PRODUCT INFORMATION

Norditropin® cartridges

Somatropin (rDNA origin) injection
5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL

Rx Only

DESCRIPTION

Norditropin® is the Novo Nordisk A/S registered trademark for somatropin, a polypeptide hormone of recombinant DNA origin. The hormone is synthesized by a special strain of *E. coli* bacteria that has been modified by the addition of a plasmid which carries the gene for human growth hormone. Norditropin contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone with a molecular weight of about 22,000 Daltons.

Norditropin cartridges are supplied as solutions in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL.

Each **Norditropin cartridge** contains the following:

Component	5 mg/ 1.5 mL	10 mg/ 1.5 mL	15 mg/ 1.5 mL
Somatropin	5 mg	10 mg	15 mg
Histidine	1 mg	1 mg	1.7 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg
Phenol	4.5 mg	4.5 mg	4.5 mg
Mannitol	60 mg	60 mg	58 mg
HCl/NaOH	q.s.	q.s.	q.s.
Water for Injection	ad 1.5 mL	ad 1.5 mL	ad 1.5 mL

CLINICAL PHARMACOLOGY

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-I, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-I levels are low in the serum of hypopituitary dwarfs 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 number of skeletal muscle cells is markedly decreased in short stature children lacking endogenous somatropin 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 human growth hormone to normal adults and patients with growth hormone deficiency 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 growth hormone deficiency is associated with increased body fat stores, including increased subcutaneous abdominal adipose tissue. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, in particular in subcutaneous 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 growth hormone deficiency 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.

g. Pharmacokinetics

A 180-min IV infusion of Norditropin (33 ng/kg/min) was given to 9 GHD patients. A mean (±SD) hGH steady-state serum level of approximately 23.1 (±15.0) ng/mL was reached at 150 min and a mean clearance rate of approximately 2.3 (±1.8) mL/min/kg or 139 (±105) mL/min for hGH was obtained. Following infusion, serum hGH levels had a biexponential decay with a terminal elimination half-life ($T_{1/2}$) of approximately 21.1 (±5.1) min.

In a study conducted in 18 GHD adult patients, where a SC dose of 0.024 mg/kg or 3 IU/m^2 was given in the thigh, the mean (±SD) C_{max} values of 13.8 (±5.8) and 17.1 (±10.0) ng/mL were obtained for the 4 and 8 mg Norditropin vials, respectively, at approximately 4 to 5 hr. post dose. The mean apparent terminal $T_{1/2}$ values were estimated to be approximately 7 to 10 hr. However, the absolute bioavailability for Norditropin after the SC route of administration is currently not known.

Norditropin cartridge formulation is bioequivalent to Norditropin vial formulation.

CLINICAL STUDIES

Adult Growth Hormone Deficiency (GHD)

A total of six randomized, double-blind, placebo-controlled studies were performed. Two representative studies, one in adult onset (AO) GHD patients and a second in childhood onset (CO) GHD patients, are described below.

Study 1

A single center, randomized, double-blind, placebo-controlled, parallel-group, six month clinical trial was conducted in 31 adults with AO GHD comparing the effects of Norditropin® (somatropin [rDNA origin] for injection) and placebo on body composition. Patients in the active treatment arm were treated with Norditropin 0.017 mg/kg/day (not to exceed 1.33 mg/day). The changes from baseline in lean body mass (LBM) and percent total body fat (TBF) were measured by total body potassium (TBP) after 6 months.

Treatment with Norditropin produced a significant (p=0.0028) increase from baseline in LBM compared to placebo (Table 1).

Table 1 - Lean Body Mass (kg) by TBP

	Norditropin (n=15)	Placebo (n=16)
Baseline (mean)	50.27	51.72
Change from baseline at 6 months (mean)	1.12	-0.63
Treatment difference (mean) 95% confidence interval p-value	1.74 (0.65, 2.83) p=0.0028	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0048) in the Norditropin-treated groups (pooled data) compared to the placebo group (Table 4).

Table 4 - Total Body Fat (%) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	34.55	34.07
Change from baseline at 6 months (mean)	-6.00	-1.78
Treatment difference (mean) 95% confidence interval p-value	-4.24 (-7.11, -1.37) p=0.0048	

Norditropin also significantly reduced intraabdominal, extraperitoneal and total abdominal fat volume, waist/hip ratio and LDL cholesterol, and significantly increased serum osteocalcin.

