CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

LABELING

Valtropin® 5 mg
Somatropin (rDNA origin) for injection, USP

DESCRIPTION

Valtropin® [somatropin (rDNA origin) for injection] is a polypeptide hormone of recombinant DNA origin. The hormone is produced by recombinant DNA technology in yeast cells *(Saccharomyces cerevisiae)*. Valtropin® has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone (hGH) of pituitary origin.

Valtropin® is a sterile, non-pyrogenic, white to almost white, lyophilized powder intended for subcutaneous injection after reconstitution. Each vial contains 5 mg somatropin (approximately 15 International Units), 10 mg glycine, 45 mg mannitol, 0.22 mg monobasic sodium phosphate, and 2.98 mg dibasic sodium phosphate. The pH is adjusted with sodium hydroxide and/or hydrochloric acid. A pre-filled syringe of 1.5 mL clear solution diluent is provided for reconstitution of the powder. The pre-filled syringe contains 1.5 mL Water for Injection and 0.3% w/v metacresol as an antimicrobial preservative. After reconstitution with 1.5 mL diluent, the solution contains 3.33 mg/mL of somatropin.

CLINICAL PHARMACOLOGY

General
In vitro, pre-clinical and clinical testing have demonstrated that somatropin is therapeutically equivalent to pituitary-derived human growth hormone (pit-hGH). Clinical studies in normal adults also demonstrate equivalent pharmacokinetics.

a. Tissue Growth
The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in children with somatropin deficiency.

1. **Skeletal growth – the measurable increase in** bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGF). The somatomedins, among them IGF-1, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-1 levels are low in the serum of growth hormone deficient children with short stature and hypophysectomized humans or animals, but its presence can be demonstrated after treatment with somatropin.

2. **Cell growth – it has been shown that the total nu**mber of skeletal muscle cells is markedly decreased in children with short stature lacking endogenous growth hormone compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

3. **Organ growth – somatropin influences the size of** internal organs, and it also increases red cell mass.

b. Protein Metabolism
Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention, which can be quantitated by observing the decline in urinary nitrogen excretion and blood urea nitrogen following the initiation of somatropin therapy.

c. Carbohydrate Metabolism
Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, large doses of somatropin may impair glucose tolerance. Although the precise mechanism of the diabetogenic effect of somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase. Administration of somatropin to normal adults and patients with growth hormone deficiency (GHD) results in increases in mean serum fasting and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A_{1C} levels remain in the normal range.

d. Lipid Metabolism
Somatropin stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids and triglycerides. Untreated GHD is associated with increased body fat stores, including increased subcutaneous and visceral adipose tissue in the abdomen. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, in particular in subcutaneous and visceral abdominal tissue and decreased serum levels of low-density lipoprotein (LDL) cholesterol.

e. Mineral Metabolism
Administration of somatropin results in the retention of total body potassium and phosphorus, and to a lesser extent sodium. This retention is thought to be the result of cell growth. Serum levels of phosphate increase in patients with GHD after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

f. Connective Tissue Metabolism
Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics
In a single dose study in 24 healthy volunteers, subcutaneous administration of 0.073 mg/kg of body weight of Valtropin® resulted in a mean maximum serum concentration (C_{max}) of 43.97 ng/mL and an area under the curve ($AUC_{0\text{-}24h}$) of 369.90 ng·hr/mL. C_{max} was reached at 4.00 hr and terminal elimination half-life was 3.03 hr.

The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products is returned to the systemic circulation.

Special Populations
Pediatric – **The pharmacokinetics of somatropin** is similar in children and adults.

Geriatric – **The pharmacokinetic properties of somatropin** have not been studied in patients greater than 60 years of age.

Gender – **No gender studies have been performed.**

Race – **No race studies have been performed.**

Renal Insufficiency – **No studies have been performed in** patients with renal insufficiency.

Hepatic Insufficiency – **No studies have been performed in** patients with hepatic insufficiency.

CLINICAL TRIALS

Pediatric Patients With Growth Hormone Deficiency (GHD)
A one-year, multicenter, multinational, randomized, double-blind, parallel-group, active- controlled study was conducted in treatment-naive children with GHD and short stature comparing the linear growth effect of Valtropin® with another approved formulation of somatropin. All patients were treated with somatropin 0.033 mg/kg/day administered subcutaneously (SC). One hundred and forty nine children were randomized in a 2:1 ratio to receive Valtropin® (n=99) or the active control (n=50). Combining both treatment groups, mean age was 8.2, 60-70% of patients were male, ~95% were Caucasian, baseline height standard deviation score for chronological age (height SDS_{CA}) was -3.43, and pre-treatment height velocity (HV) was 3.34 cm/yr. These demographic and baseline characteristics were similar in the two treatment groups.

Greater than 90% of patients completed the study. The results presented below were obtained from the intent-to-treat (ITT) population (which excluded patients whose height had not been measured with the appropriate stadiometer, who discontinued before 6 months on treatment or whose pre-treatment HV was incomplete) with last observation carried forward (LOCF); and consisted of 88 patients in the Valtropin® group and 41 patients in the active control group.

