin (rDNA origin) for injection]	LF0563
Manufactured by:	(4834502)
Genentech, Inc.	FDA Approval Date June 2006
1 DNA Way	Code Revision Date June 2006
South San Francisco, CA 94080–4990	©2005 Genentech, Inc.
Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), Manufactured for: Genentech, Inc.	

717

1 **Nutropin AQ[®]**
2 **[somatotropin (rDNA origin) injection]**

3 **DESCRIPTION**

4 Nutropin AQ[®] [somatotropin (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 somatotropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and
20 10 mM sodium citrate.

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

24 **CLINICAL PHARMACOLOGY**

25 **General**

26 In vitro and in vivo preclinical and clinical testing have demonstrated that Nutropin AQ is
27 therapeutically equivalent to pituitary-derived human GH (hGH). Pediatric patients who lack
28 adequate endogenous GH secretion, patients with chronic renal insufficiency, and patients
29 with Turner syndrome that were treated with Nutropin AQ or Nutropin[®]
30 [somatotropin (rDNA origin) for injection] resulted in an increase in growth rate and an

31 increase in insulin-like growth factor-I (IGF-I) levels similar to that seen with
32 pituitary-derived hGH.

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

35 **A. Tissue Growth**

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

49 **B. Protein Metabolism**

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

53 **C. Carbohydrate Metabolism**

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

60 mean fasting and postprandial glucose and hemoglobin A_{1c} levels remained in the normal
61 range.

62 **D. Lipid Metabolism**

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

65 **E. Mineral Metabolism**

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

74 **F. Connective Tissue Metabolism**

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

77 **Pharmacokinetics**

78 Subcutaneous Absorption—The absolute bioavailability of recombinant human growth
79 hormone (rhGH) after subcutaneous administration in healthy adult males has been
80 determined to be $81 \pm 20\%$. The mean terminal $t_{1/2}$ after subcutaneous administration is
81 significantly longer than that seen after intravenous administration
82 (2.1 ± 0.43 hours vs. 19.5 ± 3.1 minutes) indicating that the subcutaneous absorption of the
83 compound is slow and rate-limiting.

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

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

91 Elimination—The mean terminal $t_{1/2}$ after intravenous administration of rhGH in healthy
92 adult males is estimated to be 19.5 ± 3.1 minutes. Clearance of rhGH after intravenous
93 administration in healthy adults and children is reported to be in the range of
94 116–174 mL/hr/kg.

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

97 SPECIAL POPULATIONS

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

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

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

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

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

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

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

124 Hepatic Insufficiency—A reduction in rhGH clearance has been noted in patients with severe
125 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

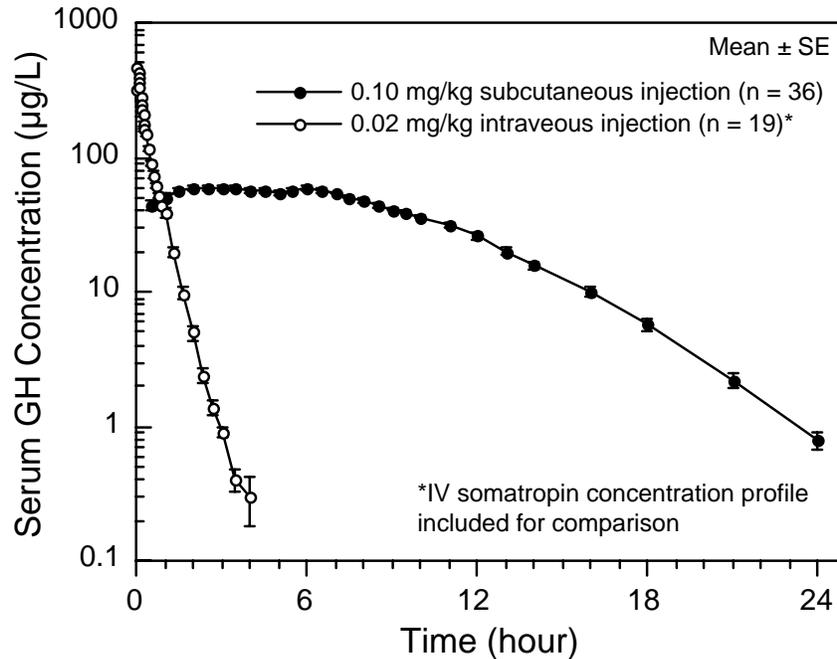
^a Based on current International Standard of 3 IU = 1 mg

