

**Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**  
Clean Version

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2 **[somatropin (rDNA origin) injection]**

3 **DESCRIPTION**

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

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

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

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

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

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

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

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Clean Version

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

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

## **36 CLINICAL PHARMACOLOGY**

### **37 General**

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

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

### **47 A. Tissue Growth**

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

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

61 **B. Protein Metabolism**

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

65 **C. Carbohydrate Metabolism**

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

74 **D. Lipid Metabolism**

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

77 **E. Mineral Metabolism**

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

86 **F. Connective Tissue Metabolism**

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

89 **Pharmacokinetics**

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

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

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

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

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

109 **SPECIAL POPULATIONS**

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

**Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**  
Clean Version

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

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

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

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

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

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

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

**Summary of Nutropin AQ Pharmacokinetic  
Parameters in Healthy Adult Males  
0.1 mg (approximately 0.3 IU<sup>a</sup>)/kg SC**

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

Abbreviations:

C<sub>max</sub> = maximum concentration

t<sub>1/2</sub> = half-life

AUC<sub>0-∞</sub> = area under the curve

CL/F<sub>sc</sub> = systemic clearance

F<sub>sc</sub> = subcutaneous bioavailability (not determined)

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

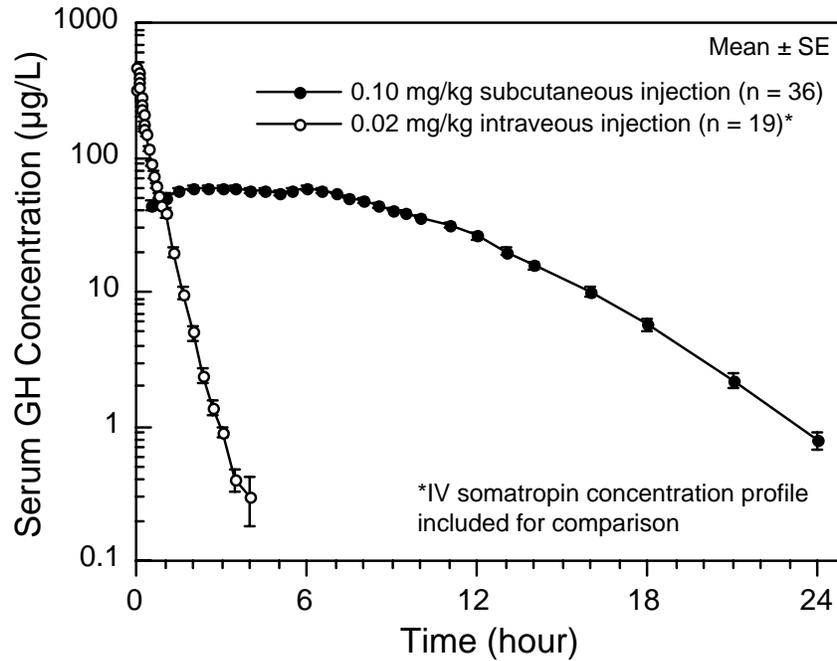
<sup>a</sup> Based on current International Standard of 3 IU = 1 mg

<sup>b</sup> n = 36

138

139  
140

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



141

142 **CLINICAL STUDIES**

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

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

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

**Last Measured Height\* by Sex and Nutropin Dose**

	Age (yr)	Last Measured Height* (cm)		Height Difference Between Groups (cm)
		0.3 mg/kg/wk	0.7 mg/kg/wk	
	Mean ± SD (range)	Mean ± SD	Mean ± SD	Mean ± SE
<b>Male</b>	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
<b>Female</b>	15.8 ± 1.8 (11.9 to 19.3)	154.7 ± 6.3 (n=7)	157.6 ± 6.3 (n=7)	2.9 ± 3.4

\*Adjusted for baseline height

153

154 The mean height SD score at last measured height (n=97) was  $-0.7 \pm 1.0$  in the  
155 0.3 mg/kg/wk group and  $-0.1 \pm 1.2$  in the 0.7 mg/kg/wk group. For patients completing 3.5  
156 or more years (mean 4.1 years) of Nutropin treatment (15/49 patients in the 0.3 mg/kg/wk  
157 group and 16/48 patients in the 0.7 mg/kg/wk group), the mean last measured height was  
158  $166.1 \pm 8.0$  cm in the 0.3 mg/kg/wk group and  $171.8 \pm 7.1$  cm in the 0.7 mg/kg/wk group,  
159 adjusting for baseline height and sex.

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

164 Thirty-one patients had bone mineral density (BMD) determined by dual energy x-ray  
165 absorptiometry (DEXA) scans at study conclusion. The two dose groups did not differ  
166 significantly in mean SD score for total body BMD ( $-0.9 \pm 1.9$  in the 0.3 mg/kg/wk group  
167 vs.  $-0.8 \pm 1.2$  in the 0.7 mg/kg/wk group, n = 20) or lumbar spine BMD ( $-1.0 \pm 1.0$  in the  
168 0.3 mg/kg/wk group vs.  $-0.2 \pm 1.7$  in the 0.7 mg/kg/wk group, n = 21).

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

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

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

194 **Post-Transplant Growth**

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

203 **Turner Syndrome**

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

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

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

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

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

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

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

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Clean Version

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

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

Study/ Group	Study Design <sup>a</sup>	N at Adult Height	GH Age (yr)	Estrogen Age (yr)	GH Duration (yr)	Adult Height Gain (cm) <sup>b</sup>
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 <sup>c</sup>

<sup>a</sup> RCT: randomized controlled trial; MHT: matched historical controlled trial;  
 RDT: randomized dose-response trial

<sup>b</sup> Analysis of covariance vs. controls

<sup>c</sup> Compared with historical data

\* A=GH age <11 yr, estrogen age 15 yr

B=GH age <11 yr, estrogen age 12 yr

C=GH age >11 yr, estrogen at Month 12

239

240 **Idiopathic Short Stature (ISS)**

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

**Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**  
Clean Version

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

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

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

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

<sup>a</sup>  $p < 0.0001$  versus zero.

268

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

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

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

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

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

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

**Mean Changes from Baseline to Month 12 in Proportion of Fat and Lean by DEXA for Studies M0431g and M0381g (Adult-onset and Childhood-onset GHD, respectively)**

Proportion	M0431g			M0381g			Placebo vs. Pooled Nutropin t-test p-value
	Placebo (n=62)	Nutropin (n=63)	Between-Groups t-test p-value	Placebo (n=13)	Nutropin 0.0125 mg/kg/day (n=15)	Nutropin 0.025 mg/kg/day (n=15)	
<b>Total body percent fat</b>							
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	<b>-0.1</b>	<b>-3.6</b>	< 0.0001	<b>+ 0.2</b>	<b>-5.8</b>	<b>-6.3</b>	< 0.0001
Post-washout	36.4	32.2		NA	NA	NA	
Baseline to post-washout change	<b>-0.4</b>	<b>-2.8</b>	< 0.0001	NA	NA	NA	
<b>Trunk percent fat</b>							
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	<b>0.0</b>	<b>-4.3</b>	< 0.0001	<b>+ 0.6</b>	<b>-7.3</b>	<b>-7.6</b>	< 0.0001
Post-washout	34.9	30.5		NA	NA	NA	
Baseline to post-washout change	<b>-0.3</b>	<b>-3.4</b>		NA	NA	NA	
<b>Total body percent lean</b>							
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	<b>+ 0.2</b>	<b>+ 3.6</b>	< 0.0001	<b>-0.2</b>	<b>+ 6.0</b>	<b>+ 6.4</b>	< 0.0001
Post-washout	60.9	65.0		NA	NA	NA	
Baseline to post-washout change	<b>+ 0.4</b>	<b>+ 2.8</b>	< 0.0001	NA	NA	NA	

297

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

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

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

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

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

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

336

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 <sup>2</sup> ) (mean)	126.2	123.3		
Change in VAT (cm <sup>2</sup> ) (adjusted mean)	-10.7	+8.4	-19.1	0.013 <sup>a</sup>
Percent change in VAT (adjusted mean)	-6.7	+7.5	-14.2	0.012 <sup>a</sup>