As seen in Table 1, the adjusted mean HV ± SE at 12 months was 11.21 ± 0.23 cm/year in the Valtropin® group versus 11.00 ± 0.32 cm/year in the active control group, and the mean treatment difference was 0.21. Therefore, Valtropin® was non-inferior to the active control.

Table 1
Difference Between Groups in Height Velocity (Cm/Yr) at Month 12 in a Double Blind Study in Pediatric Patients with GHD

ITT population with LOCF	Valtropin®	Comparator
Raw Mean ± SD (n) at Baseline	3.50 ± 1.45 (88)	3.39 ± 1.02 (41)
Raw Mean ± SD (n) at Month 12	11.36 ± 2.92 (88)	10.54 ± 2.61 (41)
Adjusted Mean ± SE* (n) at Month 12	11.21 ± 0.23 (88)	11.00 ± 0.32 (41)
Treatment Difference (Adjusted Mean)*	0.21	
(95% CI)**	(-0.48, 0.90)	

*Adjusted least-squares means were obtained using an ANCOVA model, where treatment and country were the fixed factors and baseline HV, CA, and log maximum GH level after stimulation were the covariates.

**Confidence Intervals

The within-group changes from baseline to Month 12 for the Valtropin® group only for HV, HV SDS_{CA}, height SDS_{CA}, and predicted adult height (PAH) by the Bayley-Pinneau (B-P) method expressed both in cm and as a SDS are displayed in Table 2. All within-group changes were significant. The 1.21 unit change in height SDS_{CA} and the 8.05 unit change in HV SDS_{CA} are robust and indicate substantial catch-up growth. The results observed in the active control group were similar.

Table 2
Valtropin® Group Only
Within-Group Change from Baseline to Month 12 in Height Velocity and Other Auxological Secondary Efficacy Endpoints

ITT with LOCF Efficacy Variable	Valtropin®: Mean ± SD (n)		Mean Change from Baseline	(95% CI)
	Baseline	Month 12		
HV (cm/year)	3.50 ± 1.45 (88)	11.36 ± 2.92 (88)	7.87	(7.18, 8.55)
HV SDS_{CA}	-2.34 ± 1.78 (88)	5.71 ± 3.44 (88)	8.05	(7.16, 8.94)
Height SDS_{CA}	-3.54 ± 1.24 (88)	-2.33 ± 1.01 (88)	1.21	(1.08, 1.34)
PAH (B-P) (cm)	162.27 ± 9.7 (32)	165.77 ± 10.0 (32)	3.51	(1.57, 5.44)
PAH SDS (B-P)	-1.71 ± 1.10 (32)	-1.22 ± 1.08 (32)	0.49	(0.22, 0.76)

Bone maturation expressed as the ratio of change from baseline to Month 12 in bone age (BA) to change from baseline to Month 12 in CA was 1.5 ± 0.9 in the Valtropin® group and 1.5 ± 0.7 in the active control group, and not accelerated.

Furthermore, as expected after somatropin replacement therapy in children with GHD, mean serum insulin-like growth factor 1 (IGF-1) levels in both groups were significantly increased after 12 months of treatment compared to baseline levels.

During the 12-month, open-label extension phase, 82 children continued Valtropin® treatment providing 24-month data for Valtropin®, and 40 patients were switched from the active control to Valtropin®. Growth continued at expected levels for patients on continuous Valtropin® treatment and patients on active control/Valtropin treatment.

Pediatric Patients With Turner Syndrome (TS)

Two open-label, single-arm, uncontrolled clinical trials were conducted that evaluated the efficacy and safety of Valtropin® and Eutropin™ INJ (a 4 IU formulation qualitatively identical to the 15 IU formulation, Valtropin®) in TS patients with short stature. During Study 1 (conducted at a single center in Russia), 30 Caucasian girls (mean age = 6.9 yr) were treated with Valtropin® 0.053 mg/kg/day SC for 12 months. During Study 2 (conducted at four centers in Korea), 60 Asian girls (mean age = 10.8 yr) were treated with Eutropin™ INJ 0.048 mg/kg/day SC (or 0.056 mg/kg SC 6 days per week) for 12 months. In Studies 1 and 2, pre-treatment HV were 3.75 cm/yr and 3.48 cm/yr, respectively, and baseline height SDS_{CA} were -2.42 and -3.02, respectively. All of the results presented below were obtained from the ITT population.

As seen in Table 3, mean change in HV from baseline to Month 12 (the primary efficacy variable for both studies) was 5.98 cm/yr (mean HV at Month 12 = 9.73 cm/yr) and 3.49 cm/yr (mean HV at Month 12 = 6.97 cm/yr) in Studies 1 and 2, respectively.

The results obtained with respect to other auxological secondary efficacy parameters are also presented for both studies in Table 3. A significant increase in height SDS_{CA} was observed in both studies (0.88 and 0.35 in Studies 1 and 2, respectively), and a substantial increase in HV SDS_{CA} was seen in Study 1 (6.22). B-P PAH increased significantly as well (~4 cm) in Study 1.

Bone maturation (calculated as the ratio of change in BA to change in CA) was not accelerated (1.02 ± 0.35) in Study 1. In Study 2, height age (HA)/BA ratio increased from 0.85 at baseline to 0.88 at Month 12, indicating that HA advanced more rapidly than BA (Table 3).

