

1 **Nutropin Depot<sup>®</sup>**  
2 **[somatropin (rDNA origin) for injectable suspension]**

3 **DESCRIPTION**

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

13 Somatropin is a highly purified preparation. Biological potency is determined using a  
14 cell proliferation bioassay.

15 The Nutropin Depot formulation consists of micronized particles of rhGH embedded in  
16 biocompatible, biodegradable polylactide-coglycolide (PLG) microspheres. Nutropin  
17 Depot is packaged in vials as a sterile, white to off-white, preservative-free, free-flowing  
18 powder. Before administration, the powder is suspended in Diluent for Nutropin Depot  
19 (a sterile aqueous solution).

20 Each 13.5 mg 3 cc single-use vial of Nutropin Depot contains 13.5 mg somatropin,  
21 1.2 mg zinc acetate, 0.8 mg zinc carbonate, and 68.9 mg PLG.

22 Each 18 mg 3 cc single-use vial of Nutropin Depot contains 18 mg somatropin,  
23 1.6 mg zinc acetate, 1.1 mg zinc carbonate, and 91.8 mg PLG.

24 Each 22.5 mg 3 cc single-use vial of Nutropin Depot contains 22.5 mg somatropin,  
25 2.0 mg zinc acetate, 1.4 mg zinc carbonate, and 114.8 mg PLG.

26 Each dosage size contains an overage of rhGH microspheres to ensure delivery of  
27 labeled contents.

28 Each 1.5 mL single-use vial of Diluent for Nutropin Depot contains 30 mg/mL  
29 carboxymethylcellulose sodium salt, 1 mg/mL polysorbate 20, 9 mg/mL sodium chloride,  
30 and sterile water for injection; pH 5.8–7.2.

31 **CLINICAL PHARMACOLOGY**

32 **General**

33 In vivo preclinical and clinical testing has demonstrated that growth hormone (GH)  
34 stimulates longitudinal bone growth and elevates insulin-like growth factor-I (IGF-I)  
35 levels.

36 Actions that have been demonstrated for hGH include:

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

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

54 **C. Carbohydrate Metabolism** - GH is a modulator of carbohydrate metabolism.  
55 Patients with inadequate endogenous secretion of GH sometimes experience  
56 fasting hypoglycemia that is improved by treatment with GH. GH therapy may  
57 decrease insulin sensitivity. Administration of hGH formulated for daily dosing  
58 resulted in increased mean fasting and postprandial insulin levels, more commonly  
59 in overweight or obese individuals. Mean trough levels for fasting and postprandial  
60 insulin were unchanged after 3 or 6 months of Nutropin Depot therapy in GHD  
61 children. As with daily GH, mean trough levels for fasting glucose, postprandial  
62 glucose, and hemoglobin A<sub>1c</sub> remained unchanged after 3 or 6 months of Nutropin  
63 Depot therapy.

64 **D. Lipid Metabolism** - In GHD patients, administration of GH formulated for daily  
65 dosing resulted in lipid mobilization, reduction in body fat stores, increased plasma  
66 fatty acids, and decreased plasma cholesterol levels.

67 **E. Mineral Metabolism** - The retention of total body potassium in response to  
68 GH administration apparently results from cellular growth. Serum levels of  
69 inorganic phosphorus may increase slightly in patients with inadequate secretion of  
70 endogenous GH due to metabolic activity associated with bone growth as well as  
71 increased tubular reabsorption of phosphate by the kidney. Serum calcium is not  
72 significantly altered in these patients. Sodium retention also occurs. (See  
73 PRECAUTIONS: Laboratory Tests.) GH therapy results in increases in serum  
74 alkaline phosphatase.

75 **F. Connective Tissue Metabolism** - GH stimulates the synthesis of chondroitin  
76 sulfate and collagen as well as the urinary excretion of hydroxyproline.

### 77 **Pharmacokinetics**

78 Nutropin Depot is a long-acting dosage form of somatropin designed to be administered  
79 by subcutaneous (SC) injection once or twice monthly. Following the injection, bioactive  
80 rhGH is released from the microspheres into the SC environment initially by diffusion,  
81 followed by both polymer degradation and diffusion. Although no studies have been  
82 performed that address the distribution, elimination, or metabolism of Nutropin Depot,  
83 once released and absorbed the rhGH is believed to be distributed and eliminated in a  
84 manner similar to somatropin formulated for daily administration.