<sup>a</sup>ANCOVA using baseline VAT as a covariate

337

338 **INDICATIONS AND USAGE**

339 **Pediatric Patients**

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

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

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

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

354 **Adult Patients**

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

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

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

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

368 **CONTRAINDICATIONS**

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

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

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

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

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

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

### 391 **WARNINGS**

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

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

### 413 **PRECAUTIONS**

#### 414 **General:**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

521 Experience with prolonged somatropin treatment in adults is limited.

522 **Information for Patients:**

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

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

534 **Laboratory Tests:**

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

537 **Drug Interactions:**

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

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

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

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

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

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

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

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

571 **Pregnancy:**

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

576 **Nursing Mothers:**

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

580 **Geriatric Usage:**

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

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

586

## 587 **ADVERSE REACTIONS**

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

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

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

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

610

Protocol-Defined Targeted Adverse Events in the ISS NCGS Cohort

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

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

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

611

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

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

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

## 628 **OVERDOSAGE**

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

## 632 **DOSAGE AND ADMINISTRATION**

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

### 639 *Dosage*

#### 640 **Pediatric Growth Hormone Deficiency (GHD)**

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

#### 644 **Adult Growth Hormone Deficiency (GHD)**

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

## **Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**

Clean Version

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

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

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

### **665 Chronic Renal Insufficiency (CRI)**

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

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

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

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

### **678 Turner Syndrome**

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

681 **Idiopathic Short Stature (ISS)**

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

684 ***Administration***

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

690 **For Nutropin AQ<sup>®</sup> Vial**

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

697 **For Nutropin AQ Pen<sup>®</sup> 10 mg Cartridge**

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

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

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

708 **For Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**

**Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**  
Clean Version

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

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

716 **For Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 10**

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

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

724 **For Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**

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

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

732 **For Nutropin AQ Pen<sup>®</sup> 20 mg Cartridge**

733 The Nutropin AQ Pen<sup>®</sup> 20 mg Cartridge must be used with its corresponding color-coded  
734 Nutropin AQ Pen<sup>®</sup> 20. The Nutropin AQ Pen<sup>®</sup> 20 mg Cartridge must not be inserted into a  
735 pen with a different color code.

**Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**  
Clean Version

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

741 The Nutropin AQ Pen<sup>®</sup> 20 allows for administration of a minimum dose of 0.2 mg to a  
742 maximum dose of 8.0 mg, in 0.2 mg increments.

743 **STABILITY AND STORAGE**

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

749 **HOW SUPPLIED**

750 Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection] is supplied as either 10 mg  
751 (approximately 30 International Units) of sterile liquid somatropin per vial, a 10 mg  
752 (approximately 30 International Units) of sterile liquid somatropin per pen cartridge, or a 20  
753 mg (approximately 60 International Units) of sterile liquid somatropin per pen cartridge, or  
754 as 5 mg (approximately 15 International Units) of sterile liquid somatropin per Nutropin AQ  
755 NuSpin 5, or as 10 mg (approximately 30 International Units) of sterile liquid somatropin per  
756 Nutropin AQ NuSpin 10, or as 20 mg (approximately 60 International Units) of sterile liquid  
757 somatropin per Nutropin AQ NuSpin 20.

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

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

**Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]**

Clean Version

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

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

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

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

Nutropin AQ<sup>®</sup>

[somatropin (rDNA origin) injection]

Manufactured by:

**Genentech, Inc.**

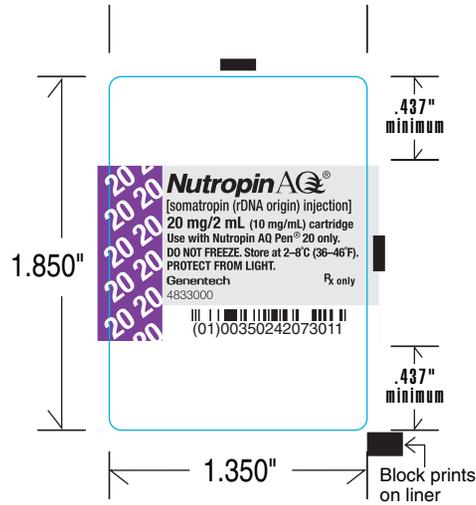
1 DNA Way

South San Francisco, CA 94080-4990

778

**NDA 20-522/S-026 Labeling**

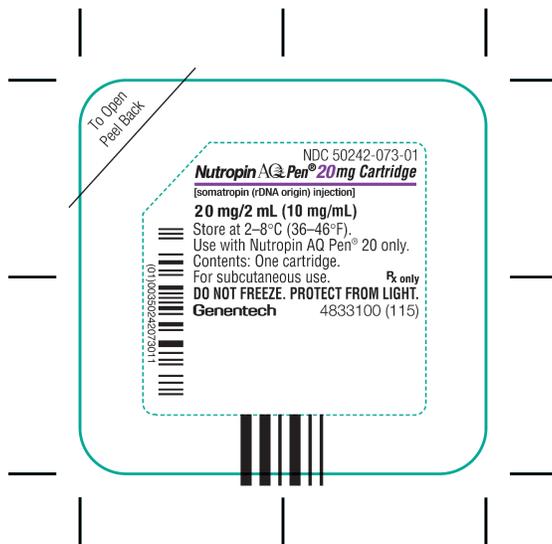
**Cartridge Label**



09-20-07 revised  
**GENENTECH INC**  
 225047  
 P/N 4833000

<b>Topflight CORPORATION</b> <b>PROOF APPROVAL</b>		
CUST NAME		GENENTECH INC
ORDER No.		225047
Proof Has Been Reviewed and Approved for:		
<u>Art</u>	<u>Customer Service</u>	<u>Quality Control</u>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Spelling/Copy	
	Layout/Dimensions	
	Colors/Color Breakdown	
	Signature	Date
Art	<b>Ron Hengst</b>	09-20-07
Customer Service		
Quality Control		
Customer		

**Cartridge Lidstock Label**



651 S ML King Jr Ave • Waukegan, IL 60085 • Phone (847) 336-4200 • FAX (847) 360-4924

**Proof D**

**Product Information**

**P/N: 4833100**  
**J/N: 122696**  
 Cust.: Genentech  
 Size: 2.125X2.062  
 Die#: NA  
 RCR: 0.25

Die Line Does Not Print

**Printing Colors**

 Black	 PMS 2593	 Die	 Varnish
 White			

**Art Checked By**

Artist: KS Date: 09/24/07

Proof Reader: Date:

**CAUTION**

Nosco could not verify copy and/or color break on this proof because:  
 Supplied Copy was illegible.  
 No copy was provided.  
 No color breaks were provided.

**Approved By**

Customer: Date:

Art OK to print  Another proof required  
 See Attached

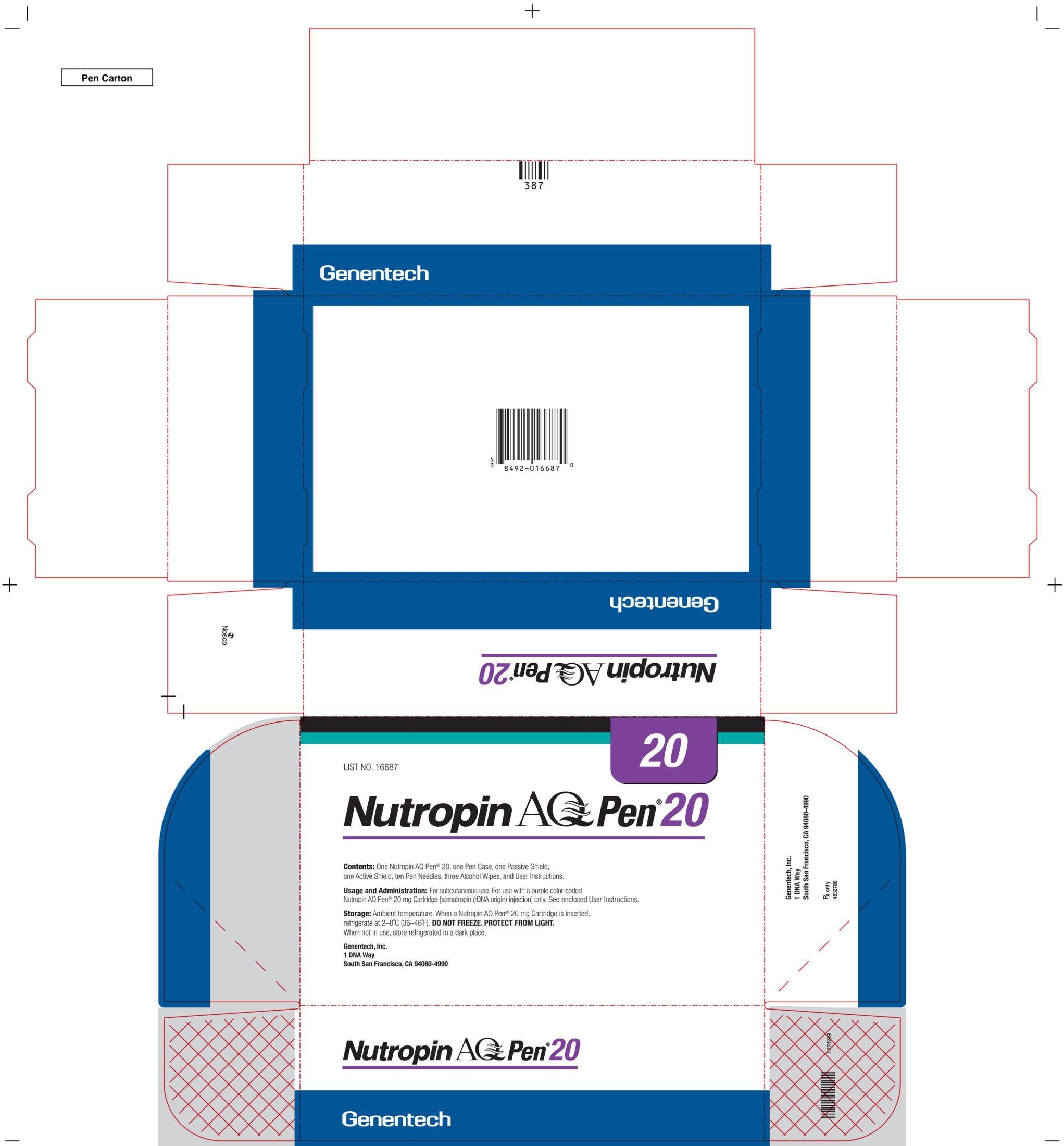
Note: We must have a signed proof before we can begin production.