As expected after somatropin treatment, mean serum IGF-1 levels in both studies were significantly increased after 12 months of treatment compared to baseline levels.

Table 3
Change from Baseline to Month 12 in Height Velocity and Other Auxological Secondary Efficacy Endpoints After Treatment with Somatropin in Girls with Short Stature Associated with Turner Syndrome in 2 Open Label Studies

Efficacy Variable	Study	Mean ± SD (n)		Mean Change from Baseline	(95% CI)
		Month 0	Month 12		
HV (cm/yr)*	***Study 1***	***3.75 ± 1.76 (30)***	***9.73 ± 1.55 (30)***	***5.98***	***(5.20, 6.76)***
	Study 2	***3.48 ± 1.40 (58)***	***6.97 ± 1.84 (58)***	***3.49***	***(2.94, 4.03)***
HV SDS_{CA}	Study 1	-2.39 ± 1.90 (30)	3.82 ± 1.95 (30)	6.22	(5.22, 7.21)
	Study 2	NA	NA	NA	NA
Height SDS_{CA}	Study 1	-2.42 ± 0.91 (30)	-1.54 ± 0.94 (30)	0.88	(0.78, 0.98)
	Study 2	-3.02 ± 0.96 (58)	-2.67 ± 0.99 (58)	0.35	(0.23, 0.46)
PAH (B-P) (cm)	Study 1	152.0 ± 5.23 (14)	156.0 ± 4.21 (14)	4.04	(2.89, 5.19)
	Study 2	NA	NA	NA	NA
HA/BA	Study 1	NA	NA	NA	NA
	Study 2	0.85 ± 0.15 (58)	0.88 ± 0.12 (58)	0.03	(0.00, 0.05)

*Change in HV was the primary efficacy endpoint in both studies and the results are therefore ***boldened and italicized.***
NA=Not available.

Adult Patients With Growth Hormone Deficiency (GHD)

A 6-month, multicenter, randomized, double-blind, placebo-controlled, 3-arm (with 2 arms having a crossover design) clinical trial was conducted in 92 adults (mean age 45-55) with either adult onset (AO) (93.5% of the ITT population) or childhood onset (CO) GHD comparing the effects of **Eutropin™ INJ (a 4 IU formulation qualitatively** identical to the 15 IU formulation, Valtropin®) and placebo. During treatment period 1 (baseline through the end of Month 3), patients in the active treatment arms (groups A and B) were treated with **Eutropin™ INJ at an in**itial dose of 0.33 mg/day administered SC (6 days per week) for 1 month. During the next 2 months, the dose was up-titrated as necessary in small increments to a maximum of 0.66 mg/day (6 days per week) if serum IGF-1 levels were less than optimal or down-titrated in the presence of significant adverse events or inappropriately elevated serum IGF-1 levels. Patients in group C received placebo for the entire 3 month period. During treatment period 2 (Month 4 through the end of Month 6), patients in group A continued to **receive Eutropin™ INJ, patients in group B were cr**ossed over to placebo, and patients in group C were **crossed over to Eutropin™ INJ.**

Change in fat mass (FM) was the primary efficacy variable and change in lean body mass (LBM) was the most consequential secondary efficacy variable.

The results obtained for changes (decreases) in FM are presented in Tables 4, 5 and 6. As seen in Table 4, after 3 months of treatment with Eutropin™ INJ vs. placebo, there was a significant (p=0.003) between-group treatment difference for the change in FM (-1.35 kg). Table 5 depicts the significant (p<0.0001) within-group change in FM (-1.3 kg) after 3 months of treatment with Eutropin™ INJ for groups A+B combined (for group A alone, the significant within-group change in FM after 3 months of treatment was -1.7 kg [see Table 6]; during treatment period 2, when patients in group C were crossed over to Eutropin™ INJ from placebo, a similar significant within-group change in FM was observed [-1.2 kg; data not shown in a table]). Table 6 also reflects the significant (p<0.0001) within-group change in FM (-2.3 kg) after 6 months of treatment with Eutropin™ INJ for group A alone. Furthermore, as seen in Table 6, the within-group change in FM between Month 4 and the end of Month 6 for group A alone was -0.6 kg; this change was not statistically significant suggesting that most of the decrease in FM after treatment with Eutropin™ INJ occurred by the end of Month 3.

Table 4
Between-Group Change in Fat Mass After 3 Months of Treatment with Eutropin™ INJ (Groups A+B) vs. Placebo (Group C)

ITT Population with LOCF	Groups A and B Combined (n=58) Eutropin™ INJ	Group C (n=31) Placebo
Baseline (Mean ± SD)	23.0 ± 7.7	19.9 ± 3.7
Change from Baseline to Month 3 (Mean ± SD)	-1.25 ± 2.18	+0.16 ± 1.50
Change from Baseline to Month 3 (Adjusted Mean ± SE)*	-1.17 ± 0.25	+0.18 ± 0.35
Treatment Difference (Adjusted Mean)* (95% CI) p-value	-1.35 (-0.48, -2.22) p = 0.003	

*Adjusted least-squares means were obtained using an ANCOVA model, where baseline FM and age were the covariates.

