# Product Information Form for Hospitals

## Indications and Usage

Norditropin® (somatropin) injection is indicated for the treatment of pediatric patients with:

- growth failure due to inadequate secretion of endogenous growth hormone (GH)
- short stature associated with Noonan syndrome,
- short stature associated with Turner syndrome,
- short stature born small for gestational age (SGA) with no catch-up growth by age 2 years to 4 years of age
- Idiopathic Short Stature (ISS), height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range
- growth failure due to Prader-Willi syndrome (PWS)

Norditropin® is also indicated for the replacement of endogenous GH in adults with growth hormone deficiency (GHD)

## Important Safety Information

### Contraindications

Norditropin® is contraindicated in patients with:

- **Acute critical illness** after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin
- **Pediatric patients with Prader-Willi syndrome** who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of sudden death
- **Active Malignancy**
- **Hypersensitivity** to Norditropin® or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products
- Active proliferative or severe non-proliferative **diabetic retinopathy**
- Pediatric patients with **closed epiphyses**

# Product Information Form for Hospitals

## 1 AHFS CLASSIFICATION NUMBER

68:28 Hormones and Synthetic Substitutes: Pituitary

## 2 GENERIC NAME

Somatropin injection

## 3 SOURCE OF SUPPLY

Norditropin® is manufactured by Novo Nordisk A/S. Norditropin® RT is distributed by Novo Nordisk Inc.

## 4 BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

- N019721, Norditropin®, May 8, 1995: FDA approval for children with growth hormone deficiency (GHD)
- NDA 21-148/S-007, Norditropin®, November 1, 2004: FDA approval for adult GHD
- NDA 21-148/S-016, Norditropin®, May 31, 2007: FDA approval for short stature in children with Noonan syndrome
- NDA 21-148/S-017, Norditropin®, September 20, 2007 FDA approval for short stature in children with Turner syndrome
- NDA 21-148/S-017, Norditropin®, September 20, 2007: FDA approval for short stature in children with Turner syndrome
- NDA 21-148/S-023, Norditropin®, October 31, 2008: FDA approval for short stature in children born small for gestational age (SGA) with no catch-up growth by 2 to 4 years of age
- NDA 21-148/S-037, Norditropin®, February 23, 2018: FDA approval for idiopathic short stature (ISS)
- BLA 021148, Norditropin®, March 23, 2020: former new drug application (NDA) deemed BLA



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## 5 PHYSICAL PROPERTIES

### a. Macroscopic appearance

Norditropin® injection is a clear and colorless solution available as FlexPro® prefilled pens:

- Norditropin® FlexPro® 5 mg/1.5 mL (orange) NDC 0169-7704-21
- Norditropin® FlexPro® 10 mg/1.5 mL (blue) NDC 0169-7705-21
- Norditropin® FlexPro® 15 mg/1.5 mL (green) NDC 0169-7708-21
- Norditropin® FlexPro® 30 mg/3 mL (purple) NDC 0169-7703-21

### b. Solubility

Norditropin® is supplied as a sterile solution for subcutaneous (SC) use in ready-to-administer prefilled pens with a volume of 1.5 mL or 3 mL. Inspect visually for particulate matter and discoloration. Norditropin® should be clear and colorless. If the solution is cloudy or contains particulate matter, do not use.

## 6 CHEMICAL PROPERTIES

### a. Structural similarities to other available compounds or groups of compounds

Norditropin® (somatropin) for injection is a recombinant human growth hormone. It is a polypeptide of recombinant DNA origin and 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.

### b. Recommended storage conditions for Norditropin®

Unused Norditropin® FlexPro® prefilled pens must be stored at 2 °C to 8 °C/36 °F to 46 °F (refrigerator) until expiration date. Do not freeze. Avoid direct light.