**Note:** This proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.



		651 S ML King Jr Ave • Waukegan, IL 60085 • Phone (847) 336-4200 • FAX (847) 360-4924		Proof E	
<b>Product Information</b>		<b>Printing Colors</b>		<b>Art Checked By</b>	
P/N: 4832900 J/N: 122700 Cust.: Genentech Size: Die#: 041103 RCR: NA Die Line Does Not Print		Black	PMS 294	PMS 2593	PMS 3272
		PMS 032	White	Die	Varnish KO
Note: This proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.		CAUTION Nosco could not verify copy and/or color break on this proof because: <input type="checkbox"/> Supplied Copy was illegible. <input type="checkbox"/> No copy was provided. <input type="checkbox"/> No color breaks were provided.		Artist: TH Date: 10/05/07 Proof Reader: Date:	
		<b>Approved By</b> Customer: Date:		<input type="checkbox"/> Art OK to print <input type="checkbox"/> Another proof required <input type="checkbox"/> See Attached	
		Note: We must have a signed proof before we can begin production.			

Pen Carton



LIST NO. 16687

# Nutropin AQ Pen<sup>®</sup> 20

20

**Contents:** One Nutropin AQ Pen<sup>®</sup> 20, one Pen Case, one Passive Shield, one Active Shield, ten Pen Needles, three Alcohol Wipes, and User Instructions.

**Usage and Administration:** For subcutaneous use. For use with a purple color-coded Nutropin AQ Pen<sup>®</sup> 20 mg Cartridge (somatropin (rDNA origin) injection) only. See enclosed User Instructions.

**Storage:** Ambient temperature. When a Nutropin AQ Pen<sup>®</sup> 20 mg Cartridge is inserted, refrigerate at 2–8°C (36–46°F). **DO NOT FREEZE. PROTECT FROM LIGHT.** When not in use, store refrigerated in a dark place.

Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990

Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990  
Rx only  
4832700

# Nutropin AQ Pen<sup>®</sup> 20

Genentech

<b>Nosco</b>		651 S ML King Jr Ave • Waukegan, IL 60085 • Phone (847) 336-4200 • FAX (847) 360-4924		<b>Proof C</b>
<b>Product Information</b>	<b>Printing Colors</b>			
<b>P/N:</b> 4832700				
<b>J/N:</b> 122699	Black	PMS 2593	PMS 294	PMS 3272
<b>Cust.:</b> Genentech				
<b>Size:</b> N/A	Dieline	Varnish KO	White	
<b>Die#:</b> 040899				
<b>RCR:</b> N/A				
<b>Die Line Does Not Print</b>				
<b>Note:</b> This digital proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.				
<b>Art Checked By</b>		<b>Approved By</b>		
Artist: BO	Date: 10/05/07	Customer:	Date:	
Proof Reader:	Date:	<input type="checkbox"/> Art OK to print	<input type="checkbox"/> Another proof required	
<p align="center"><b>CAUTION</b></p> <p>Nosco could not verify copy and/or color break on this proof because:</p> <input type="checkbox"/> Supplied copy was illegible. <input type="checkbox"/> No hard copy was provided. <input type="checkbox"/> No color breaks were provided.				
<b>Note:</b> We must have a signed proof before we can begin production.				
The printed piece may not be a perfect match to a PDF. The finished piece should be verified against the customer approved hard copy or a signed hard copy proof.				

**Pen Case Label**



		651 S ML King Jr Ave • Waukegan, IL 60085 • Phone (847) 336-4200 • FAX (847) 360-4924		<b>Proof A</b>																
<b>Product Information</b>		<b>Printing Colors</b>		<b>Art Checked By</b>																
P/N: 4832500 J/N: 122698 Cust.: Genentech Size: 2.0X1.0 Die#: NA RCR: 0.125  Die Line Does Not Print		<table border="1"> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Black</td> <td>PMS 2593</td> <td>Die</td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>White</td> <td>Overall Varnish</td> <td></td> <td></td> </tr> </table>						Black	PMS 2593	Die						White	Overall Varnish			Artist: RB <span style="float: right;">Date: 09/17/07</span> Proof Reader: <span style="float: right;">Date:</span>
																				
Black	PMS 2593	Die																		
																				
White	Overall Varnish																			
<b>Note:</b> This proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.		<p align="center"><b>CAUTION</b></p> <p align="center">Nosco could not verify copy and/or color break on this proof because:                  Supplied Copy was illegible.                  No copy was provided.                  No color breaks were provided.</p>		<b>Approved By</b> Customer: <span style="float: right;">Date:</span> <input type="checkbox"/> Art OK to print <span style="float: right;"><input type="checkbox"/> Another proof required</span> <input type="checkbox"/> See Attached																
				<b>Note:</b> We must have a signed proof before we can begin production.																

**Instructions for the Patient/Parent**

**Part IV: Commonly Asked Questions**

**Q: Do I need to change the needle every time I use my Nutropin AQ Pen?**

A: Yes. We recommend that a new needle be used for every injection. The needle is only sterile on the first use.

**Q: Where should I store my Nutropin AQ Pen?**

A: Your Nutropin AQ Pen should be stored in the case, inside a refrigerator when a cartridge is inserted. When traveling, place your pen case in a cooler. **DO NOT FREEZE. KEEP DRY.**

**Q: Why do I keep my medication in the refrigerator?**

A: To maintain the potency of Nutropin AQ.

**Q: Can I store my Nutropin AQ Pen in the freezer?**

A: No. Freezing will damage the pen and drug.

**Q: How long can I keep my Nutropin AQ Pen and Cartridge outside the refrigerator?**

A: We recommend no longer than one hour. Your healthcare provider will advise you regarding pen storage.

**Q: What is the maximum dose the Nutropin AQ Pen can deliver in one injection?**

A: The maximum dose that may be delivered in one injection depends on the strength of the Nutropin AQ Pen and Cartridge you are using. The maximum dose that may be delivered in one injection is **40 clicks**, which equals:

**4 mg for the Nutropin AQ Pen 10**  
**8 mg for the Nutropin AQ Pen 20**

If you attempt to dose more than the maximum dose at one time, the drug will either be forced out of the needle and wasted or excess pressure will be placed upon the cartridge.

**Q: Is it possible to turn the black dose knob back if I click too many times?**

A: Yes. You can turn the black dose knob backwards until the correct number appears in the LCD.

**Q: What should I do if there is not enough medication left in the cartridge to meet my dosing requirements?**

A: Your healthcare provider will advise you on the procedure for the last dose in the cartridge.

**Q: Why do I have to rewind the black dose knob on my Nutropin AQ Pen every time I replace the cartridge?**

A: This ensures that the plunger push rod completely resets itself back to the starting position. If this is not done, liquid will come out of the needle when a new cartridge is placed into the pen.

**Q: Can I use my Nutropin AQ Pen without the shields?**

A: Yes. Your Nutropin AQ Pen is fully functional without the shields. The shields are optional to help you administer your injection.

**Q: Where is the best place to inject my medication?**

A: Consult your healthcare provider for proper injection sites.

**Q: What should I do if I drop my Nutropin AQ Pen?**

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

**Q: How long can I use my Nutropin AQ Pen?**

A: The Nutropin AQ Pen is designed to last approximately 24 months from the time you first use your pen.