Forty four men were enrolled in an open label follow up study and treated with Norditropin for as long as 30 additional months. During this period, the reduction in waist/hip ratio achieved during the initial six months of treatment was maintained.

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0004) in the Norditropin-treated group compared to the placebo group (Table 2).

Table 2 - Total Body Fat (%) by TBP

	Norditropin (n=15)	Placebo (n=16)
Baseline (mean)	44.74	42.26
Change from baseline at 6 months (mean)	-2.83	1.92
Treatment difference (mean) 95% confidence interval p-value	-4.74 (-7.18, -2.30) p=0.0004	

Fifteen (48.4%) of the 31 randomized patients were male. The adjusted mean treatment differences on the increase in LBM and decrease in percent TBF from baseline were larger in males compared to females.

Norditropin also significantly increased serum osteocalcin (a marker of osteoblastic activity).

Study 2

A single center, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, six month clinical trial was conducted in 49 men with CO GHD comparing the effects of Norditropin and placebo on body composition. Patients were randomized to placebo or one of three active treatment groups (0.008, 0.016, and 0.024 mg/kg/day). Thirty three percent of the total dose to which each patient was randomized was administered during weeks 1-4, 67% during weeks 5-8, and 100% for the remainder of the study. The changes from baseline in LBM and percent TBF were measured by TBP after 6 months.

Treatment with Norditropin produced a significant (p=0.0079) increase from baseline in LBM compared to placebo (pooled data) (Table 3).

Table 3 - Lean Body Mass (kg) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	48.18	48.90
Change from baseline at 6 months (mean)	2.06	0.70
Treatment difference (mean) 95% confidence interval p-value	1.40 (0.39, 2.41) p=0.0079	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0048) in the Norditropin-treated groups (pooled data) compared to the placebo group (Table 4).

Table 4 - Total Body Fat (%) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	34.55	34.07
Change from baseline at 6 months (mean)	-6.00	-1.78
Treatment difference (mean) 95% confidence interval p-value	-4.24 (-7.11, -1.37) p=0.0048	

Norditropin also significantly reduced intraabdominal, extraperitoneal and total abdominal fat volume, waist/hip ratio and LDL cholesterol, and significantly increased serum osteocalcin.

Forty four men were enrolled in an open label follow up study and treated with Norditropin for as long as 30 additional months. During this period, the reduction in waist/hip ratio achieved during the initial six months of treatment was maintained.

INDICATIONS AND USAGE

Pediatric Patients:

Norditropin is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

Adult Patients:

Norditropin cartridges [somatropin (rDNA origin) injection] is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

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

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

Norditropin cartridges is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients.

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 pre-existing 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% vs. 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, Norditropin cartridges is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

WARNINGS

Norditropin cartridges (somatropin [rDNA origin] injection) must be used with their corresponding color-coded NordiPen® delivery device. A Norditropin cartridge must not be inserted into a pen with a different color code.

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

PRECAUTIONS

General

Norditropin® cartridges (somatropin [rDNA origin] injection) therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of pediatric patients with growth hormone deficiency 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 occurred 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.

As is the case with any protein product, 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 General Precautions)
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.

Adult Patients (see General Precautions)
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.

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

Drug Interactions
Somatropin inhibits 11ß-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, mutagenicity, and fertility studies have not been conducted with Norditropin.

Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with Norditropin. It is not known whether Norditropin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Norditropin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether Norditropin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin is administered to a nursing woman.

Geriatric Use
The safety and effectiveness of Norditropin 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).

Information For Patients
Patients being treated with Norditropin cartridges (and/or their parents) should be informed about the potential benefits and risks associated with Norditropin cartridges 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 Norditropin cartridges should receive appropriate training and instruction on the proper use of Norditropin cartridges 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.

If patients are prescribed Norditropin NordiFlex, physicians should instruct patients to read the PATIENT INFORMATION and INSTRUCTIONS FOR USE provided with the Norditropin NordiFlex prefilled pen.

ADVERSE REACTIONS

Growth Hormone Deficient Pediatric Patients
As with all protein drugs, a small percentage of patients may develop antibodies to the protein. Growth hormone antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In some patients, when binding capacity was greater than 2 mg/L, interference with growth response was observed. In clinical trials, patients receiving Norditropin for up to 12 months were tested for induction of antibodies and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Amongst these patients, 165 had previously been treated with other preparations of growth hormone and 193 were previously untreated naive patients. Any patient with well-documented growth hormone deficiency who fails to respond to Norditropin therapy should be tested for antibodies to human growth hormone and have thyroid function tests performed.