^b n = 36

126

127
128

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



129

130 **CLINICAL STUDIES**

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

132 One open label, multicenter, randomized clinical trial of two dosages of Nutropin[®]
133 [somatropin (rDNA origin) for injection] was performed in pubertal patients with GHD.
134 Ninety-seven patients (mean age 13.9 years, 83 male, 14 female) currently being treated with
135 approximately 0.3 mg/kg/wk of GH were randomized to 0.3 mg/kg/wk or 0.7 mg/kg/wk
136 Nutropin doses. All patients were already in puberty (Tanner stage ≥ 2) and had bone ages
137 ≤ 14 years in males or ≤ 12 years in females. Mean baseline height standard deviation (SD)
138 score was -1.3 .

139 The mean last measured height in all 97 patients after a mean duration of 2.7 ± 1.2 years, by
140 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

141

142 The mean height SD score at last measured height (n=97) was -0.7 ± 1.0 in the
143 0.3 mg/kg/wk group and -0.1 ± 1.2 in the 0.7 mg/kg/wk group. For patients completing 3.5
144 or more years (mean 4.1 years) of Nutropin treatment (15/49 patients in the 0.3 mg/kg/wk
145 group and 16/48 patients in the 0.7 mg/kg/wk group), the mean last measured height was
146 166.1 ± 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,
147 adjusting for baseline height and sex.

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

152 Thirty-one patients had bone mineral density (BMD) determined by dual energy x-ray
153 absorptiometry (DEXA) scans at study conclusion. The two dose groups did not differ
154 significantly in mean SD score for total body BMD (-0.9 ± 1.9 in the 0.3 mg/kg/wk group
155 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
156 0.3 mg/kg/wk group vs. -0.2 ± 1.7 in the 0.7 mg/kg/wk group, n=21).

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

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

162 Two multicenter, randomized, controlled clinical trials were conducted to determine whether
163 treatment with Nutropin prior to renal transplantation in patients with chronic renal
164 insufficiency could improve their growth rates and height deficits. One study was a
165 double-blind, placebo-controlled trial and the other was an open-label, randomized trial. The
166 dose of Nutropin in both controlled studies was 0.05 mg/kg/day (0.35 mg/kg/week)
167 administered daily by subcutaneous injection. Combining the data from those patients
168 completing two years in the two controlled studies results in 62 patients treated with
169 Nutropin and 28 patients in the control groups (either placebo-treated or untreated). The
170 mean first year growth rate was 10.8 cm/yr for Nutropin-treated patients, compared with a
171 mean growth rate of 6.5 cm/yr for placebo/untreated controls ($p < 0.00005$). The mean
172 second year growth rate was 7.8 cm/yr for the Nutropin-treated group, compared with
173 5.5 cm/yr for controls ($p < 0.00005$). There was a significant increase in mean height
174 standard deviation (SD) score in the Nutropin group (-2.9 at baseline to -1.5 at Month 24,
175 $n = 62$) but no significant change in the controls (-2.8 at baseline to -2.9 at Month 24, $n = 28$).
176 The mean third year growth rate of 7.6 cm/yr in the Nutropin-treated patients ($n = 27$)
177 suggests that Nutropin stimulates growth beyond two years. However, there are no control
178 data for the third year because control patients crossed over to Nutropin treatment after two
179 years of participation. The gains in height were accompanied by appropriate advancement of
180 skeletal age. These data demonstrate that Nutropin therapy improves growth rate and
181 corrects the acquired height deficit associated with chronic renal insufficiency.

182 **Post-Transplant Growth**

183 The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has
184 reported data for growth post-transplant in children who did not receive GH prior to
185 transplantation as well as children who did receive Nutropin during the clinical trials prior to
186 transplantation. The average change in height SD score during the initial two years
187 post-transplant was 0.15 for the 2391 patients who did not receive GH pre-transplant and
188 0.28 for the 57 patients who did (J Pediatr. 2000;136:376-382). For patients who were
189 followed for 5 years post-transplant, the corresponding changes in height SD score were also
190 similar between groups.

191 **Turner Syndrome**

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

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

196 In the randomized study GDCT, comparing GH-treated patients to a concurrent control group
197 who received no GH, the GH-treated patients who received a dose of 0.3 mg/kg/week given
198 6 times per week from a mean age of 11.7 years for a mean duration of 4.7 years attained a
199 mean near final height of 146.0 cm (n=27) as compared to the control group who attained a
200 near final height of 142.1 cm (n=19). By analysis of covariance, the effect of GH therapy
201 was a mean height increase of 5.4 cm (p=0.001).