In-use (after first injection) Norditropin® FlexPro® prefilled pens can be stored as:

- Storage Option 1 (refrigeration): 2 °C to 8 °C/36 °F to 46 °F for 4 weeks
- Storage Option 2 (room temperature): Up to 25 °C/77 °F for 3 weeks

## 6 CHEMICAL PROPERTIES (cont'd)

### c. Excipients contained in the commercially available product

- Each Norditropin® FlexPro® prefilled 5 mg pen contains: 5 mg of somatropin, 1 mg of histidine, 4.5 mg of poloxamer 188, 4.5 mg of phenol, 60 mg of mannitol, hydrochloric acid/sodium hydroxide as needed, and water up to 1.5 mL.
- Each Norditropin® FlexPro® prefilled 10 mg pen contains: 10 mg of somatropin, 1 mg of histidine, 4.5 mg of poloxamer 188, 4.5 mg of phenol, 60 mg of mannitol, hydrochloric acid/sodium hydroxide as needed, and water up to 1.5 mL.
- Each Norditropin® FlexPro® prefilled 15 mg pen contains: 15 mg of somatropin, 1.7 mg of histidine, 4.5 mg of poloxamer 188, 4.5 mg of phenol, 58 mg mannitol, hydrochloric acid/sodium hydroxide as needed, and water up to 1.5 mL.
- Each Norditropin® FlexPro® prefilled 30 mg pen contains: 30 mg of somatropin, 3.3 mg of histidine, 9 mg of poloxamer 188, 9 mg of phenol, 117 mg of mannitol, hydrochloric acid/sodium hydroxide as needed, and water up to 3 mL.

## 7 PHARMACOLOGIC CLASSIFICATION

### a. Pharmacologic class

Hormone and synthetic substances

### b. Mechanism of action

Somatropin binds to dimeric growth hormone (GH) receptors located within the cell membranes of target tissue cells. This interaction results in intracellular signal transduction and subsequent induction of transcription and translation of GH-dependent proteins including insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGF BP-3) and acid-labile subunit. Somatropin has direct tissue and metabolic effects or mediated indirectly by IGF-1, including stimulation of chondrocyte differentiation, and proliferation, stimulation hepatic glucose output, protein synthesis and lipolysis.

Somatropin stimulates skeletal growth in pediatric patients with GHD as a result of effects on the growth plates (epiphyses) of long bones. The stimulation of skeletal growth increases linear growth rate (height velocity) in most somatropin-treated pediatric patients. Linear growth is facilitated in part by increased cellular protein synthesis.

### c. Pharmacokinetic data

**Absorption** — Somatropin has been studied following subcutaneous and intravenous administration in adult healthy subjects and GHD patients. A single-dose administration of 4 mg Norditropin® in healthy subjects (n=26) with suppressed endogenous growth hormone resulted in a mean (SD) $C_{max}$ of 34.9 (10.4) ng/mL after approximately 3.0 hours. After a 180-min intravenous (IV) infusion of Norditropin® (33 ng/kg/min) administered to GHD patients (n=9), a mean (SD) hGH steady state serum level of approximately 23.1 (15.0) ng/mL was reached at 150 min.



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## 7 PHARMACOLOGIC CLASSIFICATION (cont'd)

After a SC dose of 0.024 mg/kg or 3 IU/$m^2$ given in the thigh to adult GHD patients (n=18), mean (SD) $C_{max}$ values of 13.8 (5.8) and 17.1 (10.0) ng/mL were observed for the 4 and 8 mg Norditropin® vials, respectively, at approximately 4 to 5 hr. post dose. The absolute bioavailability for Norditropin® after the SC route of administration is currently not known.

**Distribution** — The mean (SD) apparent volume of distribution of somatropin after single dose subcutaneous administration of 4 mg Norditropin® in healthy subjects is 43.9 (14.9) L.

**Elimination**

*Metabolism* — Extensive metabolism studies have not been conducted. The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys.

*Excretion* — The mean apparent terminal half-life ($T_{1/2}$) values in healthy adult subjects (n=26) was 2.0 (0.5) hours. In GHD patients receiving a 180-minute IV infusion of Norditropin® (33 ng/kg/min), a mean clearance rate of approximately 2.3 (1.8) mL/min/kg or 139 (105) mL/min for hGH was observed. Following infusion, serum hGH levels had a biexponential decaywith a terminal elimination $T_{1/2}$ of approximately 21.1 (5.1) minutes. The mean apparent terminal $T_{1/2}$ values in GHD patients receiving a SC dose of 0.024 mg/kg or 3 IU/$m^2$ was estimated to be approximately 7 to 10 hr. The longer half-life observed after subcutaneous administration is due to slow absorption from the injection site. Urinary excretion of intact somatropin has not been measured.