The following adverse events have been reported during clinical studies in growth hormone deficient children: headache, local reactions at the injection site, localized muscle pain, rash, weakness, mild hyperglycemia, glucosuria and arthralgia.

Fluid retention and peripheral edema may occur.

Leukemia has been reported in a small number of growth hormone deficient children treated with growth hormone, including recombinant somatropin, recombinant somatrem and growth hormone of pituitary origin. On the basis of current evidence, experts have not been able to conclude that growth hormone therapy per se was responsible for these cases of leukemia. The risk, if any, remains to be established.

Growth Hormone Deficient Adult Patients
Adverse events with an incidence of ≥5% occurring in patients with AO GHD during the 6 month placebo-controlled portion of the largest of the six adult GHD Norditropin trials are presented in Table 5. Peripheral edema, other types of edema, arthralgia, myalgia, and paraesthesia were common in the Norditropin-treated patients and reported much more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. In general, these adverse events were mild and transient in nature. During the placebo-controlled portion of this study, approximately 5% of patients without preexisting diabetes mellitus treated with Norditropin were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group, consistent with the known hyperglycemic effects of somatropin. Anti-GH antibodies were not detected.

Of note, the doses of Norditropin employed during this study (completed in the mid 1990s) were substantially larger than those currently recommended by the Growth Hormone Research Society, and, more than likely, resulted in a greater than expected incidence of fluid retention- and glucose intolerance-related adverse events. A similar incidence and pattern of adverse events were observed during the other three placebo-controlled AO GHD trials and during the two placebo-controlled CO GHD trials.

Table 5 - ISS: Adverse Events with ≥5% Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin During a Six Month Placebo-Controlled Clinical Trial

	Norditropin (N=53)		Placebo (N=52)	
Adverse Event	n	%	n	%
Peripheral Edema	22	42	4	8
Edema	13	25	0	0
Arthralgia	10	19	8	15
Leg Edema	8	15	2	4
Myalgia	8	15	4	8
Infection (non-viral)	7	13	4	8
Paraesthesia	6	11	3	6
Skeletal Pain	6	11	1	2
Headache	5	9	3	6
Bronchitis	5	9	0	0
Flu-like symptoms	4	8	2	4
Hypertension	4	8	1	2
Gastroenteritis	4	8	4	8
Other Non-Classifiable Disorders (excludes accidental injury)	4	8	3	6
Increased sweating	4	8	1	2
Glucose tolerance abnormal	3	6	1	2
Laryngitis	3	6	3	6

The adverse event pattern observed during the open label phase of the study was similar to the one presented above.

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 human growth hormone.

DOSAGE AND ADMINISTRATION

Pediatric Patients
The Norditropin dosage and schedule of administration must be individualized for each patient. For the treatment of growth hormone insufficiency in children, a dosage of 0.024 - 0.034 mg/kg body weight/day, 6-7 times a week, by subcutaneous injection is recommended. The thighs are recommended as the preferred sites of injection and the injection site should be rotated.

Treatment with Norditropin of growth failure due to growth hormone deficiency should be discontinued when the epiphyses are fused. Patients who fail to respond adequately while on Norditropin therapy should be evaluated to determine the cause of unresponsiveness.

Adult Patients
Based on the weight-based dosing utilized in the original pivotal study described herein, the recommended dosage at the start of therapy is not more than 0.004 mg/kg given as a daily subcutaneous injection. The dosage may be increased to not more than 0.016 mg/kg/day after approximately 6 weeks according to individual patient requirements. 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 more recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. 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.

All Patients
Norditropin cartridges must be administered using the NordiPen injection pen. Each cartridge size has a color-coded corresponding pen which is graduated to deliver the appropriate dose based on the concentration of Norditropin in the cartridge.

Norditropin MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

Measuring The Prescribed Dose
Norditropin® cartridges 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Each cartridge of Norditropin must be inserted into its corresponding NordiPen injection pen. Instructions for delivering the dosage are provided in the NordiPen instruction booklet.

Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Instructions for delivering the dosage are provided in the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflet enclosed with the Norditropin NordiFlex® prefilled pen.