202 In two of the studies (85-023 and 85-044), the effect of long-term GH treatment
203 (0.375 mg/kg/week given either 3 times per week or daily) on adult height was determined
204 by comparing adult heights in the treated patients with those of age-matched historical
205 controls with Turner syndrome who never received any growth-promoting therapy. In
206 Study 85-023, estrogen treatment was delayed until patients were at least age 14. GH
207 therapy resulted in a mean adult height gain of 7.4 cm (mean duration of GH therapy of
208 7.6 years) vs. matched historical controls by analysis of covariance.

209 In Study 85-044, patients treated with early GH therapy were randomized to receive
210 estrogen-replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily) at
211 either age 12 or 15 years. Compared with matched historical controls, early GH therapy
212 (mean duration of GH therapy 5.6 years) combined with estrogen replacement at age
213 12 years resulted in an adult height gain of 5.9 cm (n=26), whereas girls who initiated
214 estrogen at age 15 years (mean duration of GH therapy 6.1 years) had a mean adult height
215 gain of 8.3 cm (n=29). Patients who initiated GH therapy after age 11 (mean age 12.7 years;
216 mean duration of GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

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

219 In a randomized, blinded, dose-response study, GDCl, patients were treated from a mean age
220 of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or
221 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients
222 receiving growth hormone was 148.7 cm (n=31). This represents a mean gain in adult

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223 height of approximately 5 cm compared with previous observations of untreated Turner
224 syndrome girls.

225 In these studies, Turner syndrome patients (n=181) treated to final adult height achieved
226 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

227

228 **Idiopathic Short Stature (ISS)**

229 A long-term, open-label, multicenter study (86-053) was conducted to examine the safety and
230 efficacy of Nutropin in pediatric patients with idiopathic short stature, also called non-GH
231 deficient short stature. For the first year, 122 pre-pubertal subjects over the age of 5 years
232 with stimulated serum GH ≥ 10 ng/mL were randomized into two treatment groups of
233 approximately equal size; one group was treated with Nutropin 0.3 mg/kg weekly divided
234 into three doses per week (TIW) and the other group served as untreated controls. For the
235 second and subsequent years of the study, all subjects were re-randomized to receive the
236 same total weekly dose of Nutropin (0.3 mg/kg weekly) administered either daily or TIW.
237 Treatment with Nutropin was continued until a subject's bone age was > 15.0 years (boys) or
238 > 14.0 years (girls) and the growth rate was < 2 cm/yr, after which subjects were followed
239 until adult height was achieved. The mean baseline values were: height SD score -2.8, IGF-I
240 SD score -0.9, age 9.4 years, bone age 7.8 years, growth rate 4.4 cm/yr, mid-parental target
241 height SD score -0.7, and Bayley-Pinneau predicted adult height SD score -2.3. Nearly all
242 subjects had predicted adult height that was less than mid-parental target height.

243 During the one-year controlled phase of the study, the mean height velocity increased by
244 0.5±1.8 cm (mean ± SD) in the no-treatment control group and by 3.1±1.7 cm in the
245 Nutropin group (p<0.0001). For the same period of treatment the mean height SD score
246 increased by 0.4±0.2 and remained unchanged (0.0±0.2) in the control group (p<0.001).

247 Of the 118 subjects who were treated with Nutropin in Study 86-053, 83 (70%) reached
248 near-adult height (hereafter called adult height) after 2–10 years of Nutropin therapy. Their
249 last measured height, including post-treatment follow-up, was obtained at a mean age of
250 18.3 years in males and 17.3 years in females. The mean duration of therapy was 6.2 and
251 5.5 years, respectively. Adult height was greater than pretreatment predicted adult height in
252 49 of 60 males (82%) and 19 of 23 females (83%). The mean difference between adult
253 height and pretreatment predicted adult height was 5.2 cm (2.0 inches) in males and 6.0 cm
254 (2.4 inches) in females (p<0.0001 for both). The table (below) summarizes the efficacy
255 data.

Long-Term Efficacy in
Study 86-053 (Mean ±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±5.0 ^a	+6.0±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±0.7 ^a	+0.9±0.8 ^a

^a p<0.0001 versus zero.