*Geriatric patients* — The pharmacokinetics of somatropin have not been studied in patients greater than 65 years of age.

*Pediatric patients* — The pharmacokinetics of somatropin in pediatric patients are similar to those of adults.

*Male and female patients* — No gender-specific pharmacokinetic studies have been performed with somatropin. The available literature indicates that the pharmacokinetics of somatropin are similar in men and women.

*Patients with renal or hepatic impairment* — No studies have been performed with somatropin.

## 8 DOSAGE RANGE

### a. Dosage range and route of administration

**Pediatric Dosage**

- Individualize dosage for each patient based on the growth response.
- Divide the calculated weekly Norditropin® dosage into equal doses given either 6 or 7 days per week.

## 8 DOSAGE RANGE (cont'd)

- The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is:
  - **Pediatric GH Deficiency:** 0.17 mg/kg/week to 0.24 mg/kg/week (0.024 to 0.034 mg/kg/day)
  - **Noonan Syndrome:** Up to 0.46 mg/kg/week (up to 0.066 mg/kg/day)
  - **Turner Syndrome:** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day)
  - **Small for Gestational Age:** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day)
  - In very short pediatric patients, HSDS less than -3, and older pubertal pediatric patients consider initiating treatment with a larger dose of Norditropin® (up to 0.067 mg/kg/day). Consider a gradual reduction in dosage if substantial catch-up growth is observed during the first few years of therapy. In pediatric patients less than 4 years of age with less severe short stature, baseline HSDS values between -2 and -3, consider initiating treatment at 0.033 mg/kg/day and titrate the dose as needed.
- **Idiopathic Short Stature:** Up to 0.47 mg/kg/week (up to 0.067 mg/kg/day)
- **Prader-Willi Syndrome:** 0.24 mg/kg/week (0.034 mg/kg/day)
- Assess compliance and evaluate other causes of poor growth such as hypothyroidism, under-nutrition, advanced bone age and antibodies to recombinant human growth hormone if patients experience failure to increase height velocity, particularly during the first year of treatment.
- Discontinue Norditropin® for stimulation of linear growth once epiphyseal fusion has occurred.

### Adult Dosage

- Patients who were treated with somatropin for GH deficiency in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin for GH deficient adults.
- Consider using a lower starting dose and smaller dose increment increases for geriatric patients, as they may be at increased risk for adverse reactions with Norditropin® than younger individuals.
- Estrogen-replete women and patients receiving oral estrogen may require higher doses.
- Administer the prescribed dose daily.



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## 8 DOSAGE RANGE (cont'd)

- Either of two Norditropin® dosing regimens may be used:
  - Non-weight based
    - Initiate Norditropin® with a dose of approximately 0.2 mg/day (range, 0.15 mg/day to 0.3 mg/day) and increase the dose every 1 to 2 months by increments of approximately 0.1 mg/day to 0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-1 concentrations.
    - Decrease the dose as necessary on the basis of adverse reactions and/or serum IGF-1 concentrations above the age- and gender-specific normal range.
    - Maintenance dosages will vary considerably from person to person, and between male and female patients.
  - Weight-based
    - Initiate Norditropin® at 0.004 mg/kg daily and increase the dose according to individual patient requirements to a maximum of 0.016 mg/kg daily.
    - Use the patient's clinical response, adverse reactions, and determination of age- and gender-adjusted serum IGF-1 concentrations as guidance in dose titration.
    - Not recommended for obese patients as they are more likely to experience adverse reactions with this regimen

### Administration and Use Instructions

- Therapy with Norditropin® should be supervised by a physician who is experienced in the diagnosis and management of patients with the conditions for which Norditropin® is indicated.
- Fundoscopic examination should be performed routinely before initiating treatment with Norditropin® to exclude preexisting papilledema, and periodically thereafter.
- Administer Norditropin® by SC injection to the back of the upper arm, abdomen, buttocks, or thigh with regular rotation of injection sites to avoid lipoatrophy.
- Inspect visually for particulate matter and discoloration. Norditropin® should be clear and colorless. If the solution is cloudy or contains particulate matter do not use.
- Instructions for delivering the dosage are provided in the Patient Information and Instructions for Use leaflets enclosed with the Norditropin® FlexPro® prefilled pen.