85 The serum hGH concentration-time profiles of single doses of 0.75 mg/kg and  
86 1.5 mg/kg of Nutropin Depot have been characterized in pediatric GHD patients (refer to  
87 Figure 1). The in vivo profiles are characterized by an initial rapid release followed by a  
88 slow decline in GH concentration. Both the maximum concentrations achieved ( $C_{max}$ )  
89 and total exposure ( $AUC_{0-28 \text{ days}}$ ) appear to be proportional to dose. Serum hGH levels  
90 greater than 1  $\mu\text{g/L}$  persist for approximately 11–14 days postdose for the two doses.  
91 Repeated dosing of Nutropin Depot over 6 months showed no progressive  
92 accumulation of GH.

93 Absorption—In a study of Nutropin Depot in pediatric patients with GHD, an SC dose of  
94 0.75 mg/kg ( $n=12$ ) or 1.5 mg/kg ( $n=8$ ) was administered. The mean  $\pm$  SD hGH  $C_{max}$   
95 values were  $48\pm 26 \mu\text{g/L}$  and  $90\pm 23 \mu\text{g/L}$ , respectively, at 12–13 hours postdose. The  
96 corresponding  $AUC_{0-28 \text{ days}}$  values were  $83\pm 49 \mu\text{g} \cdot \text{day/L}$  and  $140\pm 34 \mu\text{g} \cdot \text{day/L}$ ,  
97 respectively, for the two doses. For the 0.75 mg/kg and 1.5 mg/kg doses, the  $AUC_{0-2 \text{ days}}$   
98 accounted for approximately  $52\pm 16$  percent and  $61\pm 10$  percent of the total  $AUC_{0-28 \text{ days}}$ ,  
99 respectively. Estimates of relative bioavailability in GHD children for a single dose of  
100 Nutropin Depot ranged from 33% to 38% when compared to a single dose of Nutropin  
101 AQ<sup>®</sup> [somatropin (rDNA origin) injection] in healthy adults, and from 48% to 55% when  
102 compared to chronically dosed Protropin<sup>®</sup> (somatrem for injection) in GHD children.

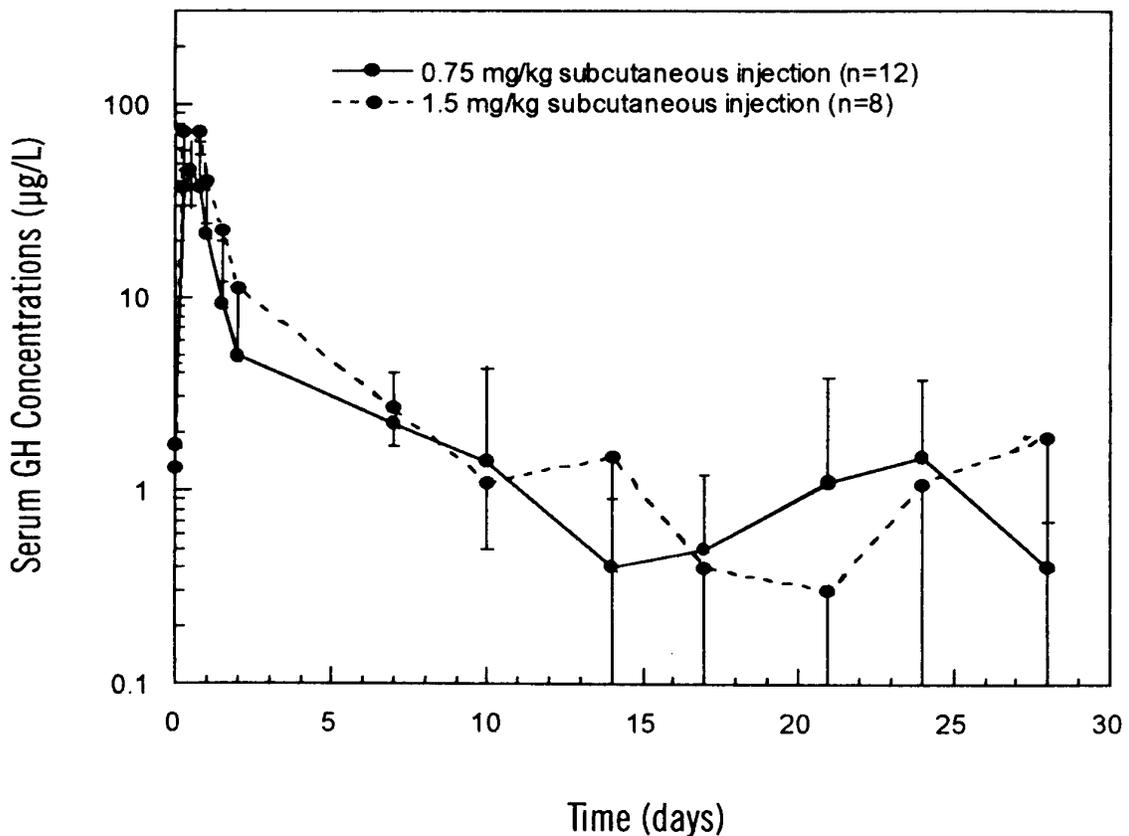
103 Distribution—Animal studies with rhGH formulated for daily administration showed that  
104 GH localizes to highly perfused organs, particularly the liver and kidney. The volume of  
105 distribution at steady state for rhGH formulated for daily administration in healthy adult  
106 males is about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