256

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

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

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

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

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

280 In the childhood-onset study, the high-dose Nutropin group improved mean total body fat
281 from 38.4% to 32.1%, mean trunk fat from 36.7% to 29.0%, and mean lean body mass from
282 59.1% to 65.5%; the low-dose Nutropin group improved mean total body fat from 37.1% to
283 31.3%, mean trunk fat from 37.9% to 30.6%, and mean lean body mass from 60.0% to
284 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	

285

286 In the adult-onset study, significant decreases from baseline to Month 12 in LDL cholesterol
287 and LDL:HDL ratio were seen in the Nutropin group compared to the placebo group,
288 $p < 0.02$; there were no statistically significant between-group differences in change from
289 baseline to Month 12 in total cholesterol, HDL cholesterol, or triglycerides. In the
290 childhood-onset study, significant decreases from baseline to Month 12 in total cholesterol,
291 LDL cholesterol, and LDL:HDL ratio were seen in the high-dose Nutropin group only,
292 compared to the placebo group, $p < 0.05$. There were no statistically significant
293 between-group differences in HDL cholesterol or triglycerides from baseline to Month 12.

294 In the childhood-onset study, 55% of the patients had decreased spine bone mineral density
295 (BMD) ($z\text{-score} < -1$) at baseline. The administration of Nutropin ($n = 16$) (0.025 mg/kg/day)
296 for two years resulted in increased spine BMD from baseline when compared to placebo
297 ($n = 13$) (4.6% vs. 1.0%, respectively, $p < 0.03$); a transient decrease in spine BMD was seen
298 at six months in the Nutropin-treated patients. Thirty-five percent of subjects treated with
299 this dose had supraphysiological levels of IGF-I at some point during the study, which may
300 carry unknown risks. No significant improvement in total body BMD was found when
301 compared to placebo. A lower GH dose (0.0125 mg/kg/day) did not show significant
302 increments in either of these bone parameters when compared to placebo. No statistically
303 significant effects on BMD were seen in the adult-onset study where patients received GH
304 (0.0125 mg/kg/day) for one year.

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

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

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

318 The mean absolute change in VAT from baseline to Week 32 was -10.7 cm^2 in the Nutropin
319 AQ group and $+8.4 \text{ cm}^2$ in the untreated group ($p = 0.013$ between groups). There was a
320 6.7% VAT loss in the Nutropin AQ group (mean percent change from baseline to Week 32)
321 compared with a 7.5% increase in the untreated group ($p = 0.012$ between groups). The
322 effect of reducing VAT in adult GHD patients with Nutropin AQ on long-term
323 cardiovascular morbidity and mortality has not been determined.

324

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

325

326 **INDICATIONS AND USAGE**

327 **Pediatric Patients**

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

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

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

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

342 **Adult Patients**

343 Nutropin AQ[®] [somatotropin (rDNA origin) injection] is indicated for replacement of
344 endogenous growth hormone in adults with growth hormone deficiency who meet either of
345 the following two criteria:

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

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

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

356 **CONTRAINDICATIONS**

357 Somatotropin should not be used for growth promotion in pediatric patients with closed
358 epiphyses.

359 Somatotropin is contraindicated in patients with active proliferative or severe non-proliferative
360 diabetic retinopathy.

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

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

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

374 Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese
375 or have severe respiratory impairment (see WARNINGS). Unless patients with Prader-Willi
376 syndrome also have a diagnosis of growth hormone deficiency, Nutropin AQ is not indicated
377 for the long-term treatment of pediatric patients who have growth failure due to genetically
378 confirmed Prader-Willi syndrome.

379 **WARNINGS**

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

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

401 **PRECAUTIONS**

402 **General:**

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

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

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

422 Nutropin therapy in adults with GH deficiency of adult onset was associated with an increase
423 of median fasting insulin level in the Nutropin 0.0125 mg/kg/day group from 9.0 μU/mL at
424 baseline to 13.0 μU/mL at Month 12 with a return to the baseline median level after a 3-week
425 post-washout period of GH therapy. In the placebo group there was no change from
426 8.0 μU/mL at baseline to Month 12, and after the post-washout period, the median level was
427 9.0 μU/mL. The between-treatment groups difference on the change from baseline to
428 Month 12 in median fasting insulin level was significant, $p < 0.0001$. In childhood-onset
429 subjects, there was an increase of median fasting insulin level in the Nutropin
430 0.025 mg/kg/day group from 11.0 μU/mL at baseline to 20.0 μU/mL at Month 12, in the
431 Nutropin 0.0125 mg/kg/day group from 8.5 μU/mL to 11.0 μU/mL, and in the placebo group
432 from 7.0 μU/mL to 8.0 μU/mL. The between-treatment groups differences for these changes
433 were significant, $p = 0.0007$.