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## 8 DOSAGE RANGE (cont'd)

### b. Use in specific populations

**Pregnancy**

**Risk Summary**

Limited available data with somatropin use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, there was no evidence of fetal or neonatal harm when pregnant rats were administered subcutaneous Norditropin® during organogenesis or during lactation at doses approximately 10 times higher than the maximal clinical dose of 0.016 mg/kg, based on body surface area. The estimated background risk of birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Data**

*Animal Data*

In an embryo-fetal development study, Norditropin® was administered via subcutaneous injection to pregnant rats from gestation Day 6 to 17, corresponding with the period of organogenesis. Norditropin® did not adversely affect fetal viability or developmental outcomes at maternal doses that were approximately 10-times the clinical dose of 0.016 mg/kg, based on body surface area.

In a pre- and post-natal development study in pregnant rats, Norditropin® was administered from gestation Day 17 through lactation Day 21 (weaning). No adverse developmental effects were observed in the offspring at doses up to 1.1 mg/kg (approximately 10 times the clinical dose of 0.016 mg/kg, based on body surface area).

**Lactation**

**Risk Summary**

There is no information regarding the presence of somatropin in human milk. Limited published data indicate that exogenous somatropin does not increase normal breastmilk concentrations of growth hormone. No adverse effects on the breastfed infant have been reported with somatropin. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Norditropin® and any potential adverse effects on the breastfed infant from Norditropin® or from the underlying maternal condition.

**Pediatric Use**

Safety and effectiveness of Norditropin® in pediatric patients have been established in growth failure due to inadequate secretion of endogenous growth hormone, short



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## 8 DOSAGE RANGE (cont'd)

stature associated with Noonan syndrome, short stature associated with Turner syndrome, short stature in children born small for gestational age (SGA) with no catch-up growth by age 2 years to 4 years of age, idiopathic short stature (ISS), and growth failure due to Prader-Willi syndrome (PWS).

*Growth Failure due to Inadequate Secretion of Endogenous Growth Hormone*

Safety and effectiveness of Norditropin® have been established in pediatric patients with growth failure due to growth hormone deficiency in a multicenter, prospective, randomized, open-label, dose-response study in 111 pediatric patients conducted for a two-year period.

*Short Stature Associated with Noonan Syndrome*

Safety and effectiveness of Norditropin® have been established in pediatric patients with Noonan syndrome in a prospective, open-label, randomized, parallel group study in 21 pediatric patients conducted for 2 years.

*Short Stature Associated with Turner Syndrome*

Safety and effectiveness of Norditropin® have been established in pediatric patients with short stature associated with Turner syndrome in two randomized, parallel group, open-label, multicenter studies in 87 pediatric patients.

*Short Stature in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2 Years to 4 Years of Age*

Safety and effectiveness of Norditropin® have been established in pediatric patients with short stature born SGA with no catch-up growth in a multi-center, randomized, double-blind, 2-arm study to final height in 53 pediatric patients and in a randomized study of 84 prepubertal, non-GHD, Japanese pediatric patients.

*Idiopathic Short Stature*

Safety and effectiveness of Norditropin® have been established in pediatric patients with ISS based on data from a Norditropin® open-label clinical study with another somatropin product in 105 pediatric patients.

*Growth Failure Due to Prader-Willi Syndrome*

Safety and effectiveness of Norditropin® have been established in pediatric patients with growth failure due to Prader-Willi Syndrome based on data from 2 randomized, open-label, controlled clinical trials with another somatropin product in pediatric patients. There have been reports of sudden death 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

## 8 DOSAGE RANGE (cont'd)

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.

**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.

## 9 SAFETY

### a. Adverse reactions, toxicities, and special precautions

**Adverse Reactions**

The following important adverse reactions are also described elsewhere in the labeling:

- Increased mortality in patients with acute critical illness
- Sudden death in children with Prader-Willi syndrome
- Neoplasms
- Glucose intolerance and diabetes mellitus
- Intracranial hypertension
- Severe hypersensitivity
- Fluid retention
- Hypoadrenalism
- Hypothyroidism
- Slipped capital femoral epiphysis in pediatric patients
- Progression of preexisting scoliosis in pediatric patients
- Pancreatitis
- Lipoatrophy

**Clinical Trials Experience**

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin product cannot always be directly compared to the rates observed during the clinical trials performed with another somatropin product, and may not reflect the adverse reaction rates observed in practice.