STABILITY AND STORAGE

Norditropin® cartridges (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Non-injected/unused Norditropin cartridges must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

Norditropin cartridges retain their biological potency until the date of expiry indicated on the label.

5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) cartridges:
After a Norditropin cartridge (5 mg/1.5 mL or 10 mg/1.5 mL) has been inserted into the NordiPen injector (NordiPen 5 or NordiPen 10 respectively), it may be **EITHER** stored in the pen in the refrigerator (2-8°C/36-46°F) and used within 4 weeks **OR** may be stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) cartridges:
After a Norditropin 15 mg/1.5 mL cartridge has been inserted into the NordiPen 15 injector, it must be stored in the pen in the refrigerator (2-8°C/36-46°F) and used within 4 weeks. Discard unused portion after 4 weeks.

Norditropin NordiFlex® (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Non-injected/unused Norditropin NordiFlex prefilled pens must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

The Norditropin NordiFlex prefilled pens retain their biological potency until the date of expiry indicated on the label.

5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) prefilled pens:
After the initial injection, a Norditropin NordiFlex (5 mg/1.5 mL or 10 mg/1.5 mL) prefilled pen may be **EITHER** stored in the refrigerator (2-8°C/36-46°F) and used within 4 weeks **OR** may be stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) prefilled pens:
After the initial injection, a Norditropin NordiFlex 15 mg/1.5 mL prefilled pen must be stored in the refrigerator (2-8°C/36-46°F) and used within 4 weeks. Discard unused portion after 4 weeks.

HOW SUPPLIED

Norditropin® cartridges (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Norditropin is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL cartridges which must be administered using the corresponding color-coded NordiPen® injection pen.

Norditropin cartridge 5 mg/1.5 mL (orange)
NDC 0169-7768-11
Norditropin cartridge 10 mg/1.5 mL (blue)
NDC 0169-7769-11
Norditropin cartridge 15 mg/1.5 mL (green)
NDC 0169-7770-11

Norditropin NordiFlex® (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Norditropin NordiFlex is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL prefilled pens.

Norditropin NordiFlex 5 mg/1.5 mL (orange)
NDC 0169-7704-11
Norditropin NordiFlex 10 mg/1.5 mL (blue)
NDC 0169-7705-11
Norditropin NordiFlex 15 mg/1.5 mL (green)
NDC 0169-7708-11

Date of Issue: June 2006

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2880 Bagsvaerd, Denmark

novo nordisk®

PRODUCT INFORMATION

Norditropin® cartridges

Somatropin (rDNA origin) injection
5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL

Rx Only

DESCRIPTION

Norditropin® is the Novo Nordisk A/S registered trademark for somatropin, a polypeptide hormone of recombinant DNA origin. The hormone is synthesized by a special strain of *E. coli* bacteria that has been modified by the addition of a plasmid which carries the gene for human growth hormone. Norditropin contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone with a molecular weight of about 22,000 Daltons. Norditropin cartridges are supplied as solutions in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL.

Each **Norditropin cartridge** contains the following:

Component	5 mg/ 1.5 mL	10 mg/ 1.5 mL	15 mg/ 1.5 mL
Somatropin	5 mg	10 mg	15 mg
Histidine	1 mg	1 mg	1.7 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg
Phenol	4.5 mg	4.5 mg	4.5 mg
Mannitol	60 mg	60 mg	58 mg
HCl/NaOH	q.s.	q.s.	q.s.
Water for Injection	ad 1.5 mL	ad 1.5 mL	ad 1.5 mL

CLINICAL PHARMACOLOGY

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-I, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-I levels are low in the serum of hypopituitary dwarfs 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 number of skeletal muscle cells is markedly decreased in short stature children lacking endogenous somatropin 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 human growth hormone to normal adults and patients with growth hormone deficiency 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 growth hormone deficiency is associated with increased body fat stores, including increased subcutaneous abdominal adipose tissue. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, in particular in subcutaneous 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 growth hormone deficiency 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.

g. Pharmacokinetics

A 180-min IV infusion of Norditropin (33 ng/kg/min) was given to 9 GHD patients. A mean (±SD) hGH steady-state serum level of approximately 23.1 (±15.0) ng/mL was reached at 150 min and a mean clearance rate of approximately 2.3 (±1.8) mL/min/kg or 139 (±105) mL/min for hGH was obtained. Following infusion, serum hGH levels had a biexponential decay with a terminal elimination half-life ($T_{1/2}$) of approximately 21.1 (±5.1) min.