**Q: What does "bt" (blinking or steady) mean in the LCD?**

A: The battery in your Nutropin AQ Pen is losing its charge. Please contact your healthcare provider/distributor for a replacement pen. Batteries typically last 24 months and have a 4-week life from the time the "bt" first appears.

**Q: How do I replace my Nutropin AQ Pen?**

A: Contact your healthcare provider/distributor if you need a replacement part or if you need to replace your entire pen.

**Q: How do I use the dose recall function?**

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

**Q: Is the Nutropin AQ Pen waterproof?**

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

**Q: What does it mean when either three or six bars flash or appear steady on the digital dose display?**

A: When this occurs, it means this pen has been used for 2 years and should be replaced. Your pen has 4 weeks of life remaining from the time that the flashing bars first appear. Ask your healthcare provider for a replacement Nutropin AQ Pen.

**Nutropin AQ Pen<sup>®</sup>10**  
for use with  
**Nutropin AQ Pen<sup>®</sup>10 mg Cartridge**  
[somatropin (rDNA origin) injection]

**Nutropin AQ Pen<sup>®</sup>20**  
for use with  
**Nutropin AQ Pen<sup>®</sup>20 mg Cartridge**  
[somatropin (rDNA origin) injection]

For more information, visit us at [Nutropin.com](http://Nutropin.com) or call **1-866-NUTROPIN (1-866-688-7674)**.

**Genentech, Inc.**  
1 DNA Way  
South San Francisco, CA 94080-4990

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Revision Date September 2007

**INSTRUCTIONS FOR THE PATIENT/PARENT**



4831700 (612)

**Nutropin AQ Pen<sup>®</sup>10**  
for use with  
**Nutropin AQ Pen<sup>®</sup>10 mg Cartridge**  
[somatropin (rDNA origin) injection]

**Nutropin AQ Pen<sup>®</sup>20**  
for use with  
**Nutropin AQ Pen<sup>®</sup>20 mg Cartridge**  
[somatropin (rDNA origin) injection]

**Instructions for the use of the Nutropin AQ Pen 10 & 20 using the Nutropin AQ Pen 10 mg & 20 mg Cartridges.**

**INFORMATION FOR THE PATIENT/PARENT**

**PLEASE KEEP THESE INSTRUCTIONS FOR FUTURE REFERENCE.**

**DO NOT INJECT THE DRUG UNTIL YOUR HEALTHCARE PROVIDER HAS THOROUGHLY TRAINED YOU IN THE PROPER TECHNIQUES.**

**Each Nutropin AQ cartridge must be used with its corresponding color-coded Nutropin AQ Pen. A Nutropin AQ cartridge must not be inserted into a pen with a different color code.**

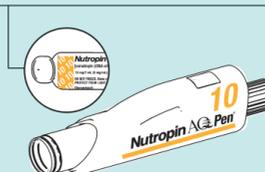
**Caution:**

Before using your Nutropin AQ Pen 10 or Nutropin AQ Pen 20, please read the following instructions carefully. We also suggest you consult your healthcare provider for a demonstration.

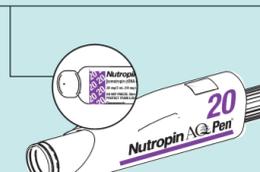
The Nutropin AQ Pen is designed for use only with Genentech's Nutropin AQ Pen Cartridges (for subcutaneous use only).

**Prior to use, always check to make sure that you are using your prescribed strength Nutropin AQ Pen Cartridge (10 mg or 20 mg) and the corresponding color-coded Nutropin AQ Pen for that cartridge.**

**Only use the Nutropin AQ Pen 10 mg Cartridge (yellow band with 10 on label) with the Nutropin AQ Pen 10 (yellow 10 and yellow stripe on Pen).**



**Only use the Nutropin AQ Pen 20 mg Cartridge (purple band with 20 on label) with the Nutropin AQ Pen 20 (purple 20 and purple stripe on Pen).**



Only use the pen needles recommended in Part III or by your healthcare provider.

The dosage scale located beside the window of the cartridge holder should not be used as a dose measurement. It should only be used to estimate the dosage remaining in the cartridge. Always refer to the LCD, not audible clicks, for setting an injection of Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection]. The clicks are audible confirmation that the black dose knob has been moved.

Always store the pen and cartridges in the refrigerator at a temperature between 2–8°C/36–46°F and out of children's reach. Protect from intense light. Use a cooler to store your Nutropin AQ Pen when traveling and ensure the pen is kept dry. The Nutropin AQ Pen Cartridge is designed to withstand a nominal (one hour maximum) period of time outside of the refrigerator on a daily basis. Avoid areas of extreme temperature. Check the expiration date of the cartridge prior to use.

**To guard against the spread of infection, follow these safety measures:**

- Wash your hands before using your pen.
- Clean the cartridge rubber seal with an alcohol swab.
- Avoid touching the cartridge rubber seal at all times.
- If you unintentionally touch the rubber seal, clean it with an alcohol swab.
- Use needles only once.
- Do not use the same needle for more than one person.

**Your Nutropin AQ Pen comes with the following:**

- Alcohol wipes
- Pen needles
- Active shield
- Passive shield

**Your Nutropin AQ Pen Cartridges are supplied separately.**

**Prior to use, always check to make sure that you are using your prescribed strength Nutropin AQ Pen Cartridge (10 mg or 20 mg) and the corresponding color-coded Nutropin AQ Pen for that cartridge.**

<b>Nosco</b>		651 S ML King Jr Ave • Waukegan, IL 60085 • Phone (847) 336-4200 • FAX (847) 360-4924		<b>Proof C</b>
<b>Product Information</b>		<b>Printing Colors</b>		<b>Art Checked By</b>
P/N: 4831700 J/N: 122701 Cust.: Genentech Size: 14.0X13.5 Die#: NA RCR: 0.0				Artist: KS Date: 09/21/07
Die Line Does Not Print				Proof Reader: Date:
<b>Note:</b> This proof is to show size, copy placement and color breaks. Actual colors will be matched on press to approved color standards and/or PMS color swatches.				<b>CAUTION</b> Nosco could not verify copy and/or color break on this proof because: <input type="checkbox"/> Supplied Copy was illegible. <input type="checkbox"/> No copy was provided. <input type="checkbox"/> No color breaks were provided.
				<b>Approved By</b>
				Customer: Date:
				<input type="checkbox"/> Art OK to print <input type="checkbox"/> Another proof required
				<input type="checkbox"/> See Attached
				<b>Note:</b> We must have a signed proof before we can begin production.

## Part I: Preparing and Injecting

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

**Prior to use, always check to make sure that you are using your prescribed strength Nutropin AQ Pen® Cartridge [somatropin (rDNA origin) injection] (10 mg or 20 mg) and the corresponding Nutropin AQ Pen for that cartridge.**

Inspect all new cartridges prior to use. If the solution is cloudy or contains any solid matter, the cartridge should not be used.

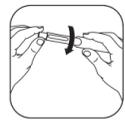


1. Remove the green pen cap and unscrew the cartridge holder from the pen. If necessary, remove the empty cartridge and discard it properly.

2. Press the white reset button.



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



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

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

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



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

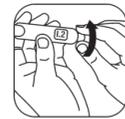


8. If no drop of medicine appears, push the white reset button again. Now turn the black dose knob clockwise (see illustration) by one click, which equals:
  - 0.1 mg for the Nutropin AQ Pen 10**
  - 0.2 mg for the Nutropin AQ Pen 20**

If you accidentally turn it too far, go back one click.

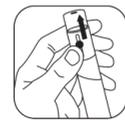
9. While still holding the pen in the upright position, push in the black dose knob again and watch the needle tip for a drop of medicine to appear. Repeat steps 8 and 9 until it appears.

10. Press the white reset button.



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

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



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



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

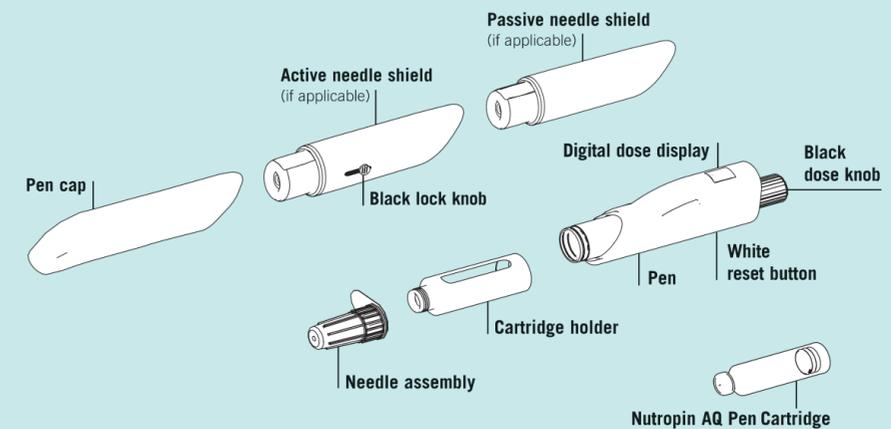


14. Pull the needle shield off the pen (if applicable) and place the larger needle cap on a flat surface. Slide the needle in to pick it up and push the cap completely down over the needle. Twist off the needle and discard it properly.

