**PRODUCT INFORMATION**

**Norditropin® cartridges**

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

**Rx Only**

**INDICATIONS**

Norditropin® is the Novo Nordisk A/S registered trademark for somatropin, a recombinant human growth hormone (hGH) of rDNA origin. It is comprised of a pentapeptide hormone with a molecular weight of about 22,000 Daltons.

Norditropin cartridges are supplied as solutions in 5-mg/1.5-mL, 10-mg/5-mL, or 15-mg/5-mL cartridges.

Each Norditropin cartridge contains the following:

- Component
  - 5 mg/1.5 mL
  - 10 mg/5 mL
  - 15 mg/5 mL

- Somatropin
  - 10 mg
  - 20 mg
  - 30 mg

- HCl
  - 25 mg

- NaOH
  - 50 mg

- Phenol
  - 10 mg

- Methylparaben
  - 0.025 mg

- Propylparaben
  - 0.025 mg

- Water for Injection
  - 0.5 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 vivo have shown that the incorporation of sulfur into proteoglycans is increased in the growth plate of the epiphyses, but 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 are involved in the normal development of cartilage and the hypothalamic/pituitary hormone sensitization. IGF-I, but not other somatomedins, 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 number and size of muscle cells.

3. Organ growth - somatropin influences the size of internal organs, and it also increases the cell mass in the liver and skeletal muscle.

**B. Protein Metabolism**

Somatropin exerts its influence 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 nitrogen following the initiation of somatropin treatment.

**C. Carbohydrate Metabolism**

Somatropin may influence the postprandial experience of fasting hypoglycemia which may be improved by somatropin in certain situations. In general, large doses of somatropin may impair glucose tolerance. This effect appears to be the result of the precise mechanism of the diabetogenic effect of somatropin is not known to be due to the binding of insulin rather than blocking insulin secretion. Insulin sensitivity, as assessed by glucose tolerance level, may improve as somatropin levels increase. Administration of human somatropin to normal adults and patients with growth hormone deficiency results in increased in mean fasting serum and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A1c levels remain in the normal range.

**d. Lipid Metabolism**

Somatropin stimulates intracellular IGF-I, 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 reduction of fat stores, in particular in subcutaneous abdominal tissue and decreased serum levels of low density lipoprotein (LDL) cholesterol.

Approximately 23.1 (±15.0) ng/mL was reached with growth hormone deficiency results in growth hormone to normal adults and patients with either childhood-onset or adult-onset growth hormone deficiency may also be increased in the development of children with 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.

**CONTRAINDICATIONS**

Norditropin 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 congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of growth hormone deficiency in both groups usually requires an appropriate growth hormone stimulation test. However, confirmed growth hormone stimulation testing may not be required in patients with congenital/growth hormone deficiency or type I IGF-1 deficiencies due to organic disease.

**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 or 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 (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 treatment, since the doses of antidiabetic medication may need to be adjusted 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 progres- sion or recurrence of the underlying intracranial tumor. 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. The risk of second malignant neoplasms, in particular meningiomas, in patients treated with somatropin for 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.

**CLINICAL STUDIES**

**Adult Growth Hormone Deficiency (GHD)**

A total of six randomized, double-blind, placebo-controlled, parallel-group, dose-finding, six-month clinical trials was conducted in 49 men with COG Cushing’s disease who were randomized, respectively, at approximately 4 to 5 yr. post dx. The mean apparent terminal T1/2 values were estimated to be approximately 7 to 10 hr. after repeated dosing with Norditropin after the S/C route of administration was used.