## 9 SAFETY (cont'd)

**Pediatric Patients**

*Growth Failure due to Inadequate Secretion of Endogenous Growth Hormone*
In one randomized, open-label clinical study the most frequent adverse reactions were headache, pharyngitis, otitis media, and fever. There were no clinically significant differences between the 3 doses assessed in the study (0.025, 0.05 and 0.1 mg/kg/day).

*Short Stature Associated with Noonan Syndrome*
Norditropin® was studied in 21 pediatric patients, 3 years to 14 years of age at doses of 0.033 mg/kg/day and 0.066 mg/kg/day. After the two-year study, patients continued Norditropin® treatment until final height was achieved; randomized dose groups were not maintained. Adverse reactions were later collected retrospectively from 18 pediatric patients; total follow-up was 11 years. An additional 6 pediatric patients were not randomized, but followed the protocol and are included in this assessment of adverse reactions.

The most frequent adverse reactions were upper respiratory infection, gastroenteritis, ear infection, and influenza. Cardiac disorders was the system organ class with the second most adverse reactions reported. Scoliosis was reported in 1 and 4 pediatric patients receiving doses of 0.033 mg/kg/day and 0.066 mg/kg/day respectively. The following additional adverse reactions also occurred once: insulin resistance and panic reaction for the 0.033 mg/kg/day dose group; injection site pruritus, bone development abnormal, depression, and self-injurious ideation in the 0.066 mg/kg/day dose group. Headache occurred in 2 cases in the 0.066 mg/kg/day dose group.

*Short Stature Associated with Turner Syndrome*
In two clinical studies in pediatric patients that were treated until final height with various doses of Norditropin®, the most frequently reported adverse reactions were influenza-like illness, otitis media, upper respiratory tract infection, otitis externa, gastroenteritis, eczema, and impaired fasting glucose. Adverse reactions in study 1 were most frequent in the highest dose groups. Three patients in study 1 had excessive growth of hands and/or feet in the high dose groups. Two patients in study 1 had a serious adverse reaction of exacerbation of preexisting scoliosis in the 0.045 mg/kg/day group.

*Small for Gestational Age (SGA) with No Catch-up Growth by Age 2-4 Years*
In a study, 53 pediatric patients were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) to final height for up to 13 years (mean duration of treatment 7.9 and 9.5 years for girls and boys, respectively). The most frequently reported adverse reactions were influenza-like illness, upper respiratory tract infection, bronchitis, gastroenteritis, abdominal pain, otitis media, pharyngitis,

## 9 SAFETY (cont'd)

arthralgia, headache, gynecomastia, and increased sweating. One pediatric patient treated with 0.067 mg/kg/day for 4 years was reported with disproportionate growth of the lower jaw, and another patient treated with 0.067 mg/kg/day developed a melanocytic nevus. Four pediatric patients treated with 0.067 mg/kg/day and 2 pediatric patients treated with 0.033 mg/kg/day of Norditropin® had increased fasting blood glucose levels after 1 year of treatment. In addition, small increases in mean fasting blood glucose and insulin levels after 1 and 2 years of Norditropin® treatment appeared to be dose-dependent.

In a second study, 98 Japanese pediatric patients were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) for 2 years or were untreated for 1 year. Adverse reactions were otitis media, arthralgia, and impaired glucose tolerance. Arthralgia and transiently impaired glucose tolerance were reported in the 0.067 mg/kg/day treatment group.

*Idiopathic Short Stature*

In two open-label clinical studies with another somatropin product in pediatric patients, the most common adverse reactions were upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia.

*Growth Failure Due to Prader-Willi Syndrome*

In two clinical studies in pediatric patients with PWS carried out with another somatropin product, the following adverse reactions were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.



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## 9 SAFETY (cont'd)

**Adult Patients**

*Adults with Growth Hormone Deficiency*

Adverse reactions with an incidence of ≥5% occurring in patients with adult-onset (AO) GHD during the 6-month placebo-controlled portion of a clinical trial for Norditropin® are presented in the following table.