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

## Nutropin AQ Pen Components:

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



## Part II: Storage and Maintenance

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

- Do not immerse the Nutropin AQ Pen in water or expose to moisture.
- If your pen requires cleaning, do not place underwater. Use a damp cloth to wipe away dirt. Do not use alcohol.
- Always keep your Nutropin AQ Pen and Cartridge refrigerated and protected from light when not in use.
- You may remove the pen and cartridge from the refrigerator up to 45 minutes prior to use.
- Do not let your Nutropin AQ Pen and/or Cartridge freeze. Contact your healthcare provider/distributor for a replacement if either the pen or cartridge malfunctions.
- Avoid excessive temperatures. Cartridge contents are stable for 28 days after first use when stored at 2–8°C/36–46°F.
- When priming a new cartridge, you may need to repeat Part I, steps 8 and 9, up to a total of 6 times to remove air bubbles. Small bubbles may remain and will not affect the dose.
- The pen should contain the Nutropin AQ Pen Cartridge that is being used. Do not remove cartridge between injections.
- Do not store the Nutropin AQ Pen with needle attached.

## Part III: Needles for the Nutropin AQ Pen

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

Name	Gauge/Length
BD Ultra-Fine™ (Original)	29 g/12.7 mm

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

**For subsequent injections with the Nutropin AQ Pen, attach a new needle, push the white reset button, and dial your dose.**

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

**Nutropin AQ Pen<sup>®</sup> 10**  
for use with  
**Nutropin AQ Pen<sup>®</sup> 10 mg Cartridge**  
[somatropin (rDNA origin) injection]

**Nutropin AQ Pen<sup>®</sup> 20**  
for use with  
**Nutropin AQ Pen<sup>®</sup> 20 mg Cartridge**  
[somatropin (rDNA origin) injection]

**NDA 20-522/S-036 Labeling**

100%

**NutropinAQ<sup>®</sup>NuSpin<sup>™</sup> 10**  
[somatropin (rDNA origin) injection] 10 mg/2 mL  
4837700

300%

**NutropinAQ<sup>®</sup>NuSpin<sup>™</sup> 10**  
[somatropin (rDNA origin) injection] 10 mg/2 mL  
4837700

100%

50242-074-01  
**Nutropin AQC<sup>®</sup> NuSpin<sup>™</sup> 10**  
[somatropin (rDNA origin) injection]  
**10 mg/2 mL (5 mg/mL)**  
**DO NOT FREEZE. Store at 2–8°C (36–46°F).**  
**PROTECT FROM LIGHT. FOR SUBCUTANEOUS USE.  $\text{Rx}$  only**  
Genentech, Inc. So. San Francisco, CA 94080-4990

FPO Bar Code  
(01) 00350242075015

4837600

300%

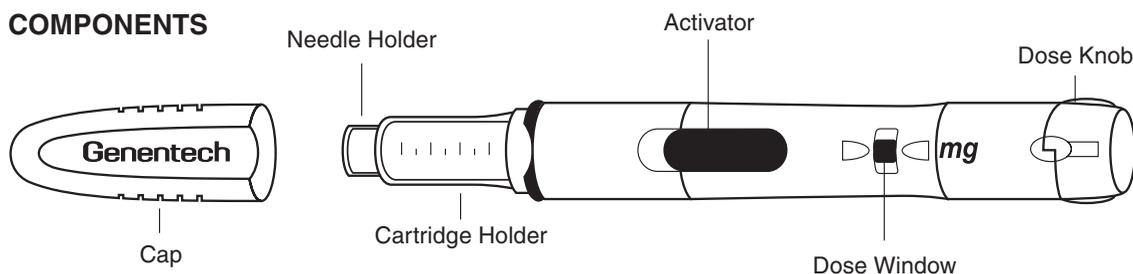
50242-074-01  
**Nutropin AQC<sup>®</sup> NuSpin<sup>™</sup> 10**  
[somatropin (rDNA origin) injection]  
**10 mg/2 mL (5 mg/mL)**  
**DO NOT FREEZE. Store at 2–8°C (36–46°F).**  
**PROTECT FROM LIGHT. For subcutaneous use.  $\text{Rx}$  only**  
Genentech, Inc. So. San Francisco, CA 94080-4990

FPO Bar Code  
(01) 00350242075015

4837600



## COMPONENTS



## INSTRUCTIONS FOR USE

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

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

## IMPORTANT NOTES

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

## FREQUENTLY ASKED QUESTIONS

### 1. What type of needles should be used?

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

### 2. Do I need to change the needle every time I use my Nutropin AQ NuSpin?

Yes. A new needle must be used for every injection. The needle is sterile only for one single injection.

### 3. Do I need to prime the Nutropin AQ NuSpin each time?

No. The NuSpin 10 only needs to be primed once, at first use. After the first use of each NuSpin 10, follow the instructions and skip Step 2.

### 4. When and how do I dispose of my Nutropin AQ NuSpin?

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

### 5. Where should I store my Nutropin AQ NuSpin?

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

### 6. What should I do if my Nutropin AQ NuSpin is dropped or damaged?

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

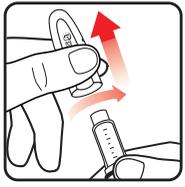
### 7. What should I do if my Nutropin AQ NuSpin needs cleaning?

Use a damp cloth to wipe away dirt. Do not place underwater. Do not use alcohol.

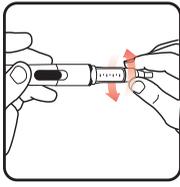
# INSTRUCTIONS FOR USE

## NEW NuSpin 10 SET UP: STEP-BY-STEP INSTRUCTIONS FOR THE FIRST USE OF EACH NEW NUTROPIN AQ NuSpin

### STEP 1: Attach the needle

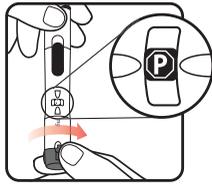


Before you begin, wash your hands.  
Twist gently and pull to remove the NuSpin 10 cap. Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject.  
Open a new needle by peeling off the paper tab from the needle package..

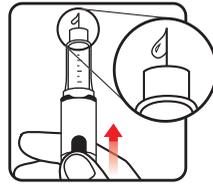


Attach the needle by carefully screwing the needle onto the needle holder. Do not overtighten. Remove both protective covers from the needle and save the outer cover.

### STEP 2: Prime the Nutropin AQ NuSpin

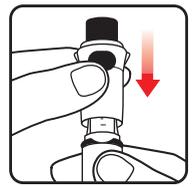


Turn the dose knob to the P position in the dose window. It may take multiple clicks to get to P. Hold the NuSpin 10 with the needle pointing upwards. Gently tap the cartridge holder to move any air bubbles to the NuSpin 10 tip.



Slide the Activator toward the needle. If you do not see fluid at the needle tip, retil to P and slide the Activator forward again. Repeat until you see fluid.

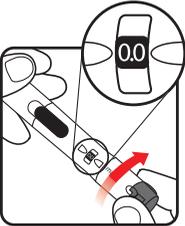
### OPTIONAL STEP: Attach the needle shield



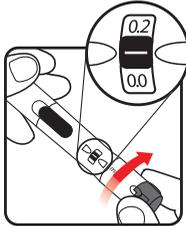
Use of the needle shield is optional. It may be obtained from your healthcare professional. Refer to the detailed instructions provided with the shield and attach it now.

## ROUTINE USE: DOSING AND ADMINISTRATION

### STEP 3: Set the dose

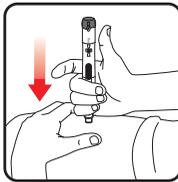


Make sure the dose window reads ► 0.0 ◀. Turn the dose knob until the dose prescribed by your healthcare professional appears in the dose window.