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434 In subjects with adult onset GH deficiency, there were no between-treatment group
435 differences on change from baseline to Month 12 in mean HbA_{1c} level, p=0.08. In
436 childhood-onset GH deficiency, the mean HbA_{1c} level increased in the Nutropin
437 0.025 mg/kg/day group from 5.2% at baseline to 5.5% at Month 12, and did not change in the
438 Nutropin 0.0125 mg/kg/day group from 5.1% at baseline or in the placebo group from 5.3%
439 at baseline. The between-treatment group differences were significant, p=0.009.

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

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

461 In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal
462 replacement therapy should be monitored closely when somatropin therapy is administered.
463 Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in
464 particular, the growth response in children. Patients with Turner syndrome have an inherently

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

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

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

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

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

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

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

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

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

502 **Adult Patients (see PRECAUTIONS, General):**

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

509 Experience with prolonged somatropin treatment in adults is limited.

510 **Information for Patients:**

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

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

522 **Laboratory Tests:**

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

525 **Drug Interactions:**

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

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

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

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

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

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

556 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

557 Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with
558 Nutropin AQ.

559 **Pregnancy:**

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

564 **Nursing Mothers:**

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

568 **Geriatric Usage:**

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

571 may be more sensitive to the action of somatropin, and therefore may be more prone to
572 develop adverse reactions. A lower starting dose and smaller dose increments should be
573 considered for older patients (see DOSING AND ADMINISTRATION).

574

575 **ADVERSE REACTIONS**

576 As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to
577 the protein. GH antibody binding capacities below 2 mg/L have not been associated with
578 growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth
579 attenuation has been observed. In clinical studies of pediatric patients that were treated with
580 Nutropin® [somatropin (rDNA origin) for injection] for the first time, 0/107 growth
581 hormone-deficient (GHD) patients, 0/125 CRI patients, 0/112 Turner syndrome, and 0/117
582 ISS patients screened for antibody production developed antibodies with binding capacities
583 ≥ 2 mg/L at six months. In a clinical study of patients that were treated with Nutropin AQ for
584 the first time, 0/38 GHD patients screened for antibody production for up to 15 months
585 developed antibodies with binding capacities ≥ 2 mg/L.

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

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

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

598

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).

599

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

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

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

616 **OVERDOSAGE**

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

620 **DOSAGE AND ADMINISTRATION**

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

627 *Dosage*

628 **Pediatric Growth Hormone Deficiency (GHD)**

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

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

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

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

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

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

653 Chronic Renal Insufficiency (CRI)

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

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

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

- 659 1. Hemodialysis patients should receive their injection at night just prior to going to sleep
660 or at least 3-4 hours after their hemodialysis to prevent hematoma formation due to the
661 heparin.
- 662 2. Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in
663 the morning after they have completed dialysis.
- 664 3. Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection
665 in the evening at the time of the overnight exchange.

666 Turner Syndrome

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

669 **Idiopathic Short Stature (ISS)**

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

672 ***Administration***

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

678 **For Nutropin AQ[®] Vial**

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

685 **For Nutropin AQ Pen[®] Cartridge**

686 The Nutropin AQ pen cartridge is intended for use only with the Nutropin AQ Pen[®]. Wipe
687 the septum of the Nutropin AQ pen cartridge with rubbing alcohol or an antiseptic solution to
688 prevent contamination of the contents by microorganisms that may be introduced by repeated
689 needle insertions. It is recommended that Nutropin AQ be administered using sterile,
690 disposable needles. Follow the directions provided in the Nutropin AQ Pen[®] Instructions for
691 Use.

692 The Nutropin AQ pen allows for administration of a minimum dose of 0.1 mg to a maximum
693 dose of 4.0 mg, in 0.1 mg increments.

694 **STABILITY AND STORAGE**

695 Vial and cartridge contents are stable for 28 days after initial use when stored at
696 2–8°C/36–46°F (under refrigeration). **Avoid freezing the vial or the cartridge of Nutropin**
697 **AQ.** The vials and cartridges of Nutropin AQ are light sensitive and they should be

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698 protected from light. Store the vial and cartridge refrigerated in a dark place when they are
699 not in use.

700 **HOW SUPPLIED**

701 Nutropin AQ[®] [somatropin (rDNA origin) injection] is supplied as either 10 mg
702 (approximately 30 International Units) of sterile liquid somatropin per vial, or as 10 mg
703 (approximately 30 International Units) of sterile liquid somatropin per pen cartridge.

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

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

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

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