In a study conducted in 18 GHD adult patients, where a SC dose of 0.024 mg/kg or 3 IU/m^2 was given in the thigh, the mean (±SD) C_{max} values of 13.8 (±5.8) and 17.1 (±10.0) ng/mL were obtained for the 4 and 8 mg Norditropin vials, respectively, at approximately 4 to 5 hr. post dose. The mean apparent terminal $T_{1/2}$ values were estimated to be approximately 7 to 10 hr. However, the absolute bioavailability for Norditropin after the SC route of administration is currently not known.

Norditropin cartridge formulation is bioequivalent to Norditropin vial formulation.

CLINICAL STUDIES

Adult Growth Hormone Deficiency (GHD)

A total of six randomized, double-blind, placebo-controlled studies were performed. Two representative studies, one in adult onset (AO) GHD patients and a second in childhood onset (CO) GHD patients, are described below.

8-2084-31-002-3

Study 1
A single center, randomized, double-blind, placebo-controlled, parallel-group, six month clinical trial was conducted in 31 adults with AO GHD comparing the effects of Norditropin® (somatropin [rDNA origin] for injection) and placebo on body composition. Patients in the active treatment arm were treated with Norditropin 0.017 mg/kg/day (not to exceed 1.33 mg/day). The changes from baseline in lean body mass (LBM) and percent total body fat (TBF) were measured by total body potassium (TBP) after 6 months.

Treatment with Norditropin produced a significant (p=0.0028) increase from baseline in LBM compared to placebo (Table 1).

Table 1 - Lean Body Mass (kg) by TBP

	Norditropin (n=15)	Placebo (n=16)
Baseline (mean)	50.27	51.72
Change from baseline at 6 months (mean)	1.12	-0.63
Treatment difference (mean) 95% confidence interval p-value	1.74 (0.65, 2.83) p=0.0028	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0004) in the Norditropin-treated group compared to the placebo group (Table 2).

Table 2 - Total Body Fat (%) by TBP

	Norditropin (n=15)	Placebo (n=16)
Baseline (mean)	44.74	42.26
Change from baseline at 6 months (mean)	-2.83	1.92
Treatment difference (mean) 95% confidence interval p-value	-4.74 (-7.18, -2.30) p=0.0004	

Fifteen (48.4%) of the 31 randomized patients were male. The adjusted mean treatment differences on the increase in LBM and decrease in percent TBF from baseline were larger in males compared to females.

Norditropin also significantly increased serum osteocalcin (a marker of osteoblastic activity).

Study 2
A single center, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, six month clinical trial was conducted in 49 men with CO GHD comparing the effects of Norditropin and placebo on body composition. Patients were randomized to placebo or one of three active treatment groups (0.008, 0.016, and 0.024 mg/kg/day). Thirty three percent of the total dose to which each patient was randomized was administered during weeks 1-4, 67% during weeks 5-8, and 100% for the remainder of the study. The changes from baseline in LBM and percent TBF were measured by TBP after 6 months.

Treatment with Norditropin produced a significant (p=0.0079) increase from baseline in LBM compared to placebo (pooled data) (Table 3).

Table 3 - Lean Body Mass (kg) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	48.18	48.90
Change from baseline at 6 months (mean)	2.06	0.70
Treatment difference (mean) 95% confidence interval p-value	1.40 (0.39, 2.41) p=0.0079	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0048) in the Norditropin-treated groups (pooled data) compared to the placebo group (Table 4).

Table 4 - Total Body Fat (%) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	34.55	34.07
Change from baseline at 6 months (mean)	-6.00	-1.78
Treatment difference (mean) 95% confidence interval p-value	-4.24 (-7.11, -1.37) p=0.0048	

Norditropin also significantly reduced intraabdominal, extraperitoneal and total abdominal fat volume, waist/hip ratio and LDL cholesterol, and significantly increased serum osteocalcin.

Forty four men were enrolled in an open label follow up study and treated with Norditropin for as long as 30 additional months. During this period, the reduction in waist/hip ratio achieved during the initial six months of treatment was maintained.

INDICATIONS AND USAGE

Pediatric Patients:

Norditropin is indicated for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.