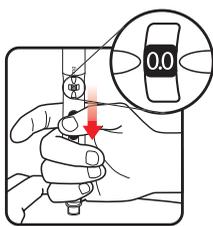
If your dose is “between” two numbers in the dose window, the ► ◀ between those two numbers indicates your dose. Turn the dose knob to ► ◀. The P position indicates a 0.7 mg dose on your NuSpin 10. If you turn the dose knob too far, simply turn it back to the correct dose. (Example above shows a dose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

### STEP 4: Give the injection

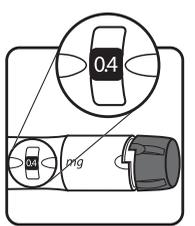


Select and prepare your injection site as instructed by your healthcare professional. Position your hand so you can easily slide the Activator. Push the needle into the skin.

If you are using the needle shield, refer to the instructions provided with the shield.



Slide the Activator toward the needle. Hold the Activator down until the dose knob returns to ► 0.0 ◀ and continue to **hold in place for 5 seconds**. Withdraw the Nutropin AQ NuSpin 10 until the needle is removed from the skin. If the dose knob returns to ► 0.0 ◀, you have received your full dose.



### Check dose given

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

## REMOVAL AND DISPOSAL OF THE NEEDLE

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

If you are using the needle shield, refer to the detailed instructions included with the shield for removing and disposing of the needle. **KEEP YOUR SHIELD FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.**

## STORAGE AND NEXT USE

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

100%

4837800

**10 mg** **Nutropin AQ® NuSpin™ 10**  
[somatropin (rDNA origin) injection]  
10 mg/2 mL (5 mg/mL)  
**PROTECT FROM LIGHT KEEP REFRIGERATED**



**Genentech, Inc.**  
1 DNA Way  
South San Francisco, CA 94080-4990

**10 mg**  
**Nutropin AQ® NuSpin™ 10**  
[somatropin (rDNA origin) injection]  
10 mg/2 mL (5 mg/mL) **KEEP REFRIGERATED**

**FPO**  
Wafer Seal

**FPO**  
UPC Code

**Nutropin AQ® NuSpin™ 10**  
[somatropin (rDNA origin) injection]  
10 mg/2 mL (5 mg/mL) **KEEP REFRIGERATED**

**FPO**  
Wafer Seal

**10 mg**

**FPO**  
Bar Code

**10 mg**  
**Nutropin AQ® NuSpin™ 10**  
[somatropin (rDNA origin) injection]  
10 mg/2 mL (5 mg/mL)  
**PROTECT FROM LIGHT KEEP REFRIGERATED**

**Genentech, Inc.**  
1 DNA Way  
South San Francisco, CA 94080-4990

**10 mg** **Nutropin AQ® NuSpin™ 10**  
[somatropin (rDNA origin) injection]  
10 mg/2 mL (5 mg/mL) **NDC 50242-074-01 List No. 17713**

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

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

**Storage:** Refrigerate at 2–8°C (36–46°F). **DO NOT FREEZE. PROTECT FROM LIGHT.**

**Rx only**



**KEEP REFRIGERATED**

**Genentech**

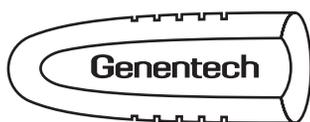
**FPO**  
Wafer Seal

**FPO**  
Wafer Seal

**Nutropin AQ® NuSpin™ 10**

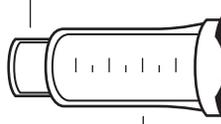
[somatropin (rDNA origin) injection]  
10 mg/2 mL (5 mg/mL)

**COMPONENTS**



Cap

Needle Holder



Cartridge Holder

Activator



Dose Window

Dose Knob



**NDA 20-522/S-037 Labeling**

100%

50242-075-01  
**NutropinAQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
[somatropin (rDNA origin) injection]  
**5 mg/2 mL (2.5 mg/mL)**  
**DO NOT FREEZE. Store at 2–8°C (36–46°F).**  
**PROTECT FROM LIGHT. For subcutaneous use.  only**  
Genentech, Inc. So. San Francisco, CA 94080-4990

FPO Bar Code  
(01) 00350242075015

4837300

300%

50242-075-01  
**NutropinAQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
[somatropin (rDNA origin) injection]  
**5 mg/2 mL (2.5 mg/mL)**  
**DO NOT FREEZE. Store at 2–8°C (36–46°F).**  
**PROTECT FROM LIGHT. For subcutaneous use.  only**  
Genentech, Inc. So. San Francisco, CA 94080-4990

FPO Bar Code  
(01) 00350242075015

4837300

100%

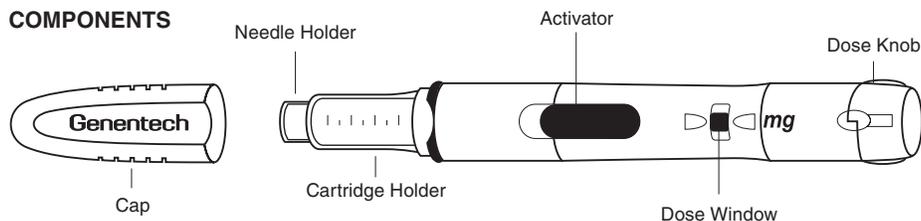
**Nutropin AQ NuSpin™ 5**  
[somatropin (rDNA origin) injection] 5 mg/2 mL  
4837400

300%

**Nutropin AQ NuSpin™ 5**  
[somatropin (rDNA origin) injection] 5 mg/2 mL  
4837400



**COMPONENTS**



**INSTRUCTIONS FOR USE**

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

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

**IMPORTANT NOTES**

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

**FREQUENTLY ASKED QUESTIONS**

**1. What type of needles should be used?**

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

**2. Do I need to change the needle every time I use my Nutropin AQ NuSpin?**

Yes. A new needle must be used for every injection. The needle is sterile only for one single injection.

**3. Do I need to prime the Nutropin AQ NuSpin each time?**

No. The NuSpin 5 only needs to be primed once, at first use. After the first use of each NuSpin 5, follow the instructions and skip Step 2.

**4. When and how do I dispose of my Nutropin AQ NuSpin?**

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

**5. Where should I store my Nutropin AQ NuSpin?**

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

**6. What should I do if my Nutropin AQ NuSpin is dropped or damaged?**

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

**7. What should I do if my Nutropin AQ NuSpin needs cleaning?**

Use a damp cloth to wipe away dirt. Do not place underwater. Do not use alcohol.

## INSTRUCTIONS FOR USE

### NEW NuSpin 5 SET UP: STEP-BY-STEP INSTRUCTIONS FOR THE FIRST USE OF EACH NEW NUTROPIN AQ NuSpin 5

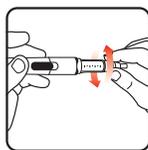
#### STEP 1: Attach the needle



Before you begin, wash your hands.

Twist gently and pull to remove the NuSpin 5 cap. Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject.

Open a new needle by peeling off the paper tab from the needle package.



Attach the needle by carefully screwing the needle onto the needle holder. Do not overtighten.

Remove both protective covers from the needle and save the outer cover.

#### STEP 2: Prime the Nutropin AQ NuSpin



Turn the dose knob to the P position in the dose window.

It may take multiple clicks to get to P. Hold the NuSpin 5 with the needle pointing upwards. Gently tap the cartridge holder to move any air bubbles to the NuSpin 5 tip.



Slide the Activator toward the needle.

If you do not see fluid at the needle tip, re-dial to P and slide the Activator forward again.

Repeat until you see fluid.

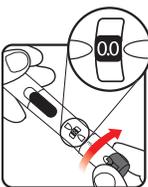
#### OPTIONAL STEP: Attach the needle shield



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

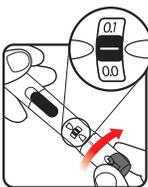
### ROUTINE USE: DOSING AND ADMINISTRATION

#### STEP 3: Set the dose



Make sure the dose window reads 0.0.

Turn the dose knob until the dose prescribed by your healthcare professional appears in the dose window.



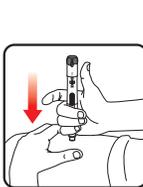
If your dose is “between” two numbers in the dose window, the — between those two numbers indicates your dose. Turn the dose knob to —.

The P position indicates a 0.35 mg dose on your NuSpin 5.

If you turn the dose knob too far, simply turn it back to the correct dose.

(Example above shows a dose of 0.05 mg, represented by —.)

#### STEP 4: Give the injection

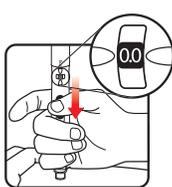


Select and prepare your injection site as instructed by your healthcare professional.

Position your hand so you can easily slide the Activator.

Push the needle into the skin.

If you are using the needle shield, refer to the instructions provided with the shield.