**Adverse Reactions with ≥5% Overall Incidence in Patients With Adult-Onset GHD Who Were Treated With Norditropin® During a 6-Month Placebo-Controlled Clinical Trial**

| | Placebo (N=52) | Norditropin® (N=53) |
|---|---|---|
| **Adverse Reactions** | **%** | **%** |
| Peripheral edema | 8 | 42 |
| Edema | 0 | 25 |
| Arthralgia | 15 | 19 |
| Leg edema | 4 | 15 |
| Myalgia | 8 | 15 |
| Infection (non-viral) | 8 | 13 |
| Paresthesia | 6 | 11 |
| Skeletal pain | 2 | 11 |
| Headache | 6 | 9 |
| Bronchitis | 0 | 9 |
| Flu-like symptoms | 4 | 8 |
| Hypertension | 2 | 8 |
| Gastroenteritis | 8 | 8 |
| Other nonclassifiable disorders (excludes accidental injury) | 6 | 8 |
| Increased sweating | 2 | 8 |
| Glucose tolerance abnormal | 2 | 6 |
| Laryngitis | 6 | 6 |
| Type 2 diabetes mellitus | 0 | 5 |





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## 9 SAFETY (cont'd)

**Immunogenicity**

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Norditropin® with the incidence of antibodies to other products may be misleading. In the case of growth hormone, antibodies with binding capacities lower than 2 mg/mL have not been associated with growth attenuation. In a very small number of patients treated with somatropin, when binding capacity was greater than 2 mg/mL, interference with the growth response was observed.

In clinical trials, GH deficient pediatric 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 somatropin formulations, and 193 were previously untreated naive patients. Eighteen of 76 children (~24%) treated with Norditropin® for short stature born SGA developed anti-recombinant human GH (rhGH) antibodies.

**Post-Marketing Experience**

Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Immune system disorders* — Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema

*Skin* — Increase in size or number of cutaneous nevi

*Endocrine disorders* — Hypothyroidism

*Metabolism and nutrition disorders* — Hyperglycemia

*Musculoskeletal and connective tissue disorders* — Slipped capital femoral epiphysis — Legg-Calvé-Perthes disease

*Investigations* — Increase in blood alkaline phosphatase level— Decrease in serum thyroxin (T4) levels

*Gastrointestinal* — Pancreatitis

*Neoplasm* — Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin



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## 9 SAFETY (cont'd)

### b. Contraindications, Warnings and Precautions

**Contraindications**

Norditropin® is contraindicated in patients with:

- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin.
- Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of sudden death.
- Active malignancy.
- Hypersensitivity to Norditropin® or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products.
- Active proliferative or severe non-proliferative diabetic retinopathy.
- Pediatric patients with closed epiphyses.

**Warnings and Precautions**

**Increased Mortality in Patients with Acute Critical Illness**

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 has been reported after treatment with pharmacologic amounts of somatropin. 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 (42% vs 19%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo. The safety of continuing Norditropin® treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Norditropin® is not indicated for the treatment of non-GH deficient adults.

**Sudden Death in Pediatric Patients with Prader-Willi Syndrome**

There have been reports of sudden death 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 Norditropin®, 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



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## 9 SAFETY (cont'd)

Norditropin® 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.

**Increased Risk of Neoplasms**

*Active Malignancy*

There is an increased risk of malignancy progression with somatropin treatment in patients with active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with Norditropin®. Discontinue Norditropin® if there is evidence of recurrent activity.

*Risk of Second Neoplasm in Pediatric Patients*

There is an increased risk of a second neoplasm in pediatric cancer survivors who were treated with radiation to the brain/head and who developed subsequent GH deficiency and were treated with somatropin. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence. Monitor all patients receiving Norditropin® who have a history of GH deficiency secondary to an intracranial neoplasm for progression or recurrence of the tumor.

*New Malignancy During Treatment*

Because pediatric patients with certain rare genetic causes of short stature have an increased risk of developing malignancies, thoroughly consider the risks and benefits of starting Norditropin® in these patients. If Norditropin® is initiated, carefully monitor patients for development of neoplasms.

Monitor all patients receiving Norditropin® carefully for increased growth, or potential malignant changes, of preexisting nevi. Advise patients/caregivers to report marked changes in behavior, onset of headaches, vision disturbances and/or changes in skin pigmentation or changes in the appearance of preexisting nevi.