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

112 Elimination—The mean terminal  $t_{1/2}$  after intravenous (IV) administration of rhGH  
113 formulated for daily administration in healthy adult males is estimated to be  
114  $19.5 \pm 3.1$  minutes. Clearance of rhGH after IV administration in healthy adults and  
115 children is reported to be in the range of 116–174 mL/hr/kg.

116  
117  
118

**Figure 1**  
**Single-Dose Mean (SD) GH Concentrations in Pediatric GHD Patients**



119  
120

121 **Special Populations**

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

124 Gender—Following administration of either 0.75 mg/kg or 1.5 mg/kg Nutropin Depot,  
125 Day 1 GH levels were higher in females compared to males. No relationship was  
126 observed between gender and pharmacodynamic marker (IGF-I and IGFBP-3) levels.

127 Race—The effect of race on Nutropin Depot disposition is unknown due to the limited  
128 number of non-Caucasian patients in the Nutropin Depot studies.

129 Growth Hormone Deficiency—Nutropin Depot has not been studied in healthy adults or  
130 children. However, reported values for clearance of rhGH formulated for daily  
131 administration in adults and children with GHD range from 138–245 mL/hr/kg and are  
132 similar to those observed in healthy adults and children. Mean terminal  $t_{1/2}$  values  
133 following IV and SC administration in adult and pediatric patients with GHD are also  
134 similar to those observed in healthy adult males.

135 Renal Insufficiency—Nutropin Depot has not been studied in patients with renal  
136 insufficiency. Children and adults with chronic renal failure (CRF) and end-stage renal  
137 disease (ESRD) tend to have decreased clearance of rhGH formulated for daily  
138 administration compared with normals. Endogenous GH production may also increase  
139 in some individuals with ESRD. However, no GH accumulation has been reported in  
140 children with CRF or ESRD dosed with daily regimens.

141 Hepatic Insufficiency—Nutropin Depot has not been studied in patients with hepatic  
142 insufficiency. A reduction in clearance of rhGH formulated for daily administration has  
143 been noted in patients with severe liver dysfunction. The clinical significance of this  
144 decrease is unknown.

145 **Pharmacodynamics**

146 IGF-I levels peaked between 1.5 and 3.5 days postdose and remained above baseline  
147 for approximately 16 to 20 days, confirming GH activity for an extended period.

148 Repeated dosing of Nutropin Depot over 6 months showed no progressive  
149 accumulation of IGF-I (as shown in Figure 2) or IGF-binding protein 3 (IGFBP-3).