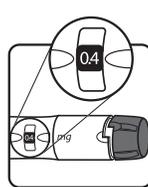
Slide the Activator toward the needle.

Hold the Activator down until the dose knob returns to 0.0 and continue to **hold in place for 5 seconds**.

Withdraw the Nutropin AQ NuSpin 5 until the needle is removed from the skin.

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

#### Check dose given



If the dose knob stops before it returns to 0.0, your Nutropin AQ NuSpin 5 is empty and you have not received your full dose.

The number shown in the dose window is the amount needed to obtain a full dose.

Your healthcare professional will advise you on the procedure for using the last dose in the NuSpin 5.

### REMOVAL AND DISPOSAL OF THE NEEDLE

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

If you are using the needle shield, refer to the detailed instructions included with the shield for removing and disposing of the needle. **KEEP YOUR SHIELD FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.**

### STORAGE AND NEXT USE

Replace the cap and store your NuSpin 5 inside the refrigerator at 2–8°C (36–46°F). Protect from light. For the next use, it is already primed. Follow the instructions and skip Step 2.

100%

4837500

**5 mg** **Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
[somatropin (rDNA origin) injection]  
5 mg/2 mL (2.5 mg/mL)  
**PROTECT FROM LIGHT KEEP REFRIGERATED**

**Genentech, Inc.**  
1 DNA Way  
South San Francisco, CA 94080-4990



FPO  
Wafer Seal

**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
[somatropin (rDNA origin) injection]  
5 mg/2 mL (2.5 mg/mL) **KEEP REFRIGERATED**

**5 mg**

FPO  
UPC Code

**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
[somatropin (rDNA origin) injection]  
5 mg/2 mL (2.5 mg/mL) **KEEP REFRIGERATED**

**5 mg**

FPO  
Wafer Seal

FPO  
Bar Code

**5 mg** [somatropin (rDNA origin) injection]  
5 mg/2 mL (2.5 mg/mL) **PROTECT FROM LIGHT KEEP REFRIGERATED**

**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990

**5 mg** **Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**  
[somatropin (rDNA origin) injection]  
5 mg/2 mL (2.5 mg/mL)

NDC 50242-075-01 List No. 17710

**Contents:** One Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5, Instructions for Use, and Package Insert. Each Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5 contains 5 mg (approximately 15 IU) of Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection] formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate in 2 mL (2.5 mg/mL).

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

**Storage:** Refrigerate at 2–8°C (36–46°F). **DO NOT FREEZE. PROTECT FROM LIGHT.**

Rx only



**KEEP REFRIGERATED**

**Genentech**

FPO  
Wafer Seal

FPO  
Wafer Seal

**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 5**

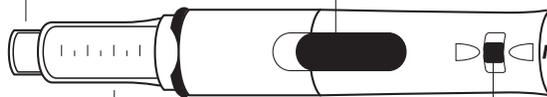
[somatropin (rDNA origin) injection]  
5 mg/2 mL (2.5 mg/mL)

**COMPONENTS**



Cap

Needle Holder



Cartridge Holder

Activator

Dose Knob

Dose Window

100%

**NutropinAQ<sup>®</sup>NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection] 20 mg/2 mL  
4838000

300%

**NutropinAQ<sup>®</sup>NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection] 20 mg/2 mL  
4838000

100%

50242-076-01  
**NutropinAQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
**20 mg/2 mL (10 mg/mL)**  
**DO NOT FREEZE. Store at 2–8°C (36–46°F).**  
**PROTECT FROM LIGHT. For subcutaneous use.  $\text{Rx}$  only**  
Genentech, Inc. So. San Francisco, CA 94080-4990

FPO Bar Code  
(01) 00350242075015

4837900

300%

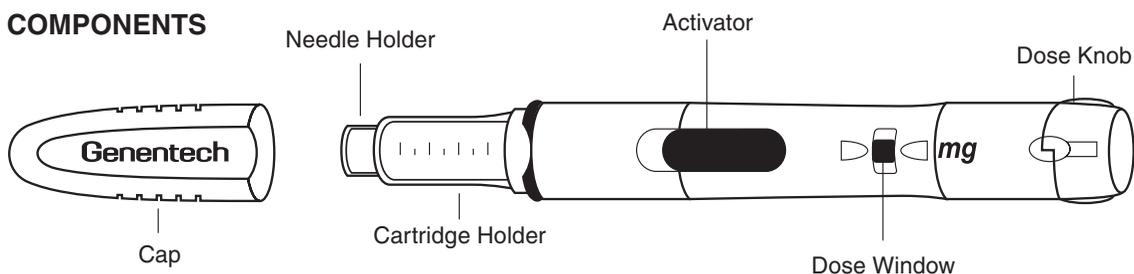
50242-076-01  
**NutropinAQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
**20 mg/2 mL (10 mg/mL)**  
**DO NOT FREEZE. Store at 2–8°C (36–46°F).**  
**PROTECT FROM LIGHT. For subcutaneous use.  $\text{Rx}$  only**  
Genentech, Inc. So. San Francisco, CA 94080-4990

FPO Bar Code  
(01) 00350242075015

4837900



## COMPONENTS



## INSTRUCTIONS FOR USE

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

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

## IMPORTANT NOTES

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

## FREQUENTLY ASKED QUESTIONS

### 1. What type of needles should be used?

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

### 2. Do I need to change the needle every time I use my Nutropin AQ NuSpin?

Yes. A new needle must be used for every injection. The needle is sterile only for one single injection.

### 3. Do I need to prime the Nutropin AQ NuSpin each time?

No. The NuSpin 20 only needs to be primed once, at first use. After the first use of each NuSpin 20, follow the instructions and skip Step 2.

### 4. When and how do I dispose of my Nutropin AQ NuSpin?

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

### 5. Where should I store my Nutropin AQ NuSpin?

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

### 6. What should I do if my Nutropin AQ NuSpin is dropped or damaged?

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

### 7. What should I do if my Nutropin AQ NuSpin needs cleaning?

Use a damp cloth to wipe away dirt. Do not place underwater. Do not use alcohol.

# INSTRUCTIONS FOR USE

## NEW NuSpin 20 SET UP: STEP-BY-STEP INSTRUCTIONS FOR THE FIRST USE OF EACH NEW NUTROPIN AQ NuSpin 20

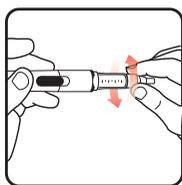
### STEP 1: Attach the needle



Before you begin, wash your hands.

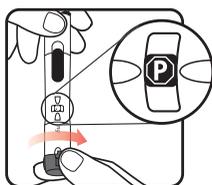
Twist gently and pull to remove the NuSpin 20 cap. Inspect the cartridge before use to ensure that the medicine in it is clear. If it is cloudy or hazy, do not inject.

Open a new needle by peeling off the paper tab from the needle package.

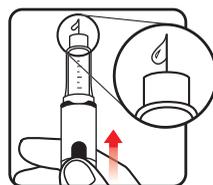


Attach the needle by carefully screwing the needle onto the needle holder. Do not overtighten. Remove both protective covers from the needle and save the outer cover.

### STEP 2: Prime the Nutropin AQ NuSpin



Turn the dose knob to the P position in the dose window. It may take multiple clicks to get to P. Hold the NuSpin 20 with the needle pointing upwards. Gently tap the cartridge holder to move any air bubbles to the NuSpin 20 tip.



Slide the Activator toward the needle. If you do not see fluid at the needle tip, retil to P and slide the Activator forward again. Repeat until you see fluid.

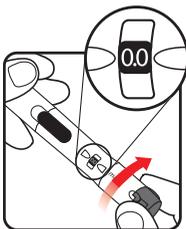
### OPTIONAL STEP: Attach the needle shield



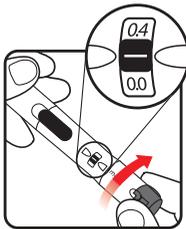
Use of the needle shield is optional. It may be obtained from your healthcare professional. Refer to the detailed instructions provided with the shield and attach it now.

## ROUTINE USE: DOSING AND ADMINISTRATION

### STEP 3: Set the dose



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

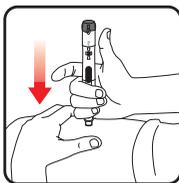


If your dose is “between” two numbers in the dose window, the ► ◀ between those two numbers indicates your dose. Turn the dose knob to ► ◀. The P position indicates a 1.4 mg dose on your NuSpin 20.

If you turn the dose knob too far, simply turn it back to the correct dose.

(Example above shows a dose of 0.2 mg, represented by ► ◀.)