Table 5
Within-Group Changes in Fat Mass After 3 Months of Treatment With Eutropin™ INJ (Groups A+B) vs. Placebo (Group C)

	Groups A+B Combined Eutropin™ INJ		Group C Placebo	
ITT Population	n		n	
Baseline (Mean ± SD)	58	23.0 ± 7.7	31	19.9 ± 3.7
Month 3 (Mean ± SD)	58	21.7 ± 7.7	31	20.2 ± 3.5
Paired t-test p-value		<0.0001*		0.5471

Table 6
Within-Group Changes in Fat Mass After 3 and 6 Months of Treatment with Eutropin™ INJ (Group A)

Fat Mass (mean ± SD)	Group A Eutropin™ INJ (n=31)
Baseline	21.9 ± 6.0 kg
Month 3	20.2 ± 6.3 kg*
Month 6	19.6 ± 5.7 kg*

*Statistically significant within-group change from baseline ($p<0.05$).

In concert with the significant decreases in FM described above, there were comcomitant significant increases in LBM (tables not provided): a) between-group treatment difference (0.88 kg) after 3 months of treatment with Eutropin™ INJ (groups A+B combined) vs. placebo (group C); b) within-group increase from baseline (0.9 kg) after treatment with Eutropin™ INJ (groups A+B combined) for 3 months; c) within-group increase from baseline (1.0 kg) after treatment with Eutropin™ INJ (group A alone) for 3 months; and d) within-group increase from baseline (2.1 kg) after treatment with Eutropin™ INJ (group A alone) for 6 months.

As expected after somatropin replacement therapy in adults with GHD, mean serum IGF-1 levels were significantly increased in group A after 3 and 6 months of Eutropin™ INJ treatment compared to baseline levels.

INDICATIONS AND USAGE

Pediatric Patients:
Valtropin® is indicated for the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone.

Valtropin® is indicated for the treatment of growth failure associated with Turner syndrome in patients who have open epiphyses.

Adult Patients:
Valtropin® is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following criteria:

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

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

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

CONTRAINDICATIONS

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

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

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

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart surgery, abdominal surgery, or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% versus 19.3%) among somatropin treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

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

WARNINGS

In the case of patients with a known sensitivity to the supplied diluent (metacresol) or, if sensitivity to metacresol becomes apparent after treatment has been initiated, Valtropin® should be reconstituted with 1.5 mL Water for Injection and used as a single use vial (see STABILITY AND STORAGE). See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery, or multiple accidental trauma, or those with acute respiratory failure. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients experiencing acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females.

Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (**see CONTRAINDICATIONS**). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Valtropin® is not indicated for the long-term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

PRECAUTIONS

General

Therapy with Valtropin® should be directed by physicians who are experienced in the diagnosis and management of pediatric patients with growth hormone deficiency and Turner syndrome, or adult patients with either childhood-onset or adult-onset growth hormone deficiency.

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

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

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

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

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

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

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site (**see DOSAGE and ADMINISTRATION).**

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

Pediatric Patients (See PRECAUTIONS, General)
Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

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

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders (see Adverse Reactions). Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

Adult Patients (See PRECAUTIONS, General)
Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. Fluid retention during somatropin replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent (see ADVERSE REACTIONS).

Experience with prolonged treatment in adults is limited.

Information for Patients

Patients being treated with Valtropin® (and/or their parents) should be informed about the potential benefits and risks associated with Valtropin® treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer Valtropin® should receive appropriate training and instruction on the proper use of Valtropin® from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.

Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase during somatropin therapy.

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

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

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with somatropin.

Somatropin was not genotoxic with and without metabolic activation in the Ames bacterial mutagenicity assay, the *in vitro* Chinese Hamster Ovary and Chinese Hamster Lung cell chromosomal aberration assay, and the *in vivo* mouse micronucleus assay.

Male and female rats given SC doses of 1, 3, 10 IU/kg/day of somatropin from premating day 60 and premating day 14 to gestation day 7, respectively, did not show any adverse effect on fertility, mating or early development. This represents systemic exposures 1 to 15 times the human therapeutic levels based on body surface area comparisons.

Pregnancy
Pregnancy Category B. There are no adequate and well controlled studies of Valtropin® in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Subcutaneous reproduction studies have been performed with somatropin in rats and rabbits at doses up to 15 and 30 times, respectively, human therapeutic levels based on body surface area comparisons.

In pregnant rats given SC doses of 1, 3, 10 IU/kg/day of somatropin from gestation day 7 and 17 through organogenesis, an increase in embryolethality was observed in all somatropin-treated groups (3.88, 4.85, 4.72 %) compared to control (0.54%), representing systemic exposures 1 to 14 times human therapeutic levels based on body surface area comparisons.

In pregnant rabbits given SC doses of 1, 3, 10 IU/kg/day of somatropin from gestation days 6 and 18 through organogenesis at doses up to 30 times the human dose, no developmental adverse effects were observed.