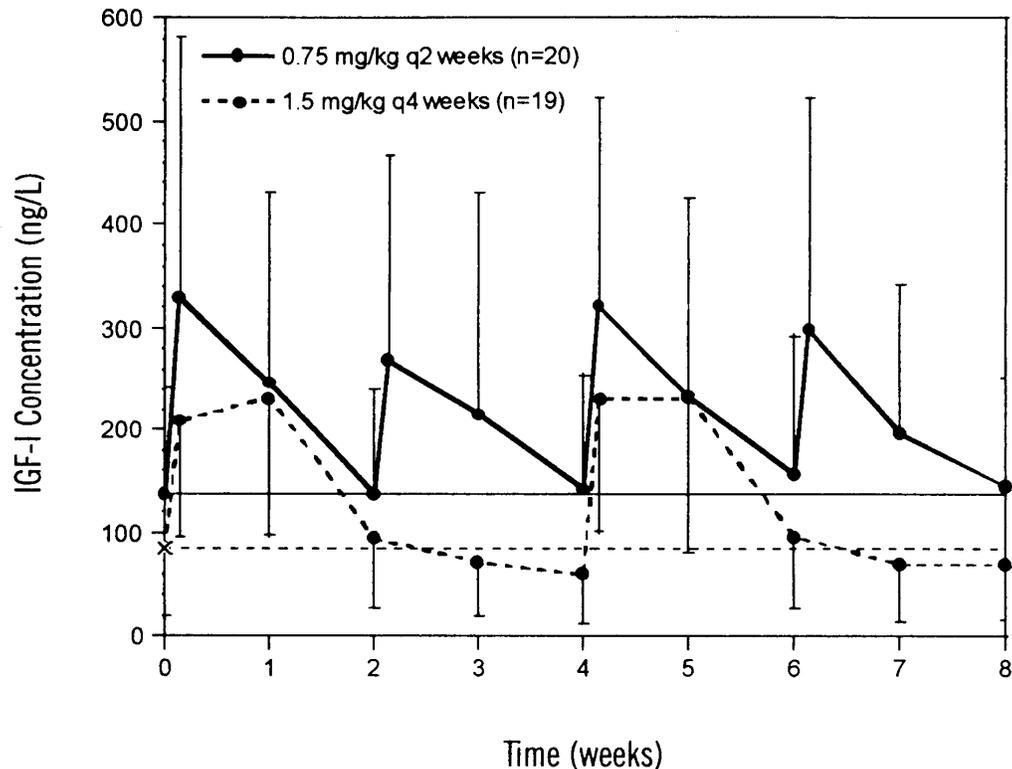
150

151

152

153

**Figure 2**  
**Repeated-Dose Mean (SD) IGF-I Concentrations in**  
**Pediatric GHD Patients**



154  
155

## 156 Efficacy Studies

### 157 Pediatric Growth Hormone Deficiency (GHD)

158 In two multicenter, open-label clinical studies in prepubertal children (mean age ( $\pm$  SD)  
159  $7.4 \pm 2.8$ ) with idiopathic or organic GHD previously untreated with rhGH, 91 patients  
160 were treated with Nutropin Depot at 1.5 mg/kg once monthly or 0.75 mg/kg twice  
161 monthly by subcutaneous injection for up to six months. (See DOSAGE AND  
162 ADMINISTRATION for the number of injections required per dose.) The mean prestudy  
163 growth rate was  $4.8 \pm 2.4$  cm/yr ( $n=89$ ). The dose-pooled, mean 6-month annualized  
164 growth rate on Nutropin Depot therapy was  $8.4 \pm 2.2$  cm/yr ( $n=89$ ).

165 Seventy-six patients continued treatment in an extension study. For patients who  
166 completed 12 months the mean growth rate was  $7.8 \pm 1.9$  cm/yr for the two dose groups  
167 combined ( $n=69$ ). Mean height SD score changed from  $-3.0 \pm 1.0$  prestudy to  $-2.5 \pm 0.9$  at  
168 Month 12 ( $n=69$ ). The mean 0 to 12 month change in bone age was  $1.0 \pm 0.4$  years  
169 ( $n=63$ ). During the long-term extension study, fourteen of seventy-five (19%) patients  
170 discontinued due to dissatisfaction with growth response. Historical studies of GHD  
171 children treated with daily Protropin® (somatrem for injection) or Nutropin® [somatropin  
172 (rDNA origin) for injection] injections for 12 months at 0.3 mg/kg weekly had the

Nutropin Depot<sup>®</sup> [somatotropin (rDNA origin) for injectable suspension]

173 following mean values: baseline growth rate 3.6 to 4.8 cm/yr; first year growth rate 10.1  
174 to 11.3 cm/yr; first year change in bone age 1.1 to 1.5 years.