Adult Patients:

Norditropin cartridges [somatropin (rDNA origin) injection] is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

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

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

Norditropin cartridges is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients.

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 pre-existing 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% vs. 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, Norditropin cartridges is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

WARNINGS

Norditropin cartridges (somatropin [rDNA origin] injection) must be used with their corresponding color-coded NordiPen® delivery device.
A Norditropin cartridge must not be inserted into a pen with a different color code.

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

PRECAUTIONS

General

Norditropin® cartridges (somatropin [rDNA origin] injection) therapy should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of pediatric patients with growth hormone deficiency 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 occurred 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.

As is the case with any protein product, 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 General Precautions)

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.

Adult Patients (see General Precautions)

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.

Laboratory Tests

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

Drug Interactions

Somatropin inhibits 11ß-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, mutagenicity, and fertility studies have not been conducted with Norditropin.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Norditropin. It is not known whether Norditropin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Norditropin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether Norditropin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin is administered to a nursing woman.

Geriatric Use

The safety and effectiveness of Norditropin 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).

Information For Patients

Patients being treated with Norditropin cartridges (and/or their parents) should be informed about the potential benefits and risks associated with Norditropin cartridges 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 Norditropin cartridges should receive appropriate training and instruction on the proper use of Norditropin cartridges 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.

If patients are prescribed Norditropin NordiFlex, physicians should instruct patients to read the PATIENT INFORMATION and INSTRUCTIONS FOR USE provided with the Norditropin NordiFlex prefilled pen.

ADVERSE REACTIONS

Growth Hormone Deficient Pediatric Patients

As with all protein drugs, a small

percentage of patients may develop antibodies to the protein. Growth hormone antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In some patients, when binding capacity was greater than 2 mg/L, interference with growth response was observed. In clinical trials, patients receiving Norditropin for up to 12 months were tested for induction of antibodies and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Amongst these patients, 165 had previously been treated with other preparations of growth hormone and 193 were previously untreated naive patients. Any patient with well-documented growth hormone deficiency who fails to respond to Norditropin therapy should be tested for antibodies to human growth hormone and have thyroid function tests performed.

The following adverse events have been reported during clinical studies in growth hormone deficient children: headache, local reactions at the injection site, localized muscle pain, rash, weakness, mild hyperglycemia, glucosuria and arthralgia.

Fluid retention and peripheral edema may occur.

Leukemia has been reported in a small number of growth hormone deficient children treated with growth hormone, including recombinant somatropin, recombinant somatrem and growth hormone of pituitary origin. On the basis of current evidence, experts have not been able to conclude that growth hormone therapy *per se* was responsible for these cases of leukemia. The risk, if any, remains to be established.

Growth Hormone Deficient Adult Patients

Adverse events with an incidence of ≥5% occurring in patients with AO GHD during the 6 month placebo-controlled portion of the largest of the six adult GHD Norditropin trials are presented in Table 5. Peripheral edema, other types of edema, arthralgia, myalgia, and paraesthesia were common in the Norditropin-treated patients and reported much more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. In general, these adverse events were mild and transient in nature. During the placebo-controlled portion of this study, approximately 5% of patients without pre-existing diabetes mellitus treated with Norditropin were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group, consistent with the known hyperglycemic effects of somatropin. Anti-GH antibodies were not detected.

Of note, the doses of Norditropin employed during this study (completed in the mid 1990s) were substantially larger than those currently recommended by the Growth Hormone Research Society, and, more than likely, resulted in a greater than expected incidence of fluid retention- and glucose intolerance-related adverse events. A similar incidence and pattern of adverse events were observed during the other three placebo-controlled AO GHD trials and during the two placebo-controlled CO GHD trials.

Table 5 - ISS: Adverse Events with ≥5% Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin During a Six Month Placebo-Controlled Clinical Trial

	Norditropin (N=53)		Placebo (N=52)	
Adverse Event	n	%	n	%
Peripheral Edema	22	42	4	8
Edema	13	25	0	0
Arthralgia	10	19	8	15
Leg Edema	8	15	2	4
Myalgia	8	15	4	8
Infection (non-viral)	7	13	4	8
Paraesthesia	6	11	3	6
Skeletal Pain	6	11	1	2
Headache	5	9	3	6
Bronchitis	5	9	0	0
Flu-like symptoms	4	8	2	4
Hypertension	4	8	1	2
Gastroenteritis	4	8	4	8
Other Non-Classifiable Disorders (excludes accidental injury)	4	8	3	6
Increased sweating	4	8	1	2
Glucose tolerance abnormal	3	6	1	2
Laryngitis	3	6	3	6

The adverse event pattern observed during the open label phase of the study was similar to the one presented above.