In perinatal and post-natal studies in rats, somatropin at doses of 1, 3, 10 IU/kg/day given from gestation day 7 to lactation day 21, did not result in adverse effects on gestation, morphogenesis, parturition, lactation or post-natal weight of offspring (the only parameter evaluated), representing systemic exposures 1 to 14 times human therapeutic levels based on body surface area comparisons.

Nursing Mothers
There have been no studies conducted with Valtropin® in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Valtropin® is administered to a nursing woman.

Geriatric Use
The safety and effectiveness of Valtropin® in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Pediatric Patients With GHD

In a clinical study in which Valtropin® 0.053mg/kg/day (vs. the same dose of an active somatropin control) was administered to 98 children with GHD for 12 months, the following adverse events were seen most frequently (≥5.0% in either treatment group): headache, pyrexia, cough, respiratory tract infection, diarrhea, vomiting and pharyngitis (see Table 7). The incidence of all of these adverse events were similar in the 2 treatment groups, and these adverse events reflect very common pediatric illnesses.

Table 7

Adverse Events Observed In Children With GHD Treated with Valtropin® vs. Comparator for 12 Months

Adverse events (Incidence ≥5.0% in either group)	**Valtropin®** (n=98)	**Comparator** (n=49)
Headache	10 (10.2%)	8 (16.3%)
Pyrexia	9 (9.2%)	8 (16.3%)
Cough	5 (5.1%)	3 (6.1%)
Respiratory tract infection (NOS)*	5 (5.1%)	1 (2.0%)
Diarrhea	3 (3.1%)	4 (8.2%)
Vomiting	4 (4.1%)	4 (8.2%)
Pharyngitis	3 (3.1%)	4 (8.2%)

n = number of patients
* NOS = not otherwise specified

During this study, a very modest degree of glucose intolerance was observed in the 98 patients treated with Valtropin® for 12 months (which was comparable to that observed in the comparator group). No *de novo* cases of overt diabetes mellitus were diagnosed. **See PRECAUTIONS, General** regarding somatropin-induced glucose intolerance.

Out of 98 patients with pediatric GHD randomized to treatment with Valtropin® in the pivotal study described above, 26 (26.5%) had preexisting central hypothyroidism. Exacerbation of this preexisting central hypothyroidism appeared to be common. During 12 months of Valtropin® treatment, 18 out of these 26 patients (~69%) with preexisting central hypothyroidism (who were being treated with a thyroxine preparation prior to study entry) required up-titration of their thyroxine replacement dose (primarily based on declining levels of free T4). On the other hand, none of the 72 patients without preexisting central hypothyroidism manifested *de novo* central hypothyroidism while on-study. **See PRECAUTIONS, Drug Interactions.**

The 1 patient with preexisting central hypoadrenalism enrolled in this study required a slight increase in her maintenance hydrocortisone replacement dose after treatment with Valtropin®, possibly compatible with somatropin-induced exacerbation of preexisting central hypoadrenalism. None of the remaining 97 patients without preexisting central hypoadrenalism manifested *de novo* central hypoadrenalism while on-study. **See PRECAUTIONS, Drug Interactions.**

In addition, during the clinical trial described above, low titer anti-rhGH antibodies* were reported in 3 patients treated with Valtropin® (vs. 1 patient treated with the comparator), and low titer anti-host cell protein antibodies were observed in 2 patients treated with Valtropin®. These antibodies appeared after 6 months of treatment, disappeared after 12 months of treatment, and did not attenuate the growth response of these children.

*As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. Anti-growth hormone antibodies with binding capacity lower than 2 mg/L have not been associated growth attenuation. In some patients, when binding capacity was greater than 2 mg/L, interference with growth response was observed in published data. Any patient with well documented pediatric GHD who fails to respond to Valtropin® therapy should be tested for neutralizing antibodies to rhGH and undergo a careful evaluation to rule out other causes of growth failure (**see DOSAGE AND ADMINISTRATION**).

In published literature, leukemia has been reported in a small number of pediatric GHD patients treated with somatropin. It is uncertain whether this increased risk is related to the pathology of GHD itself, somatropin therapy, or other associated treatments such as radiation therapy for intracranial tumors. So far, epidemiological data have failed to confirm the hypothesis of a relationship between somatropin therapy and leukemia.

Pediatric Patients With Turner Syndrome

TS children with short stature were treated with 0.37 mg/kg/week of Valtropin® (5 mg = 15 IU formulation) (n=30) and 0.33 mg/kg/week of Eutropin™ INJ (1.33 mg = 4 IU formulation qualitatively identical to Valtropin®) (n=60) during Study 1 and Study 2, respectively. Adverse events were reported by 10 (33.3%) children during Study 1. Most of these adverse events reflect very common pediatric illnesses. The most frequently (≥1.0%) reported adverse events were respiratory tract infections and **ear infections** (see Table 8). Turner syndrome patients are more prone to ear disorders and treatment with somatropin may increase the occurrence of these problems. One patient developed low titer antibodies to rhGH, and one other patient developed low titer anti-yeast antibodies which proved to be transient. During Study 2, a similar pattern of adverse events was observed (data not shown). Two patients developed low titer anti-rhGH antibodies at Month 12. Of interest, there were no reports in either study of benign intracranial hypertension, aggravation of preexisting scoliosis, slipped capital femoral epiphysis and hypertension. Somatropin-induced glucose intolerance will be discussed separately in the next paragraph. All patients with reported adverse events recovered during continued treatment.

Table 8
Adverse Events Observed In Children
With Turner Syndrome Treated with Valtropin® for 12 Months

Adverse Events (Incidence ≥1.0%)	Valtropin® (n=30)	
	n	%
Respiratory tract infection (NOS)*	4	13.3
Ear infection (NOS)	2	6.7
Otitis media (NOS)	1	3.3
Anti-rhGH antibody positive	1	3.3
Anti-yeast antibody positive	1	3.3
Edema peripheral	1	3.3
Respiratory tract infection viral (NOS)*	1	3.3
Rhinitis NOS*	1	3.3
Sinusitis NOS*	1	3.3
Influenza	1	3.3
Injection site pain	1	3.3
Pyrexia	1	3.3

n = number of patients
*NOS = not otherwise specified

During Study 1, a modest degree of glucose intolerance was observed in the 30 patients treated with Eutropin™ INJ for 12 months. No *de novo* cases of overt diabetes mellitus were diagnosed.

On the other hand, during Study 2, a much greater amount of glucose intolerance was observed: a) 3 patients (with normal fasting blood glucose [FBG] values at baseline [<100 mg/dL]) had FBG values between 130 and 145 mg/dL at Month 12 as well as at other study time points and (given the absence of follow-up data after study termination) may have developed somatropin-induced *de novo* diabetes mellitus; and b) 16 out of 41 patients (with normal FBG values at baseline) had FBG values between 100-126 mg/dL at Month 12 (and 3 of these 16 patients had FBG values >126 mg/dL transiently during the study). Since the amount of somatropin administered in Study 2 (0.33 mg/kg/week) was slightly less than the amount administered in Study 1 (0.37 mg/kg/week), these findings are difficult to interpret. It is possible that some of these patients were not actually fasting when blood samples were taken. See **PRECAUTIONS (General)** regarding the well known potential of somatropin drug products to cause or unmask glucose intolerance, especially in patients at greater inherent risk for diabetes mellitus, i.e. patients with Turner syndrome.

Adult Patients With GHD

Adult GHD patients were treated with Eutropin™ INJ (1.33 mg = 4 IU formulation; qualitatively identical to Valtropin®, a 5 mg = 15 IU formulation) vs. placebo during the pivotal clinical study. Ninety two patients received at least 3 months of treatment with Eutropin™ INJ (31 of these patients were treated with Eutropin™ INJ for an additional 3 months), and 61 patients received 3 months of treatment with placebo. Adverse events with an incidence of ≥5.0% are presented in Table 9.

The most frequent adverse event during treatment with Eutropin™ INJ was edema, which was reported more frequently than during placebo treatment. In some of these patients, edema resulted in down-titration of the dose of Eutropin™ INJ as per protocol. Myalgia was reported by 2 patients receiving Eutropin™ INJ and 2 patients treated with placebo. Arthralgia was reported by 2 patients receiving Eutropin™ INJ. There were no reports of carpal tunnel syndrome. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. Most adverse events reported during the study were mild in severity.

Table 9
Adverse Events Observed In Adults With GHD Treated With Eutropin™ INJ vs. Placebo

Adverse events (Incidence ≥5.0% in either group) n = number of patients	Eutropin™ INJ (n = 92)		Placebo (n = 61)	
	n	%	n	%
Edema	**11**	**12.0**	**5**	**8.2**
Upper respiratory tract infection	6	6.5	1	1.6
Urticaria	2	2.2	4	6.6

During the pivotal study in adult GHD patients, a modest degree of glucose intolerance was observed in the 92 patients treated with Eutropin™ INJ for at least 3 months (31 of whom were treated for an additional 3 months). Of note, however, is the fact that 2 of the 26 patients in Group C with normal FBG values at baseline (who were treated with Eutropin™ INJ for 3 months from Month 4 through the end of Month 6 after being crossed over from placebo) had FBG values at Month 6 of 251 and 132 mg/dL. Absent follow-up data after study termination, these patients may have developed somatropin-induced *de novo* diabetes mellitus. In addition, 4 of these 26 patients had FBG values between 100-126 at Month 6. See **PRECAUTIONS (General)** regarding the well known potential of somatropin drug products to cause or unmask glucose intolerance.

Eight of the 92 patients in this study were enrolled (as per protocol) with a preexisting diagnosis of diabetes mellitus (3 of these 8 patients in fact were being treated with oral agent combination therapy and the remaining 5 patients were without drug therapy). In general, these diabetic patients tolerated treatment with Eutropin™ INJ reasonably well, i.e. no post-treatment FBG values exceeded 164 mg/dL on-study.

Seventy five out of the 92 adult GHD patients in the pivotal study (~81%) had preexisting central hypothyroidism and most of them were being treated with thyroxine replacement therapy - usually in conjunction with panhypopituitarism. None of these patients manifested clinical signs/symptoms of an exacerbation of preexisting central hypothyroidism (serial thyroid function tests were not obtained per protocol) during treatment with Eutropin™ INJ, i.e. there were no changes in maintenance thyroxine dose nor adverse events related to the thyroid during Eutropin™ INJ therapy. Furthermore, none of the remaining 17 patients enrolled in this study manifested clinical evidence of *de novo* central hypothyroidism. See **PRECAUTIONS, Drug Interactions.**

Seventy five out of the 92 adult GHD patients in the pivotal study (~81%) also had preexisting central hypoadrenalism and most of them were being treated with glucocorticoid replacement therapy. None of these patients demonstrated convincing clinical evidence of an exacerbation of preexisting central hypoadrenalism; 2 patients required an increase in hydrocortisone replacement dosages while they were taking placebo approximately 2 months removed from treatment with Eutropin™ INJ. Furthermore, none of the remaining 17 patients enrolled in this study manifested clinical evidence of *de novo* central hypoadrenalism. See **PRECAUTIONS, Drug Interactions.**

OVERDOSAGE

Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Moreover, overdose with somatropin is likely to cause fluid retention.

Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess hGH.

DOSAGE AND ADMINISTRATION

Dosage

Pediatric Patients

The Valtropin® dosage and administration schedule should be individualized for each patient. Therapy should not be continued if epiphyseal fusion has occurred. Response to somatropin therapy in pediatric patients tends to decrease with time. However, failure to increase growth rate, particularly during the first year of therapy, should prompt careful assessment of compliance, a determination as to whether anti-rhGH neutralizing antibodies have developed, and an evaluation to rule out other causes of growth failure including hypothyroidism, under-nutrition, advanced bone age.

Pediatric Growth Hormone Deficiency (GHD)

The amount administered during the pivotal study described herein was 0.23 mg/kg of body weight/week (0.033 mg/kg/day). Generally, the recommended dosage is 0.17 - 0.3 mg/kg of body weight/week. The weekly dose should be divided into equal amounts given either daily or 6 days a week by subcutaneous injection.

Children with Turner Syndrome

The amount administered during the pivotal study utilizing the 5 mg (15 IU) formulation of Valtropin® described herein was 0.37 mg/kg of body weight/week (0.053 mg/kg/day). Generally, the recommended dose is up to 0.375 mg/kg of body weight/week. The weekly dose should be divided into equal amounts given either daily or 6 days a week by subcutaneous injection.

Adult Patients

Adult Growth Hormone Deficiency (GHD)

Based on the pivotal study described herein, the recommended dosage at the start of therapy is 0.33 mg/day (or 0.1 mL of reconstituted solution) (equivalent to 0.005 mg/kg/day in a 66 kg adult) (6 days/week) given as a subcutaneous injection. The dosage may be increased according to individual patient requirements to a maximum of 0.66 mg/day (equivalent to 0.010 mg/kg/day in a 66 kg adult) (6 days/week) after 4 weeks. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

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

ADMINISTRATION

The thighs are recommended as the preferred sites of injection and the injection site should be rotated to avoid lipoatrophy.

After determining the appropriate patient dose, each vial of Valtropin® should be reconstituted using the accompanying diluent. For use in patients with a known sensitivity to metacresol, Valtropin® should not be reconstituted with the supplied diluent, but instead with water for injection. The diluent supplied in the prefilled syringe or water for injection should be injected entirely into the vial of Valtropin® by aiming the stream of liquid against the glass wall. Following reconstitution, the vial should be swirled with a **GENTLE** rotary motion until the contents are completely dissolved, providing a 3.33 mg/mL solution of somatropin. **DO NOT SHAKE.** If the solution is shaken, the solution may become cloudy or develop particulate matter. The Valtropin® solution should be clear immediately after reconstitution. **DO NOT INJECT** the Valtropin® solution if it is cloudy or contains particulate matter immediately after reconstitution or after refrigeration. These kinds of solutions should be discarded.

If reconstituted with water for injection, do not store but discard after use, since it lacks preservative. If reconstituted with the supplied diluent, which contains preservative, label the vial with the date on which you prepared the solution and store in a refrigerator.

It is recommended that the volume of reconstituted Valtropin® solution required to provide the prescribed dose of Valtropin® should be withdrawn from the reconstituted solution and administered using sterile, disposable syringes and needles (a new disposable syringe and needle should be used for every injection).

The disposable syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy, and the needle should be fine enough to ensure patient comfort.

In order to prevent contamination of the contents of the reconstituted vial of Valtropin® by repeated needle insertions, ensure that before every injection, the septum of the vial (e.g., the rubber vial stopper) is wiped with an antiseptic solution before puncturing it with the needle, and after every injection the rubber vial stopper is also wiped with an antiseptic solution. Return the multiuse vial, reconstituted with supplied diluent, to the refrigerator after each use.

STABILITY AND STORAGE

Before Reconstitution
Valtropin® powder or diluent should be stored under refrigeration (2°C-8°C/36°F-46°F). Do not freeze. Expiration dates are stated on the labels.

The product should be refrigerated prior to dispensing, but may be stored at or below 25°C (77°F) for up to three months after dispensing.