175 In a dose-ranging study, 24 patients previously treated with daily GH (mean age  
176  $9.6 \pm 2.2$  years; mean duration of prior GH therapy  $2.8 \pm 1.6$  yr, range 0.9 to 6.1 yr) were  
177 switched to Nutropin Depot therapy at the above doses. The mean growth rate on  
178 previous treatment was  $8.2 \pm 3.0$  cm/yr (range 3.2 to 13.1 cm/yr) and on Nutropin Depot  
179 was  $5.1 \pm 2.0$  cm/yr (range 2.4 to 9.6 cm/yr). During a long-term extension study, four of  
180 ten previously treated patients discontinued due to dissatisfaction with growth response.  
181 Historical studies of GHD children (n=181) treated with daily Protropin or Nutropin at a  
182 dose of 0.3 mg/kg weekly had the following mean growth rates: first year growth rate  
183 9.7 to 11.4 cm/yr; second year growth rate 8.1 to 8.9 cm/yr; third year growth rate 7.5 to  
184 7.8 cm/yr; fourth year growth rate 6.6 to 7.1 cm/yr.

## 185 **INDICATIONS AND USAGE**

186 Nutropin Depot<sup>®</sup> [somatotropin (rDNA origin) for injectable suspension] is indicated for the  
187 long-term treatment of growth failure due to a lack of adequate endogenous  
188 GH secretion.

189 Considerations for use:—As with any GH treatment, patients should be monitored  
190 closely throughout therapy for growth response to Nutropin Depot. Failure to respond  
191 adequately requires careful assessment, as described under DOSAGE AND  
192 ADMINISTRATION. Patients for whom no discernible cause is found should be  
193 considered for a course of treatment with a daily form of rhGH. Experience in patients  
194 who were treated with daily GH and switched to Nutropin Depot is limited.

## 195 **CONTRAINDICATIONS**

196 Growth hormone should not be initiated to treat patients with acute critical illness due to  
197 complications following open heart or abdominal surgery, multiple accidental trauma, or  
198 to patients having acute respiratory failure. Two placebo-controlled clinical trials in  
199 non-growth hormone-deficient adult patients (n=522) with these conditions revealed a  
200 significant increase in mortality (41.9% vs. 19.3%) among somatotropin-treated patients  
201 (doses 5.3–8 mg/day) compared to those receiving placebo (see WARNINGS).

202 Nutropin Depot should not be used for growth promotion in pediatric patients with  
203 closed epiphyses.

204 Nutropin Depot should not be used in patients with active neoplasia. GH therapy should  
205 be discontinued if evidence of neoplasia develops.

206 Growth hormone is contraindicated in patients with Prader-Willi syndrome who are  
207 severely obese or have severe respiratory impairment (see WARNINGS). Unless  
208 patients with Prader-Willi syndrome also have a diagnosis of growth hormone  
209 deficiency, Nutropin Depot is not indicated for the long term treatment of pediatric  
210 patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Revised language  
per FDA letter  
dated 30 March

## 211 **WARNINGS**

212 See CONTRAINDICATIONS for information on increased mortality in patients with  
213 acute critical illnesses in intensive care units due to complications following open heart  
214 or abdominal surgery, multiple accidental trauma, or with acute respiratory failure. The  
215 safety of continuing growth hormone treatment in patients receiving replacement doses  
216 for approved indications who concurrently develop these illnesses has not been  
217 established. Therefore, the potential benefit of treatment continuation with growth  
218 hormone in patients having acute critical illnesses should be weighed against the  
219 potential risk.