**Glucose Intolerance and Diabetes Mellitus**

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been reported in patients taking somatropin. Previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked. Monitor glucose levels periodically in all patients receiving Norditropin®, especially in those with risk factors for diabetes mellitus, such as obesity, 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. The doses of antidiabetic agents may require adjustment when Norditropin® is initiated.





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## 9 SAFETY (cont'd)

### Intracranial Hypertension

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 Norditropin® to exclude preexisting papilledema, and periodically thereafter. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with Norditropin® can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome may be at increased risk for the development of IH.

### Severe Hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.

### Fluid Retention

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention (e.g. edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paresthesias) are usually transient and dose dependent.

### Hypoadrenalism

Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Norditropin® treatment. Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism.

### Hypothyroidism

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



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(somatropin) injection
5 mg, 10 mg, 15 mg, 30 mg pens

## 9 SAFETY (cont'd)

**Slipped Capital Femoral Epiphysis in Pediatric Patients**

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GH deficiency and Turner syndrome) or in patients undergoing rapid growth. Evaluate pediatric patients with the onset of a limp or complaints of hip or knee pain.

**Progression of Preexisting Scoliosis in Pediatric Patients**

Somatropin increases the growth rate, and progression of existing scoliosis can occur in patients who experience rapid growth. Somatropin has not been shown to increase the occurrence of scoliosis. Monitor patients with a history of scoliosis for progression of scoliosis.

**Pancreatitis**

Cases of pancreatitis have been reported in pediatric patients and adults receiving somatropin products. There may be a greater risk in pediatric patients compared with adults. Published literature indicates that females who have Turner syndrome may be at greater risk than other pediatric patients receiving somatropin products. Pancreatitis should be considered in patients who develop persistent severe abdominal pain.

**Lipoatrophy**

When somatropin products are administered subcutaneously at the same site over a long period of time, tissue atrophy may result. Rotate injection sites when administering Norditropin® to reduce this risk.

**Laboratory Tests**

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 may increase after Norditropin® treatment.

### c. List of potential drug-drug interactions if deemed clinically significant

The following table includes a list of drugs with clinically important drug interactions when administered concomitantly with Norditropin® and instructions for preventing or managing them.

## 9 SAFETY (cont'd)

| Clinically Important Drug Interactions with Norditropin® | |
|---|---|
| **Glucocorticoids** | |
| Clinical impact: | Microsomal enzyme 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Norditropin® inhibits 11ßHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11ßHSD-1 and serum cortisol. Initiation of Norditropin® may result in inhibition of 11ßHSD-1 and reduced serum cortisol concentrations. |
| Intervention: | Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Norditropin®. |
| Examples: | Cortisone acetate and prednisone may be affected more than others since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11ßHSD-1. |
| **Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment** | |
| Clinical impact: | Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of Norditropin® in pediatric patients. |
| Intervention: | Carefully adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth. |
| **Cytochrome P450-Metabolized Drugs** | |
| Clinical impact: | Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450)-mediated antipyrine clearance. Norditropin® may alter the clearance of compounds known to be metabolized by CP450 liver enzymes. |
| Intervention: | Careful monitoring is advisable when Norditropin® is administered in combination with drugs metabolized by CP450 liver enzymes. |
| **Oral Estrogen** | |
| Clinical impact: | Oral estrogens may reduce the serum IGF-1 response to Norditropin®. |
| Intervention: | Patients receiving oral estrogen replacement may require greater Norditropin® dosages. |
| **Insulin and/or Other Hypoglycemic Agents** | |
| Clinical impact: | Treatment with Norditropin® may decrease insulin sensitivity, particularly at higher doses. |
| Intervention: | Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other hypoglycemic agents. |

## 10 COMPARISONS

N/A



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(somatropin) injection
5 mg, 10 mg, 15 mg, 30 mg pens

## Indications and Usage

Norditropin® (somatropin) injection is indicated for the treatment of pediatric patients with:

- growth failure due to inadequate secretion of endogenous growth hormone (GH)
- short stature associated with Noonan syndrome,
- short stature associated with Turner syndrome,
- short stature born small for gestational age (SGA) with no catch-up growth by age 2 to 4 years of age
- Idiopathic Short Stature (ISS), height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range
- growth failure due to Prader-Willi syndrome (PWS)