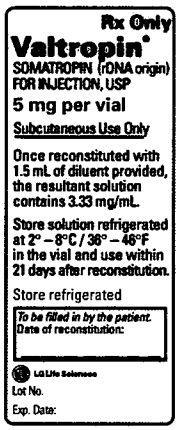
After Reconstitution With The Diluent Provided
When reconstituted with the diluent provided, the reconstituted solution may be stored under refrigeration (2°C-8°C/36°F-46°F) for up to 21 days. Avoid freezing reconstituted vials of Valtropin®.

If Reconstituted With Water For Injection
When reconstituted with sterile Water for Injection, use only one dose per Valtropin® vial and discard the unused portion if not needed immediately.

The use of Sterile Water for Injection without preservative should be reserved only for patients who have an allergy or sensitivity to metacresol or when the supplied diluent is unavailable.

How Supplied

Valtropin® is a sterile, non-pyrogenic, white to almost white, lyophilized powder supplied as a single pack containing:
- 1 vial of powder containing 5 mg somatropin
- 1 single use pre-filled syringe containing 1.5 mL diluent (Metacresol in Water for Injection).



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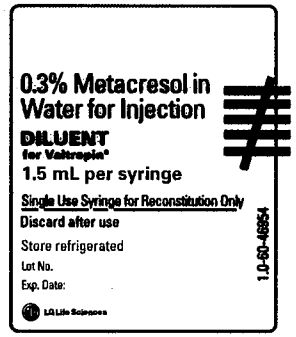

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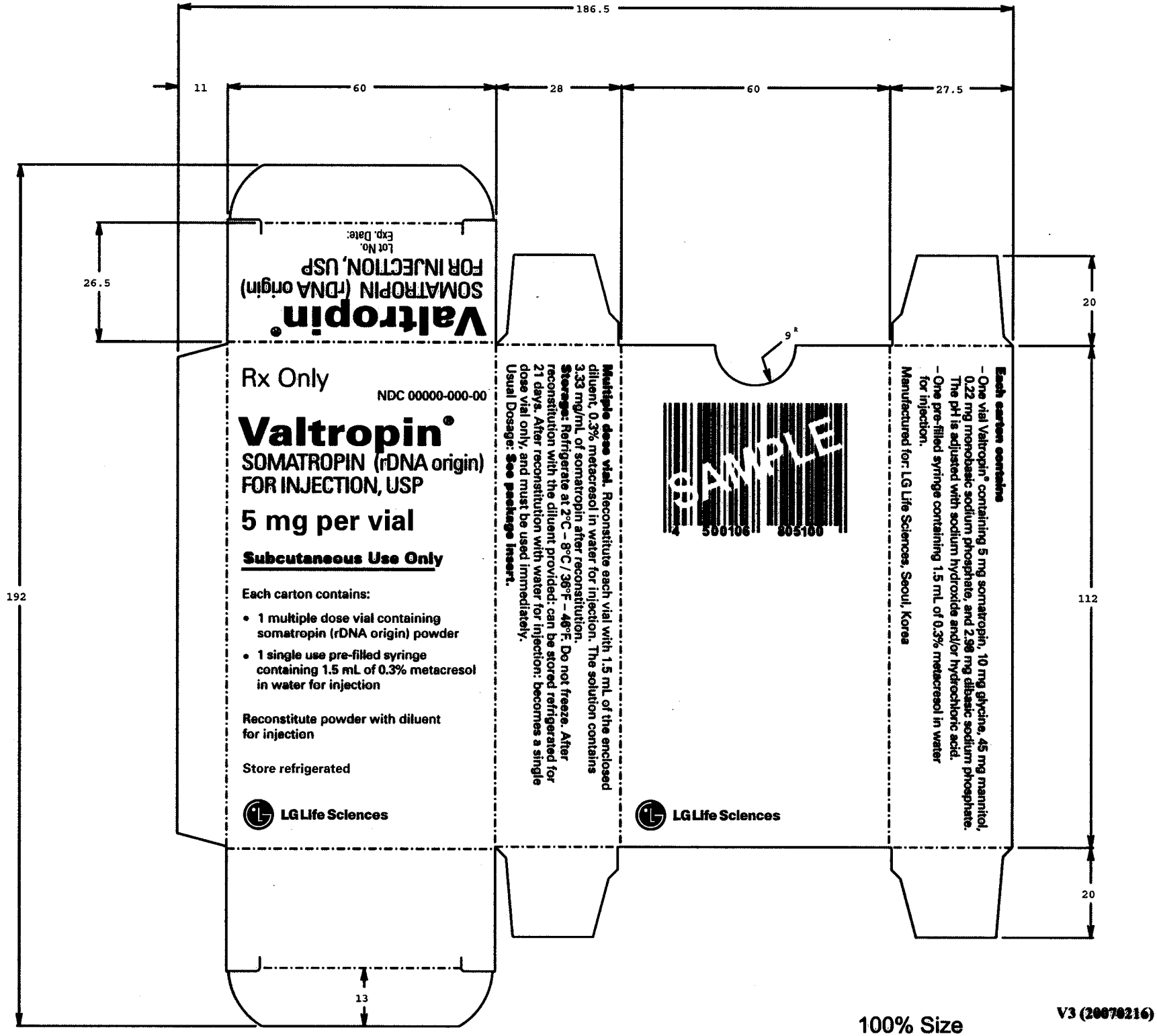

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