220 There have been reports of fatalities after initiating therapy with growth hormone in  
221 pediatric patients with Prader-Willi syndrome who had one or more of the following risk  
222 factors: severe obesity, history of upper airway obstruction or sleep apnea, or  
223 unidentified respiratory infection. Male patients with one or more of these factors may  
224 be at greater risk than females. Patients with Prader-Willi syndrome should be  
225 evaluated for signs of upper airway obstruction and sleep apnea before initiation of  
226 treatment with growth hormone. If, during treatment with growth hormone, patients  
227 show signs of upper airway obstruction (including onset of or increased snoring) and/or  
228 new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi  
229 syndrome treated with growth hormone should also have effective weight control and be  
230 monitored for signs of respiratory infection, which should be diagnosed as early as  
231 possible and treated aggressively (see CONTRAINDICATIONS). Unless patients with  
232 Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Nutropin  
233 Depot is not indicated for the long term treatment of pediatric patients who have growth  
234 failure due to genetically confirmed Prader-Willi syndrome.

Revised language  
per FDA letter  
dated 30 March

## 235 **PRECAUTIONS**

236 General: Nutropin Depot should be prescribed by physicians experienced in the  
237 diagnosis and management of patients with GHD.

238 Because GH may reduce insulin sensitivity, patients should be monitored for evidence  
239 of glucose intolerance.

240 For patients with diabetes mellitus, the insulin dose may require adjustment when  
241 GH therapy is instituted. Because GH may reduce insulin sensitivity, particularly in

242 obese individuals, patients should be observed for evidence of glucose intolerance.  
243 Patients with diabetes or glucose intolerance should be monitored closely during  
244 GH therapy.

245 Patients with symptomatic hypoglycemia associated with GHD should be  
246 closely monitored.

247 Patients with a history of an intracranial lesion should be examined frequently for  
248 progression or recurrence of the lesion. In pediatric patients, clinical literature has  
249 demonstrated no relationship between GH replacement therapy and central nervous  
250 system (CNS) tumor recurrence or new extracranial tumors.

251 Slipped capital femoral epiphysis may occur more frequently in patients with endocrine  
252 disorders or in patients undergoing rapid growth.

253 Progression of scoliosis can occur in patients who experience rapid growth. Because  
254 GH increases growth rate, patients with a history of scoliosis who are treated with GH  
255 should be monitored for progression of scoliosis. GH has not been shown to increase  
256 the incidence of scoliosis.

257 Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea,  
258 and/or vomiting has been reported in a small number of patients treated with  
259 GH products. Symptoms usually occurred within the first 8 weeks of the initiation of  
260 GH therapy. In all reported cases, IH-associated signs and symptoms resolved after  
261 termination of therapy or a reduction of the GH dose. Funduscopic examination of  
262 patients is recommended at the initiation and periodically during the course of  
263 GH therapy.

264 As with any protein, local or systemic allergic reactions may occur. Parents/Patients  
265 should be informed that such reactions are possible and that prompt medical attention  
266 should be sought if allergic reactions occur (see ADVERSE REACTIONS).

267 Laboratory Tests: Serum levels of inorganic phosphorus, alkaline phosphatase, and  
268 parathyroid hormone (PTH) may increase with GH therapy.

269 Untreated hypothyroidism prevents optimal response to GH. Changes in thyroid  
270 hormone laboratory measurements may develop during GH treatment. Therefore,  
271 patients should have periodic thyroid function tests and should be treated with thyroid  
272 hormone when indicated.

273 Drug Interactions: Excessive glucocorticoid therapy will inhibit the growth-promoting  
274 effect of human GH. Patients with ACTH deficiency should have their glucocorticoid-  
275 replacement dose carefully adjusted to avoid an inhibitory effect on growth.

276 Limited published data indicate that GH treatment increases cytochrome P450 (CP450)  
277 mediated antipyrine clearance in humans. These data suggest that GH administration  
278 may alter the clearance of compounds known to be metabolized by CP450 liver  
279 enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporin). Careful  
280 monitoring is advisable when GH is administered in combination with other drugs known  
281 to be metabolized by CP450 liver enzymes.

282 Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity,  
283 and fertility studies have not been conducted with Nutropin Depot.

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

288 Nursing Mothers: It is not known whether GH is excreted in human milk. Because  
289 many drugs are excreted in human milk, caution should be exercised when Nutropin  
290 Depot is administered to a nursing mother.

291 Information for Patients: Patients being treated with Nutropin Depot and/or their parents  
292 should be informed of the potential benefits and risks associated with treatment. If  
293 home use is determined to be desirable by the physician, instructions on appropriate  
294 use should be given, including a review of the contents of the Patient Information Insert.  
295 This information is intended to aid in the safe and effective administration of the  
296 medication. It is not a disclosure of all possible adverse or intended effects.