Norditropin® is also indicated for the replacement of endogenous GH in adults with growth hormone deficiency (GHD)

## Important Safety Information

### Contraindications

Norditropin® is contraindicated in patients with:

- **Acute critical illness** after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin
- **Pediatric patients with Prader-Willi syndrome** who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of sudden death
- **Active Malignancy**
- **Hypersensitivity** to Norditropin® or any of its excipients. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products
- Active proliferative or severe non-proliferative **diabetic retinopathy**
- Pediatric patients with **closed epiphyses**



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## Important Safety Information (cont'd)

### Warnings and Precautions

- **Increased mortality in patients with acute critical illness** due to complications following open heart or abdominal surgery or multiple accidental trauma, or those with respiratory failure has been reported.
- **Sudden death in pediatric patients with Prader-Willi Syndrome** has been reported after initiating treatment with somatropin with one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Evaluate patients for signs of upper airway obstruction and sleep apnea before initiation of treatment.
- **Increased risk of neoplasms:** Monitor patients with preexisting tumors for progression or recurrence. In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm, in particular meningiomas, has been reported. Pediatric patients with certain rare genetic causes of short stature have an increased risk of developing malignancies and should be carefully monitored for development of neoplasms. Monitor patients carefully for increased growth, or potential malignant changes, of preexisting nevi.
- **Glucose intolerance and diabetes mellitus**: Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New-onset type 2 diabetes mellitus has been reported. Monitor glucose levels in all patients. Doses of concurrent antidiabetic drugs may require adjustment.
- **Intracranial hypertension** has been reported in a small number of patients, usually within the first 8 weeks of somatropin treatment. Funduscopic examination should be performed before initiating treatment and periodically thereafter.
- **Severe hypersensitivity:** Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products.
- **Fluid retention** in adults (clinically manifesting as edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias) may frequently occur and is usually transient and dose-dependent.
- **Hypoadrenalism:** Patients who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Norditropin® treatment.



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(somatropin) injection
5 mg, 10 mg, 15 mg, 30 mg pens

## Important Safety Information (cont'd)

### Warnings and Precautions (cont'd)

- **Hypothyroidism** if undiagnosed/untreated, may prevent an optimal response to Norditropin®, in particular, the growth response in pediatric patients. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or adjusted when indicated.
- **Slipped capital femoral epiphysis in pediatric patients** may occur more frequently in patients with endocrine disorders or in patients undergoing rapid growth. Pediatric patients with the onset of a limp or complaints of hip or knee pain should be evaluated.
- **Progression of preexisting scoliosis in pediatric patients** can occur in patients who experience rapid growth. Patients with a history of scoliosis should be monitored for progression.
- **Pancreatitis:** Cases of pancreatitis have been reported. Pancreatitis should be considered in any patient who develops persistent severe abdominal pain.
- **Lipoatrophy**: Tissue atrophy may result when somatropin is administrated subcutaneously at the same site over a long period of time. Rotate injection sites when administering Norditropin® to reduce this risk.

### Adverse Reactions

- Other common adverse reactions in adults and pediatric patients include: upper respiratory infection, fever, pharyngitis, headache, otitis media, edema, arthralgia, paresthesia, myalgia, peripheral edema, flu syndrome, and impaired glucose tolerance



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## Drug Interactions

- **Glucocorticoids:** Patients treated with glucocorticoid for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Norditropin®
- **Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment:** Adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatment to avoid both hypoadrenalism and an inhibitory effect on growth
- **Cytochrome P450-Metabolized Drugs:** Norditropin® may alter the clearance. Monitor carefully if used with Norditropin®
- **Oral Estrogen:** Larger doses of Norditropin® may be required
- **Insulin and/or Other Hypoglycemic Agents:** Dose adjustment of insulin or hypoglycemic agent may be required

## Use in Specific Populations

- **Pregnancy and Nursing Mothers**: There are limited data with somatropin use in pregnant women and nursing mothers to inform a drug-associated risk for adverse developmental outcomes.
- **Geriatric Use:** The safety and effectiveness in patients aged 65 and over has not been evaluated in clinical studies.



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