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 human growth hormone.

DOSAGE AND ADMINISTRATION

Pediatric Patients

The Norditropin dosage and schedule of administration must be individualized for each patient. For the treatment of growth hormone insufficiency in children, a dosage of 0.024 - 0.034 mg/kg body weight/day, 6-7 times a week, by subcutaneous injection is recommended. The thighs are recommended as the preferred sites of injection and the injection site should be rotated.

Treatment with Norditropin of growth failure due to growth hormone deficiency should be discontinued when the epiphyses are fused. Patients who fail to respond adequately while on Norditropin therapy should be evaluated to determine the cause of unresponsiveness.

Adult Patients

Based on the weight-based dosing utilized in the original pivotal study described herein, the recommended dosage at the start of therapy is not more than 0.004 mg/kg given as a daily subcutaneous injection. The dosage may be increased to not more than 0.016 mg/kg/day after approximately 6 weeks according to individual patient requirements. 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 more recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. 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.

All Patients

Norditropin cartridges must be administered using the NordiPen injection pen. Each cartridge size has a color-coded corresponding pen which is graduated to deliver the appropriate dose based on the concentration of Norditropin in the cartridge.

Norditropin MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

Measuring The Prescribed Dose
Norditropin® cartridges
5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Each cartridge of Norditropin must be inserted into its corresponding NordiPen injection pen. Instructions for delivering the dosage are provided in the NordiPen instruction booklet.

Norditropin NordiFlex®
5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Instructions for delivering the dosage are provided in the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflet enclosed with the Norditropin NordiFlex® prefilled pen.

STABILITY AND STORAGE

Norditropin® cartridges (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Non-injected/unused Norditropin cartridges must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

Norditropin cartridges retain their biological potency until the date of expiry indicated on the label.

5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) cartridges:
After a Norditropin cartridge (5 mg/1.5 mL or 10 mg/1.5 mL) has been inserted into the NordiPen injector (NordiPen 5 or NordiPen 10 respectively), it may be **EITHER** stored in the pen in the refrigerator (2-8°C/36-46°F) and used within 4 weeks **OR** may be stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) cartridges:
After a Norditropin 15 mg/1.5 mL cartridge has been inserted into the NordiPen 15 injector, it must be stored in the pen in the refrigerator (2-8°C/36-46°F) and used within 4 weeks. Discard unused portion after 4 weeks.

Norditropin NordiFlex® (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Non-injected/unused Norditropin NordiFlex prefilled pens must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

The Norditropin NordiFlex prefilled pens retain their biological potency until the date of expiry indicated on the label.

5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) prefilled pens:
After the initial injection, a Norditropin NordiFlex (5 mg/1.5 mL or 10 mg/1.5 mL) prefilled pen may be **EITHER** stored in the refrigerator (2-8°C/36-46°F) and used within 4 weeks **OR** may be stored for up to 3 weeks at not more than 25°C (77°F). Discard unused portion.

15 mg/1.5 mL (green) prefilled pens:
After the initial injection, a Norditropin NordiFlex 15 mg/1.5 mL prefilled pen must be stored in the refrigerator (2-8°C/36-46°F) and used within 4 weeks. Discard unused portion after 4 weeks.

HOW SUPPLIED

Norditropin® cartridges (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Norditropin is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL cartridges which must be administered using the corresponding color-coded NordiPen® injection pen.

Norditropin cartridge 5 mg/1.5 mL (orange) NDC 0169-7768-11
Norditropin cartridge 10 mg/1.5 mL (blue) NDC 0169-7769-11
Norditropin cartridge 15 mg/1.5 mL (green) NDC 0169-7770-11

Norditropin NordiFlex® (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Norditropin NordiFlex is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL prefilled pens.

Norditropin NordiFlex 5 mg/1.5 mL (orange) NDC 0169-7704-11
Norditropin NordiFlex 10 mg/1.5 mL (blue) NDC 0169-7705-11
Norditropin NordiFlex 15 mg/1.5 mL (green) NDC 0169-7708-11

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