297 If home use is prescribed, a puncture-resistant container for the disposal of used  
298 syringes and needles should be recommended to the patient. Patients and/or parents  
299 should be thoroughly instructed in the importance of proper disposal and cautioned  
300 against any reuse of needles and syringes (see Patient Information Insert).

### 301 **ADVERSE REACTIONS**

302 As with all protein pharmaceuticals, patients may develop antibodies to the protein. GH  
303 antibody-binding capacities below 2 mg/L have not been associated with growth  
304 attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation  
305 has been observed. In clinical studies of pediatric patients who were treated with  
306 Nutropin Depot, 0/138 patients with GHD screened for antibody production developed

307 antibodies with binding capacities  $\geq 2$  mg/L at any time during a treatment period of up  
308 to 17.4 months.

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

312 In studies involving 138 pediatric patients treated with Nutropin Depot, the most  
313 frequent adverse reactions were injection-site reactions, which occurred in nearly all  
314 patients. On average, 2 to 3 injection-site adverse reactions were reported per  
315 injection. These reactions included nodules (61% of injections), erythema (53%), pain  
316 post-injection (47%), pain during injection (43%), bruising (20%), itching (13%),  
317 lipoatrophy (13%), and swelling or puffiness (8%). The intensity of these reactions was  
318 generally rated mild to moderate, with pain during injection occasionally rated as severe  
319 (7%).

320 Adverse reactions observed less frequently in the Nutropin Depot studies which were  
321 considered possibly, probably, or definitely related to the drug by the treating physician  
322 (usually occurring 1–3 days postdose) included: headache (13% of subjects), nausea  
323 (8%), lower extremity pain (7%), fever (7%), and vomiting (5%). These symptoms were  
324 generally self-limited and well-tolerated. One patient experienced a generalized body  
325 rash that was most likely an allergic reaction to Nutropin Depot.

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

331 Other adverse drug reactions that have been reported in GH-treated patients include  
332 the following: 1) Metabolic: mild, transient peripheral edema; 2) Musculoskeletal:  
333 arthralgia, carpal tunnel syndrome; 3) Skin: rare increased growth of pre-existing nevi;  
334 patients should be monitored for malignant transformation; 4) Endocrine:  
335 gynecomastia; and 5) Rare pancreatitis. Of these reactions, only edema (< 1% of  
336 patients) and arthralgia (4%) were reported as related to drug in the Nutropin Depot  
337 studies.

### 338 **OVERDOSAGE**

339 The recommended dosage of Nutropin Depot should not be exceeded. Acute  
340 overdosage could lead to fluid retention, headache, nausea, vomiting, and/or  
341 hyperglycemia. Long-term overdosage could result in signs and symptoms of gigantism

342 and/or acromegaly, consistent with the known effects of excess GH.  
343 (See recommended dosage instructions given below.)

344 **DOSAGE AND ADMINISTRATION**

345 The Nutropin Depot dosage and administration schedule should be individualized for  
346 each patient. Response to GH therapy in pediatric patients tends to decrease over  
347 time. However in pediatric patients, failure to increase growth rate, particularly during  
348 the first year of therapy, suggests the need for close assessment of compliance and  
349 evaluation of other causes of growth failure, such as hypothyroidism, undernutrition, and  
350 advanced bone age.

351 *Once-Monthly Injection*—It is recommended that an SC injection at a dosage of  
352 1.5 mg/kg body weight be administered on the same day of each month. Dosages  
353 above the recommended once-monthly regimen have not been studied in clinical trials.  
354 Note: subjects over 15 kg will require more than one injection per dose.

355 *Twice-Monthly Injections*—It is recommended that an SC injection at a dosage of  
356 0.75 mg/kg body weight be administered twice each month on the same days of each  
357 month (e.g., Days 1 and 15 of each month). Dosages above the recommended  
358 twice-monthly regimen have not been studied in clinical trials. Note: subjects over 30 kg  
359 will require more than one injection per dose.

360 The table below indicates the required number of injections per dose.

Patient Weight (kg)	Number of Injections Per Dose	
	0.75 mg/kg twice monthly	1.5 mg/kg once monthly
≤15	1	1
>15–30	1	2
>30–45	2	3
>45–60	2	*
>60	3	*

361 \*Twice-monthly dosing recommended

362

363 **Preparation of Dose**

364 Nutropin Depot powder may **only** be suspended in Diluent for Nutropin Depot supplied  
365 in the kit and administered with the supplied needles.

- 366 1. Using the chart below, determine the volume of diluent needed to suspend Nutropin  
367 Depot. Withdraw the diluent into a 3 cc syringe using the needle supplied in the kit.  
368 Only the diluent supplied in the kit should be used for reconstitution, and any  
369 remaining diluent should be discarded.

Nutropin Depot<sup>®</sup> [somatropin (rDNA origin) for injectable suspension]

Vial Size (mg somatropin)	Volume of Diluent to Be Added (mL)
13.5	0.8
18	1.0
22.5	1.2

Note: Since the suspension is viscous and prevents complete withdrawal of the entire vial contents, the vials are overfilled to ensure delivery of the labeled amount of somatropin. Using these diluent volumes for final suspension results in a final concentration of 19 mg/mL somatropin in each vial size.

370

371 2. Inject the diluent into the vial against the vial wall. Swirl the vial vigorously for up to  
372 2 minutes to disperse the powder in the diluent. Mixing is complete when the  
373 suspension appears uniform, thick, and milky, and all the powder is fully dispersed.  
374 Do not store the vial after reconstitution or the suspension may settle.

375 3. Withdraw the required dose. Only one vial should be used for each injection.  
376 Replace the needle with a new needle from the kit and administer the dose  
377 immediately to avoid settling of the suspension in the syringe. Deliver the dose  
378 from the syringe at a continuous rate over not more than 5 seconds. Discard  
379 unused vial contents as the product contains no preservative. An extra needle has  
380 been provided in the kit.

381 **Stability and Storage**

382 *Before Suspension*—Nutropin Depot and diluent vials must be stored at 2–8°C/36–46°F  
383 (under refrigeration). **Avoid freezing the vials of Nutropin Depot and Diluent for**  
384 **Nutropin Depot.** Do not expose the Nutropin Depot vial to temperatures above  
385 25°C (77°F). Expiration dates are stated on the labels.

386 *After Suspension*—Because Nutropin Depot contains no preservatives, all injections  
387 must be given immediately. Do not allow the suspension to settle prior to withdrawal of  
388 the dose. Suspended solution cannot be stored or used to suspend another vial of  
389 Nutropin Depot.

390 **How Supplied**

391 Nutropin Depot is supplied as single-use vials with 13.5 mg, 18 mg, or 22.5 mg sterile,  
392 preservative-free somatropin powder per vial.

393 Each 13.5 mg kit contains one single-use 13.5 mg vial of Nutropin Depot<sup>®</sup> [somatropin  
394 (rDNA origin) for injectable suspension], one 1.5 mL single-use vial of Diluent for  
395 Nutropin Depot, and three 21-gauge, 1/2" needles: NDC 50242-032-35.

Nutropin Depot<sup>®</sup> [somatropin (rDNA origin) for injectable suspension]

396 Each 18 mg kit contains one single-use 18 mg vial of Nutropin Depot<sup>®</sup> [somatropin  
397 (rDNA origin) for injectable suspension], one 1.5 mL single-use vial of Diluent for  
398 Nutropin Depot, and three 21-gauge, 1/2" needles: NDC 50242-034-41.

399 Each 22.5 mg kit contains one single-use 22.5 mg vial of Nutropin Depot<sup>®</sup> [somatropin  
400 (rDNA origin) for injectable suspension], one 1.5 mL single-use vial of Diluent for  
401 Nutropin Depot, and three 21-gauge, 1/2" needles: NDC 50242-036-54.

Nutropin Depot<sup>®</sup> [somatropin (rDNA origin) for injectable suspension]

**Nutropin Depot<sup>™</sup> [somatropin (rDNA origin) for injectable suspension] and Diluent for Nutropin Depot** are manufactured for:

**Genentech, Inc.**

1 DNA Way

South San Francisco, CA 94080-4990

©1999 Genentech, Inc.

4819504

FDA Approval Date December 1999)

Code Revision Date October 2004

402

403