### STEP 4: Give the injection

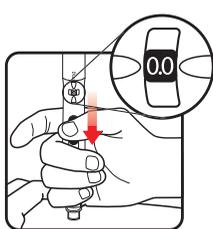


Select and prepare your injection site as instructed by your healthcare professional.

Position your hand so you can easily slide the Activator.

Push the needle into the skin.

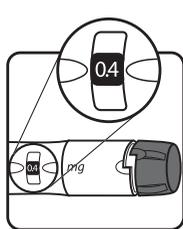
If you are using the needle shield, refer to the instructions provided with the shield.



Slide the Activator toward the needle. Hold the Activator down until the dose knob returns to ► 0.0 ◀ and continue to **hold in place for 5 seconds**.

Withdraw the Nutropin AQ NuSpin 20 until the needle is removed from the skin.

If the dose knob returns to ► 0.0 ◀, you have received your full dose.



### Check dose given

If the dose knob stops before it returns to ► 0.0 ◀, your Nutropin AQ NuSpin 20 is empty and you have not received your full dose.

The number shown in the dose window is the amount needed to obtain a full dose. Your healthcare professional will advise you on the procedure for using the last dose in the NuSpin 20.

## REMOVAL AND DISPOSAL OF THE NEEDLE

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

If you are using the needle shield, refer to the detailed instructions included with the shield for removing and disposing of the needle. **KEEP YOUR SHIELD FOR FUTURE USE WITH A NEW NEEDLE ASSEMBLY.**

## STORAGE AND NEXT USE

Replace the cap and store your NuSpin 20 inside the refrigerator at 2–8°C (36–46°F). Protect from light. For the next use, it is already primed. Follow the instructions and skip Step 2.

100%

4838100

**20 mg** **Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
20 mg/2 mL (10 mg/mL)  
**PROTECT FROM LIGHT KEEP REFRIGERATED**

**Genentech, Inc.**  
1 DNA Way  
South San Francisco, CA 94080-4990



**20 mg**  
**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
20 mg/2 mL (10 mg/mL) **KEEP REFRIGERATED**

**FPO**  
Wafer Seal

**FPO**  
UPC Code

**20 mg**  
**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
20 mg/2 mL (10 mg/mL) **KEEP REFRIGERATED**

**FPO**  
Wafer Seal

**FPO**  
Bar Code

**20 mg** **Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
20 mg/2 mL (10 mg/mL)  
**PROTECT FROM LIGHT KEEP REFRIGERATED**

**Genentech, Inc.**  
1 DNA Way  
South San Francisco, CA 94080-4990

**20 mg** **Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
20 mg/2 mL (10 mg/mL)

NDC 50242-076-01 List No. 17715

**Contents:** One Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20, Instructions for Use, and Package Insert. Each Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20 contains 20 mg (approximately 60 IU) of Nutropin AQ<sup>®</sup> [somatropin (rDNA origin) injection] formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate in 2 mL (10 mg/mL).

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

**Storage:** Refrigerate at 2–8°C (36–46°F). **DO NOT FREEZE. PROTECT FROM LIGHT.**

Rx only



**KEEP REFRIGERATED**

**Genentech**

**FPO**  
Wafer Seal

**FPO**  
Wafer Seal

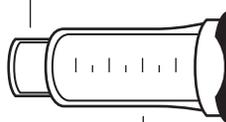
**Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup> 20**  
[somatropin (rDNA origin) injection]  
20 mg/2 mL (10 mg/mL)

**COMPONENTS**



Cap

Needle Holder



Cartridge Holder

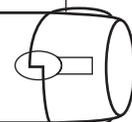
Activator



Dose Window

mg

Dose Knob



100%

**Needle Shield for use with  
Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup>**

[somatropin (rDNA origin) injection]

**See enclosed Instructions for Use**  
Contents: 1 Needle Shield and Instructions for Use  
Recommended: Use needle shield with needles  
8 mm (5/16") or longer  
AC/0424/14/0000/01  
List# NNNNN Lot# NNNN EXP Date

4839300

Genentech, Inc.  
So. San Francisco, CA 94080-4990  
Manufactured in Great Britain

300%

**Needle Shield for use with  
Nutropin AQ<sup>®</sup> NuSpin<sup>™</sup>**  
[somatropin (rDNA origin) injection]

**See enclosed Instructions for Use**  
Contents: 1 Needle Shield and Instructions for Use  
Recommended: Use needle shield with needles  
8 mm (5/16") or longer  
AC/0424/14/0000/01  
List# NNNNN Lot# NNNN EXP Date

4839300

**Genentech, Inc.**  
So. San Francisco, CA 94080-4990  
Manufactured in Great Britain



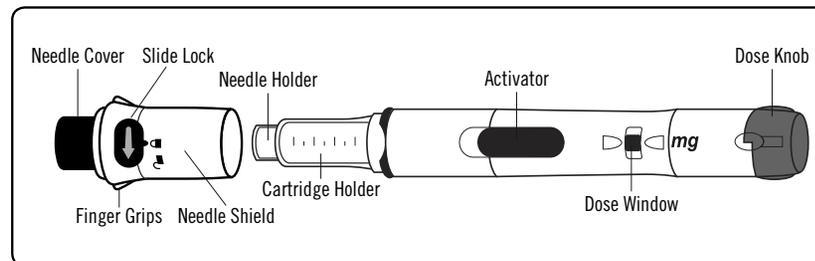
**Nutropin AQ NuSpin™**  
[somatropin (rDNA origin) injection]

## Needle Shield INSTRUCTIONS FOR USE

### IMPORTANT INFORMATION ABOUT THE NEEDLE SHIELD

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

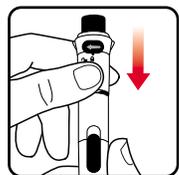
- The NuSpin can be used with or without the shield
- When using the optional needle shield, we recommend needles 8 mm (5/16") or longer to provide adequate needle length during usage
- Read the instructions below for using the shield and **keep these instructions for future reference**
- Remove both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



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

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

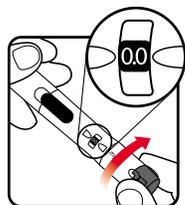
#### STEP 3: Attach the needle shield



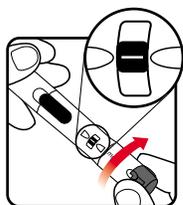
Make sure the shield is in the locked position with the slide lock in line with the .

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

#### STEP 4: Set the dose

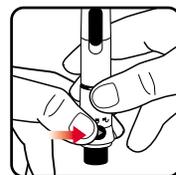


Make sure the dose window reads **► 0.0 ◀**. Turn the dose knob to the dose prescribed by your healthcare professional until it appears in the dose window.

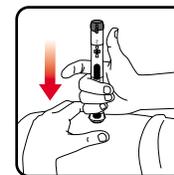


If your dose is "between" two numbers in the dose window, the **► ◀** between those two numbers indicates your dose. Turn the dose knob to **► ◀**. If you turn the dose knob too far, simply turn it back to the correct dose.

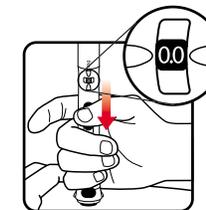
#### STEP 5: Give the injection



Select and prepare your injection site as instructed by your healthcare professional. Hold the needle shield in place with one hand. With the other hand, unlock the shield by moving the slide lock in the direction of the arrow until the pointer on the slide lock is aligned with the .

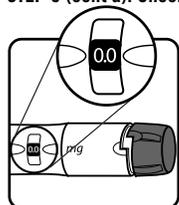


Set the tip of the needle cover flat on the prepared injection site. Without touching the Activator or slide lock, position your hand so you can easily reach the Activator. Push the needle into the skin by pushing the NuSpin downward until the needle cover is fully depressed and the needle is in the skin.

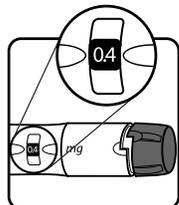


SLIDE the Activator toward the needle. Continue to hold the Activator down until the dose knob returns to **► 0.0 ◀** and hold in place for another 5 seconds. Withdraw the NuSpin until the needle is removed from the skin.

#### STEP 5 (cont'd): Check dose given

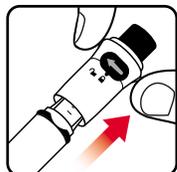


If the dose knob returns to **► 0.0 ◀**, you have received your full dose. If the dose knob stops before it returns to **► 0.0 ◀**, your NuSpin is empty and you have not received your full dose.



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

#### Removing the Shield from the NuSpin



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

#### Removal and Disposal of the Needle

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

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

**Genentech**

Rx only

1 DNA Way  
South San Francisco, CA 94080-4990  
1-866-NUTROPIN

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