**Norditropin cartridge formulation is bioequivalent to Norditropin via intranasal route.**

**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 deficiency.

**Adult Patients:**

Norditropin cartridges (somatropin [rDNA origin]) injection must be used with their corresponding in-capsule, color-coded NordiPen® delivery device. A Norditropin cartridge must not be inserted into a pen with a different color code. Norditropin cartridges (somatropin [rDNA origin]) injection must be used with their corresponding NordiPen® delivery device. A Norditropin cartridge must not be inserted into a pen with a different color code.
Data suggest that somatropin administration inhibitory effect on growth. Therapy should be carefully adjusted in children. Excessive glucocorticoid therapy may attenuate to their biologically active metabolites is dependent for patients treated with cortisone acetate dependent therapy for previously diagnosed hypoad- metabolism of cortisol and cortisone. As a con- phosphatase, parathyroid hormone (PTH), and serum levels of inorganic phosphorus, alkaline clinical trials, patients receiving Norditropin for up abnormalities 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, glaucousia and arthralgia. Fluid retention and peripheral edema may occur. Leukemia has been reported in a small number of patients with growth hormone deficient children treated with growth hormone, including recombinant somatropin, recombinant 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 AD 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 pain 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, during the placebo-controlled portion of the 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. 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 adverse events. A similar incidence and pattern of adverse events were observed in other three placebo-controlled AD GHD trials and during the Issues to consider the adverse effects of treatment. Table 5 - ISS. Adverse Events with an Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin During a Six Month Placebo-Controlled Clinical Trial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (%)</th>
<th>Norditropin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal vision</td>
<td>1 4 2 5</td>
<td>1 4 2 5</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>22 14 2 1</td>
<td>22 14 2 1</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Lesion</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Hematoma</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Other Considerations</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Other Non-Cardiac Disorders</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>10 19 19 19</td>
<td>10 19 19 19</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 9 9 9</td>
<td>5 9 9 9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 9 9 9</td>
<td>5 9 9 9</td>
</tr>
</tbody>
</table>

The adverse event pattern observed during the open label phase of the study was similar to the Study 1. OVERDOSE
Short-term overdose could lead initially to these adverse events mild and transient. Long-term overdose could result in signs and symptoms of gigantism and/or acromegaly com-
Norditropin is a synthetic human growth hormone (GH) preparation for the treatment of growth hormone deficiency (GHD) in children and adults. The product contains somatropin, a hormone naturally produced in the body and obtained through recombinant DNA technology. Norditropin is indicated for the long-term treatment of pediatric patients with GHD, the long-term treatment of children with growth failure due to primary pituitary GH deficiency, and the long-term treatment of adult patients with GHD.

**INDICATIONS AND USAGE**

Norditropin is used for the long-term treatment of GHD in children and adults. It is also used for conditions like Turner syndrome, Prader-Willi syndrome, and GH deficiency in children and adults.

**Contraindications**

- A single center, randomized, double-blind, placebo-controlled study conducted in 49 men with Turner syndrome showed that Norditropin significantly reduced serum total cholesterol levels at 6 months (mean) -2.83 1.92 95% confidence interval (-7.18, -2.30).
- Treatment with Norditropin significantly increased insulin levels in serum, which is increased in patients with diabetes mellitus.
- Following infusion, serum sodium is increased, there is a simultaneous increase in bone length after administration of somatropin. This retention is thought to be due to increased activity associated with increased bone growth.
- Norditropin also significantly increased somatropin levels in patients with Turner syndrome, which is attributed to blocking the action of somatomedin inhibitors.
- Norditropin is also used for the treatment of Turner syndrome, Prader-Willi syndrome, and adults with GHD.

**WARMING**

- Norditropin is contraindicated in patients with hyperglycemia due to diabetes mellitus.
- Patients being treated with Norditropin should be monitored closely when somatropin administration is increased to avoid hypoglycemia.

**PRECAUTIONS**

- Patients should be monitored closely for diabetes mellitus.
- Patients should be monitored for hyperglycemia, which can occur more frequently in patients with Turner syndrome, Prader-Willi syndrome, and adults with GHD.
- Patients should be monitored for the development of diabetes mellitus.
- Patients should be monitored for the development of hypoglycemia.
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**ADVERSE REACTIONS**

- Adverse reactions to Norditropin include hypothyroidism, hypocalcemia, and hypercalcemia. These reactions are usually transient and dose-dependent.
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**NURSING MONITORS**

- Patients who have growth failure due to primary pituitary GH deficiency in children and adults should be monitored closely when somatropin administration is increased to avoid hypoglycemia.
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**DOSAGE AND Administration**

- Norditropin is administered subcutaneously once daily, usually at bedtime.
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**SUGGESTED USES**

- Norditropin is used for the treatment of growth hormone deficiency in children and adults.
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**ABBREVIATIONS**

- GHD: Growth Hormone Deficiency
- HSD-1: 11β-hydroxysteroid dehydrogenase type 1
- CNS: Central Nervous System
- IH: Insulin Resistance
- HSD-1 enzyme: 11β-hydroxysteroid dehydrogenase type 1
- RHSH: Randomized, placebo-controlled, double-blind, parallel-group, multicenter, 6-month study of the effect of teriparatide on bone mineral density and bone turnover in postmenopausal women with osteoporosis
- PTHrP: Parathyroid Hormone-related Protein
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**PRODUCT INFORMATION**

Norditropin (somatropin [rDNA origin] for injection) is a growth hormone preparation for injection. Norditropin is a recombinant human growth hormone, modified by the addition of somatropin. In healthy subjects, large increases in plasma insulin-like growth factor-1 (IGF-1) have been observed following treatment with Norditropin. However, these increases are not associated with significant changes in glucose metabolism. Following administration of Norditropin, there is a significant (p<0.002) increase from baseline in lean body mass (LBM) and percent TBF. Norditropin Placebo

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Adverse Events with Growth Hormone Deficient Adults

Adverse events with a frequency of ≥5% in adults with growth hormone deficiency treated with Norditropin are presented in Table 5. The incidence is likely to be somewhat lower in adults than in the paediatric group. These types of adverse events are thought to be related to the fluid accumulating effects of excess human growth hormone. After the initial injection, the Norditropin NordiFlex prefilled pens and Norditropin® cartridges must be stored 2-8°C/36-46°F (refrigerator). Non-injected/unused Norditropin cartridges retain their clear and colorless. If the solution is cloudy or contains precipitate, and/or serum IGF-I levels above the age- and gender-specific normal range.

Table 5: Adverse Events with Growth Hormone Deficient Patients Treated with Norditropin During a 4-Month Randomized Controlled Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Patients (225)</th>
<th>Number of Patients (224)</th>
<th>Number of Patients (223)</th>
<th>Number of Patients (222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose tolerance</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Disaccharides</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Infection (non-viral)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Leg edema</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

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

OVERDOSE

Severe overdose could lead initially to hypoglycemia and subsequently to hyperglycemia. Abruptly stopping therapy or injection of neutralizing antibodies for excess human growth hormone.

DOSAGE AND ADMINISTRATION

Pediatric Patients

The Norditropin NordiFlex and Norditropin® cartridges are provided in the PATIENT INFORMATION and INSTRUCTIONS leaflets enclosed with the Norditropin NordiFlex prefilled pens and Norditropin® cartridges, respectively. The Norditropin NordiFlex pen which is graduated to deliver 0.2 mg/kg every 4 weeks.

Adult Patients

Based on the weight-based dosing utilized in the original adult clinical trials (3 mg/kg/day or 1.5 mg/kg/day), the starting dose at the start of therapy is not more than 0.004 mg/kg given as a daily subcutaneous injection. The dose should be increased every 2-4 weeks according to individual patient requirements. Clinical responses, side effects, and determination of age- and gender-related serum IGF-I levels may be used to guide dose titration.

Alternatively, taking into account more recent literature, a starting dose of approximately 0.2 mg/kg (range, 0.15-0.25 mg/kg) may be used without consideration of body weight. This dose can be increased gradually every 2-4 weeks according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the occurrence of adverse events or failure to reach the defined treatment goal, weight-based regimen. It is to reach the defined target dose, which can be used to guide the dose in women may need higher doses than men. Oral antihypoglycemic therapy should be used as guidance in dose requirements in women.

How Supplied

Norditropin (Norditropin NordiFlex) injected (somatropin [rDNA origin]) injection: 5 mg/1.5 mL and 10 mg/1.5 mL. Norditropin is individually packaged in 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL cartridges which must be administered using Norditropin NordiFlex pen.

Norditropin cartridge 5 mg/1.5 mL (orange) NDC 0169-7704-11
Norditropin cartridge 10 mg/1.5 mL (orange) NDC 0169-7705-11
Norditropin cartridge 15 mg/1.5 mL (orange) NDC 0169-7706-11
Norditropin NordiFlex (somatropin [rDNA origin]) injection 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL.