HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use Norditropin Cartridges safely and effectively. See full prescribing information for Norditropin Cartridges.

Norditropin® Cartridges [somatropin (rDNA origin) injection], for subcutaneous use
Initial U.S. Approval: 1987

·····RECENT MAJOR CHANGES·····

Indications and Usage (1.1)	
Short Stature in Small for Gestational Age (SGA) with No Catch-up Growth by Age 2-4 Years	10/2008
Dosage and Administration (2.1)	
Short Stature in SGA with No Catch-up Growth by Age 2-4 Years	10/2008

····· INDICATIONS AND USAGE·····

Norditropin is a recombinant human growth hormone indicated for:

- ***Pediatric***: Treatment of children with growth failure due to growth hormone deficiency (GHD), short stature associated with Noonan syndrome, short stature associated with Turner syndrome and short stature born SGA with no catch-up growth by age 2-4 years (1.1)
- ***Adult***: Treatment of adults with either adult onset or childhood onset GHD (1.2)

·····DOSAGE AND ADMINISTRATION·····

Norditropin should be administered subcutaneously (2).

- ***Pediatric GHD:*** 0.024 – 0.034 mg/kg/day, 6-7 times a week (2.1)
- ***Noonan Syndrome:*** Up to 0.066 mg/kg/day (2.1)
- ***Turner Syndrome:*** Up to 0.067 mg/kg/day (2.1)
- ***SGA:*** Up to 0.067 mg/kg/day (2.1)
- ***Adult GHD:*** 0.004 mg/kg/day to be increased as tolerated to not more than 0.016 mg/kg/day after approximately 6 weeks, or a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day (2.2)
- Norditropin cartridges must be used with their corresponding color-coded NordiPen® delivery systems (2.3)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

·····DOSAGE FORMS AND STRENGTHS·····

Cartridges are available for use with the corresponding NordiPen delivery systems or preloaded in the Norditropin NordiFlex pens (3):

- 5 mg/1.5 mL (orange): cartridge and Norditropin NordiFlex pen
- 10 mg/1.5 mL (blue): Norditropin NordiFlex pen only
- 15 mg/1.5 mL (green): cartridge and Norditropin NordiFlex pen
- 30 mg/3 mL (purple): Norditropin NordiFlex pen only

·····CONTRAINDICATIONS·····

- Acute Critical Illness (4.1, 5.1)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment – reports of sudden death (4.2, 5.2)
- Active Malignancy (4.3)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4.4)
- Children with closed epiphyses (4.5)
- Known hypersensitivity to somatropin or excipients (4.6)

·····WARNINGS AND PRECAUTIONS·····

- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk (5.1)
- Prader-Willi Syndrome in Children: Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment for GHD. Discontinue treatment if these signs occur (5.2).
- Neoplasm: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin - in particular meningiomas in patients treated with radiation to the head for their first neoplasm (5.3).
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary (5.6).
- Hypothyroidism: May first become evident or worsen (5.7)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.8).
- Progression of Preexisting Scoliosis: May develop (5.9)

·····ADVERSE REACTIONS·····

Other common somatropin-related adverse reactions include injection site reactions/rashes and lipoatrophy (6.1) and headaches (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-NOVO-444 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

·····DRUG INTERACTIONS·····

- Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1).
- Glucocorticoid Replacement: Should be carefully adjusted (7.2)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.3)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.4)
- Insulin and/or Oral Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH).

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of children with short stature associated with Noonan syndrome.

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of children with short stature associated with Turner syndrome.

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2-4 years.

1.2 Adult Patients

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

- Adult Onset (AO): Patients who have GHD, 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 (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

According to current standards, confirmation of the diagnosis of adult growth hormone deficiency in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection.

Therapy with Norditropin should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with short stature associated with GHD, Noonan syndrome, Turner syndrome or SGA, and adult patients with either childhood onset or adult onset GHD.

2.1 Dosing of Pediatric Patients

General Pediatric Dosing Information

The Norditropin dosage and administration schedule should be individualized based on the growth response of each patient. Serum insulin-like growth factor I (IGF-I) levels may be useful during dose titration.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human GH (rhGH).

Treatment with Norditropin for short stature should be discontinued when the epiphyses are fused.

Pediatric Growth Hormone Deficiency (GHD)

A dosage of 0.024 – 0.034 mg/kg/day, 6-7 times a week, is recommended.

Pediatric Patients with Short Stature Associated with Noonan Syndrome

Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, prior to initiating Norditropin for a patient with Noonan syndrome, establish that the patient does have short stature.

A dosage of up to 0.066 mg/kg/day is recommended.

Pediatric Patients with Short Stature Associated with Turner Syndrome

A dosage of up to 0.067 mg/kg/day is recommended.

Pediatric Patients with Short Stature Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2-4 Years

A dosage of up to 0.067 mg/kg/day is recommended.

Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.067 mg/kg/day), especially in very short children (i.e., HSDS < -3), and/or older/early pubertal children, and that a reduction in dosage (e.g., gradually towards 0.033

mg/kg/day) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g., approximately < 4 years) (who respond the best in general) with less severe short stature (i.e., baseline HSDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.033 mg/kg/day), and titrating the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the rhGH dose as necessary.

2.2 Dosing of Adult Patients

Adult Growth Hormone Deficiency (GHD)
Based on the weight-based dosing utilized in the clinical studies, the recommended dosage at the start of therapy is not more than 0.004 mg/kg/day. The dose 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 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.

2.3 Preparation and Administration

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

Norditropin® Cartridges 5 mg/1.5 mL and 15 mg/1.5 mL:
Each cartridge of Norditropin must be inserted into its corresponding NordiPen delivery system. Instructions for delivering the dosage are provided in the NordiPen INSTRUCTION booklet.

Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL and 30 mg/3 mL:
Instructions for delivering the dosage are provided in the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflets enclosed with the Norditropin NordiFlex prefilled pen.

Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Norditropin MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

Injection sites should always be rotated to avoid lipoatrophy.

3 DOSAGE FORMS AND STRENGTHS

Cartridges are available for use with the corresponding NordiPen delivery systems or preloaded in the Norditropin NordiFlex pens:

- 5 mg/1.5 mL (orange): cartridge and Norditropin NordiFlex prefilled pen
- 10 mg/1.5 mL (blue): Norditropin NordiFlex prefilled pen only
- 15 mg/1.5 mL (green): cartridge and Norditropin NordiFlex prefilled pen
- 30 mg/3 mL (purple): Norditropin NordiFlex prefilled pen only

4 CONTRAINDICATIONS

4.1 Acute Critical Illness

Treatment with pharmacologic amounts of somatropin is contraindicated 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. 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 and Precautions (5.1)]*.

4.2 Prader-Willi Syndrome in Children

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment *[see Warnings and Precautions (5.2)]*. There have been reports of

sudden death when somatropin was used in such patients *[see Warnings and Precautions (5.2)]*. Norditropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

4.3 Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since GHD 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.

4.4 Diabetic Retinopathy

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

4.5 Closed Epiphyses

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

4.6 Hypersensitivity

Norditropin is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Localized reactions are the most common hypersensitivity reactions.

5 WARNINGS AND PRECAUTIONS

5.1 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 *[see Contraindications (4.1)]*. 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.

5.2 Prader-Willi Syndrome in Children

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 (4.2)]*. Norditropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

5.3 Neoplasms

Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored 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.

Patients should be monitored carefully for potential malignant transformation of skin lesions, i.e. increased growth of preexisting nevi.

5.4 Glucose Intolerance

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, 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.

5.5 Intracranial Hypertension (IH)

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 may be at increased risk for the development of IH.

5.6 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

5.7 Hypothyroidism

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 GHD, 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.

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

5.8 Slipped Capital Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD 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.

5.9 Progression of Preexisting Scoliosis in Pediatric Patients

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 patients with Turner syndrome and Noonan syndrome. 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.

5.10 Otitis Media and Cardiovascular Disorders in Turner Syndrome

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

5.11 Confirmation of Childhood Onset Adult GHD

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in *Indications and Usage (1.2)* before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults.

5.12 Local and Systemic Reactions

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site *[see Dosage and Administration (2.3)]*.

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

5.13 Laboratory Tests

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

6 ADVERSE REACTIONS

6.1 Most Serious and/or Most Frequently Observed Adverse Reactions

This list presents the most serious[b] and/or most frequently observed[a] adverse reactions during treatment with somatropin:

- [b]Sudden death in pediatric patients with Prader-Willi syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*
- [b]Intracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*
- [a,b]Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus *[see Warnings and Precautions (5.4)]*
- [b]Intracranial hypertension *[see Warnings and Precautions (5.5)]*
- [b]Significant diabetic retinopathy *[see Contraindications (4.4)]*
- [b]Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions (5.8)]*
- [b]Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions (5.9)]*
- [a]Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias *[see Warnings and Precautions (5.6)]*
- [a]Unmasking of latent central hypothyroidism *[see Warnings and Precautions (5.7)]*
- [a]Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) *[see Warnings and Precautions (5.12)]*

6.2 Clinical Trials Experience

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

Clinical Trials in Pediatric GHD Patients

As with all protein drugs, a small percentage of patients may develop antibodies to the protein. GH antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In a very small number of patients, when binding capacity was greater than 2 mg/L, interference with the 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 somatropin formulations, and 193 were previously untreated naive patients.

Clinical Trials in Children with Noonan Syndrome

Norditropin was studied in a two-year prospective, randomized, parallel dose group trial in 21 children, 3-14 years old, with Noonan syndrome. Doses were 0.033 and 0.066 mg/kg/day. After the initial two-year randomized trial, children continued Norditropin treatment until final height was achieved; randomized dose groups were not maintained. Final height and adverse event data were later collected retrospectively from 18 children; total follow-up was 11 years. An additional 6 children were not randomized, but followed the protocol and are included in this assessment of adverse events.

Based on the mean dose per treatment group, no significant difference in the incidence of adverse events was seen between the two groups. The most frequent adverse events were the common infections of childhood, including upper respiratory infection, gastroenteritis, ear infection, and influenza. Cardiac disorders was the system organ class with the second most adverse events reported. However, congenital heart disease is an inherent component of Noonan syndrome, and there was no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography) during this study. Children who had baseline cardiac disease judged to be significant enough to potentially affect growth were excluded from the study; therefore the safety of Norditropin in children with Noonan syndrome and significant cardiac disease is not known. Among children who received 0.033 mg/kg/day, there was one adverse event of scoliosis; among children who received 0.066 mg/kg/day, there were four adverse events of scoliosis *[see Warnings and Precautions (5.9)]*. Mean serum IGF-I standard deviation score (SDS) levels did not exceed +1 in response to somatropin treatment. The mean serum IGF-I level was low at baseline and normalized during treatment.

Clinical Trials in Children with Turner Syndrome

In two clinical studies wherein children with Turner syndrome were treated until final height with various doses of Norditropin as described in *Clinical Studies (14.2)*, the most frequently reported adverse events were common childhood diseases including influenza-like illness, otitis media, upper respiratory tract infection, otitis externa, gastroenteritis and eczema. Otitis media adverse events in Study 1 were most frequent in the highest dose groups (86.4% in the 0.045-0.067-0.089 mg/kg/day group vs. 78.3% in the 0.045-0.067 mg/kg/day group vs. 69.6% in the 0.045 mg/kg/day group) suggesting a possible dose-response relationship. Of note, approximately 40-50% of these otitis media adverse events were designated as "serious" *[see Warnings and Precautions (5.10)]*. No patients in either study developed clearcut overt diabetes mellitus; however, in Study 1, impaired fasting glucose at Month 48 was more frequent in patients in the 0.045-0.067 mg/kg/day group (n=4/18) compared with the 0.045 mg/kg/day group (n=1/20). Transient episodes of fasting blood sugars between 100 and 126 mg/dL, and, on occasion, exceeding 126 mg/dL also occurred more often with larger doses of Norditropin in both studies *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*. Three patients withdrew from the 2 high dose groups in Study 1 because of concern about excessive growth of hands or feet. In addition, in Study 1,

exacerbation of preexisting scoliosis was designated a serious adverse reaction in two patients in the 0.045 mg/kg/day group *[see Warnings and Precautions (5.9)]*.

Clinical Trials in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2-4 Years

Study 1 (Long-Term)
In a multi-center, randomized, double-blind study, 53 non-GHD children with short stature born SGA with failure to catch-up 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 events were common childhood diseases including influenza-like illness, upper respiratory tract infection, bronchitis, gastroenteritis, abdominal pain, otitis media, pharyngitis, arthralgia, and headache. Adverse events possibly/probably related to Norditropin were otitis media, arthralgia, headaches (no confirmed diagnoses of benign intracranial hypertension), gynecomastia, and increased sweating. One child treated with 0.067 mg/kg/day for 4 years was reported with disproportionate growth of the lower jaw, and another child treated with 0.067 mg/kg/day developed a melanocytic nevus *[see Warnings and Precautions (5.3)]*. There were no clear cut reports of exacerbation of preexisting scoliosis or slipped capital femoral epiphysis. No apparent differences between the treatment groups were observed. In addition, the timing of puberty was age-appropriate in boys and girls in both treatment groups. Therefore, it can be concluded that no novel adverse events potentially related to treatment with Norditropin were reported in long-term Study 1.

Study 2 (Short-Term)
In a multi-center, randomized, double-blind, parallel-group study, 98 Japanese non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin (0.033 or 0.067 mg/kg/day) for 2 years or were untreated for 1 year. The most frequently reported adverse events were common childhood diseases almost identical to those reported above for Study 1. Adverse events possibly/probably related to Norditropin were otitis media, arthralgia and impaired glucose tolerance. No apparent differences between the treatment groups were observed. However, arthralgia and transiently impaired glucose tolerance were only reported in the 0.067 mg/kg/day treatment group. Therefore, it can also be concluded that no novel adverse events potentially related to treatment with rhGH were reported in short-term Study 2.

As with all protein drugs, some patients may develop antibodies to the protein. Eighteen of the 76 children (~24%) treated with Norditropin developed anti-rhGH antibodies. However, these antibodies did not appear to be neutralizing in that the change from baseline in height SDS at Year 2 was similar in antibody positive and antibody negative children by treatment group.

In both Study 1 and Study 2, there were no clear cut cases of new onset diabetes mellitus, no children treated for hyperglycemia, and no adverse event withdrawals due to abnormalities in glucose tolerance. In Study 2, after treatment with either dose of Norditropin for 2 years, there were no children with consecutive fasting blood glucose levels between 100 and 126 mg/dL, or with fasting blood glucose levels > 126 mg/dL. Furthermore, mean hemoglobin A1c levels tended to decrease during long-term treatment in Study 1, and remained normal in Study 2. However, in Study 1, 4 children treated with 0.067 mg/kg/day of Norditropin and 2 children treated with 0.033 mg/kg/day of Norditropin shifted from normal fasting blood glucose levels at baseline to increased levels after 1 year of treatment (100 to 126 mg/dL or > 126 mg/dL). In addition, small increases in mean fasting blood glucose and insulin levels (within the normal reference range) after 1 and 2 years of Norditropin treatment appeared to be dose-dependent *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

In both Study 1 and Study 2, there was no acceleration of bone maturation. A dose-dependent increase in mean serum IGF-I SDS levels within the reference range (but including a substantial number of children with serum IGF-1 SDS > +2) was observed after both long-term (Study 1) and short-term (Study 2) Norditropin treatment.

Clinical Trials in Adult GHD 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 1. 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 *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*. 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 1 – Adverse Reactions 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 Reactions	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.

6.3 Post-Marketing Surveillance

Because these adverse events 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. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in Sections 6.1 and 6.2 in children and adults.

Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy *per se* was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*.

The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children).

7 DRUG INTERACTIONS

7.1 Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1 (11ßHSD-1)

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

7.2 Glucocorticoid Replacement

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.

7.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)- mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 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 CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.4 Oral Estrogen

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 (2.2)]*.

7.5 Insulin and/or Oral Hypoglycemic Agents

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 Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.3 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.

8.5 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 (2.2)]*.

10 OVERDOSAGE

Short-Term

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

Long-Term

Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone [see Dosage and Administration (2)].

11 DESCRIPTION

Norditropin is a registered trademark of Novo Nordisk Health Care AG 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 sterile solutions for subcutaneous injection in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL or 3 mL.

Each **Norditropin Cartridge** contains the following (see Table 2):

Table 2

Component	**5 mg/1.5 mL**	**10 mg/1.5 mL**	**15 mg/1.5 mL**	**30 mg/3mL**
Somatropin	5 mg	10 mg	15 mg	30 mg
Histidine	1 mg	1 mg	1.7 mg	3.3 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg	9.0 mg
Phenol	4.5 mg	4.5 mg	4.5 mg	9.0 mg
Mannitol	60 mg	60 mg	58 mg	117 mg
HCl/NaOH	as needed	as needed	as needed	as needed
Water for Injection	up to 1.5 mL	up to 1.5 mL	up to 1.5 mL	up to 3.0 mL

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Somatropin (as well as endogenous GH) binds to a dimeric GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by IGF-I produced in the liver and also locally (e.g., skeletal growth, protein synthesis), while others are primarily a consequence of the direct effects of somatropin (e.g., lipolysis) *[see Clinical Pharmacology (12.2)]*.

12.2 Pharmacodynamics

Tissue Growth

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

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 (IGFs). 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, and increase after treatment with somatropin.

Cell Growth

It has been shown that the total number of skeletal muscle cells is markedly decreased in children with short stature lacking endogenous GH compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

Organ Growth

Somatropin influences the size of internal organs, and it also increases red cell mass.

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.

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.

Lipid Metabolism

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

Mineral Metabolism

Administration of somatropin results in an increase in 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 children with GHD after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen, and increases the urinary excretion of hydroxyproline.

12.3 Pharmacokinetics

A 180-min IV infusion of Norditropin (33 ng/kg/min) was administered 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 observed. 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, 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 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.

The aqueous Norditropin cartridge formulation is bioequivalent to the lyophilized Norditropin vial formulation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin.

14 CLINICAL STUDIES

14.1 Short Stature in Children with Noonan Syndrome

A prospective, open label, randomized, parallel group trial with 21 children was conducted for 2 years to evaluate the efficacy and safety of Norditropin treatment for short stature in children with Noonan syndrome. An additional 6 children were not randomized, but did follow the protocol. After the initial two-year trial, children continued on Norditropin until final height. Retrospective final height and adverse event data were collected from 18 of the 21 subjects who were originally enrolled in the trial and the 6 who had followed the protocol without randomization. Historical reference materials of height velocity and adult height analyses of Noonan patients served as the controls.

The twenty-four (24) (12 female, 12 male) children 3 – 14 years of age received either 0.033 mg/kg/day or 0.066 mg/kg/day of Norditropin subcutaneously which, after the first 2 years, was adjusted based on growth response.

In addition to a diagnosis of Noonan syndrome, key inclusion criteria included bone age determination showing no significant acceleration, prepubertal status, height SDS <-2, and HV SDS <1 during the 12 months pre-treatment. Exclusion criteria were previous or ongoing treatment with growth hormone, anabolic steroids or corticosteroids, congenital heart disease or other serious disease perceived to possibly have major impact on growth, FPG >6.7 mmol/L (>120 mg/dL), or growth hormone deficiency (peak GH levels <10 ng/mL).

Patients obtained a final height (FH) gain from baseline of 1.5 and 1.6 SDS estimated according to the national and the Noonan reference, respectively. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at 18 years of age, while a height gain of 1.6 SDS (Noonan) corresponds to a mean height gain of 11.5 cm in boys and 11.0 cm in girls at 18 years of age.

A comparison of HV between the two treatment groups during the first two years of treatment for the randomized subjects was 10.1 and 7.6 cm/year with 0.066 mg/kg/day versus 8.55 and 6.7 cm/year with 0.033 mg/kg/day, for Year 1 and Year 2, respectively.

Age at start of treatment was a factor for change in height SDS (national reference). The younger the age at start of treatment, the larger the change in height SDS.

Examination of gender subgroups did not identify differences in response to Norditropin.

Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, prior to initiating Norditropin for a patient with Noonan syndrome, establish that the patient does have short stature.

14.2 Short Stature in Children with Turner Syndrome

Two randomized, parallel group, open label, multicenter studies were conducted in the Netherlands to evaluate the efficacy and safety of Norditropin for the treatment of children with short stature associated with Turner syndrome. Patients were treated to final height in both studies [height velocity (HV) < 2 cm/year]. Changes in height were expressed as standard deviation scores (SDS) utilizing reference data for untreated Turner syndrome patients as well as the national Dutch population.

In Study 1 (the primary study), 68 euthyroid Caucasian patients stratified based on age and baseline height SDS were randomized in a 1:1:1 ratio to three different Norditropin treatment regimens: 0.045 mg/kg/day (Dose A) for the entire study; 0.045 mg/kg/day for the first year and 0.067 mg/kg/day thereafter (Dose B); or 0.045 mg/kg/day for the first year, 0.067 for the second year, and 0.089 mg/kg/day thereafter (Dose C). Overall, at baseline, mean age was 6.5 years, mean height SDS (National standard) was -2.7, and mean HV during the previous year was 6.5 cm/year. Patients also received estrogen therapy after age 12 and following four years of Norditropin treatment if they did not have spontaneous puberty.

Patients were treated for a mean of 8.4 years. As seen in Table 3, overall mean final height was 161 cm in the 46 children who attained final height. Seventy percent of these children reached a final height within the normal range (height SDS > -2 using the National standard). A greater percentage of children in the two escalated dose groups reached normal final height. The mean changes from baseline to final height in height SDS after treatment with Dose B and Dose C were significantly greater than the mean changes observed after treatment with Dose A (utilizing both the National and Turner standards). The mean changes from baseline to final height in height SDS (Turner standard) in Table 3 correspond to mean height gains of 9.4, 14.1 and 14.4 cm after treatment with Doses A, B and C, respectively. The mean changes from baseline to final height in height SDS (National standard) in Table 3

correspond to mean height gains of 4.5, 9.1 and 9.4 cm after treatment with Doses A, B and C, respectively. In each treatment group, peak HV was observed during treatment Year 1, and then gradually decreased each year; during Year 4, HV was less than the pre-treatment HV. However, between Year 2 and Year 6, a greater HV was observed in the two dose escalation groups compared to the 0.045 mg/kg/day group.

Table 3 – Final Height-Related Results After Treatment of Patients with Turner Syndrome with Norditropin in a Randomized, Dose Escalating Study

	Dose A 0.045 mg/kg/day (n = 19)	Dose B up to 0.067 mg/kg/day (n = 15)	Dose C up to 0.089 mg/kg/day (n = 12)	Total (n = 46)
Baseline height (cm) [1]	105 (12)	108 (12.7)	107 (11.7)	106 (11.9)
Final height (cm) [1]	157 (6.7)	163 (6.0)	163 (4.9)	161 (6.5)
Number (%) of patients reaching normal height (height SDS >-2 using National standard)	10 (53%)	12 (80%)	10 (83%)	32 (70%)
Height SDS (Turner standard) [2]				
Final [95% CI]	1.7 [1.4, 2.0]	2.5 [2.1, 2.8][3]	2.5 [2.1, 2.9][4]	NA
Change from baseline [95% CI]	1.5 [1.2,1.8]	2.2 [1.9, 2.5][3]	2.2 [1.9, 2.6][4]	NA
Height SDS (National standard) [2]				
Final [95% CI]	-1.9 [-2.2,-1.6]	-1.2 [-1.5,-0.9][4]	-1.2 [-1.6,-0.8][5]	NA
Change from baseline [95% CI]	0.7 [0.4, 1.0]	1.4 [1.1, 1.7][4]	1.4 [1.1, 1.8][5]	NA

Values are expressed as mean (SD) unless otherwise indicated. SDS: Standard deviation score.
[1]Unadjusted (raw) means; [2]Adjusted (least squares) means based on an ANCOVA model including terms for treatment, duration of treatment, age at baseline, bone age at baseline, height SDS at baseline, age at onset of puberty and mid-parental target height SDS; [3]p=0.005 vs. Dose A; [4]p=0.006 vs. Dose A; [5]p=0.008 vs. Dose A

In Study 2 (a supportive study), 19 euthyroid Caucasian patients (with bone age ≤13.9 years) were randomized to treatment with 0.067 mg/kg/day of Norditropin as a single subcutaneous dose in the evening, or divided into two doses (1/3 morning and 2/3 evening). All subjects were treated with concomitant ethinyl estradiol. Overall, at baseline, mean age was 13.6 years, mean height SDS (National standard) was -3.5 and mean HV during the previous year was 4.3 cm/year. Patients were treated for a mean of 3.6 years. In that there were no significant differences between the two treatment groups for any linear growth variables, the data from all patients were pooled. Overall mean final height was 155 cm in the 17 children who attained final height. Height SDS changed significantly from -3.5 at baseline to -2.4 at final height (National standard), and from 0.7 to 1.3 at final height (Turner standard).

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

A multi-center, randomized, double-blind, two-arm study to final height (Study 1) and a 2-year, multi-center, randomized, double-blind, parallel-group study (Study 2) were conducted to assess the efficacy and safety of Norditropin in children with short stature born SGA with no catch-up growth. Changes in height and height velocity were compared to a national reference population in both studies.

Study 1

The pivotal study included 53 (38 male, 15 female) non-GHD, Dutch children 3-11 years of age with short stature born SGA with no catch-up growth. Catch-up growth was defined as obtaining a height of ≥ 3rd percentile within the first 2 years of life or at a later stage. These prepubertal children needed to meet the following additional inclusion criteria: birth length < 3rd percentile for gestational age, and height velocity (cm/year) for chronological age < 50th percentile. Exclusion criteria included chromosomal abnormalities, signs of a syndrome (except for Silver-Russell syndrome), serious/chronic co-morbid disease, malignancy, and previous rhGH therapy. Norditropin was administered subcutaneously daily at bedtime at a dose of approximately 0.033 (Dose A) or 0.067 mg/kg/day (Dose B) for the entire treatment period. Final height was defined as a height velocity below 2 cm/year. Treatment with Norditropin was continued to final height for up to 13 years. Mean duration of treatment was 9.5 years (boys) and 7.9 years (girls).

38 out of 53 children (72%) reached final height. Sixty-three percent (24 out of 38) of the children who reached final height were within the normal range of their healthy peers (Dutch national reference). For both doses combined, actual mean final height was 171 (SD 6.1) cm in boys and 159 (SD 4.3) cm in girls.

As seen in Table 4, for boys and girls combined, both mean final height SDS (Dose A, -1.8 vs. Dose B, -1.3), and increase in height SDS from baseline to final height (Dose A, 1.4 vs. Dose B, 1.8), were significantly greater after treatment with Dose B (0.067 mg/kg/day). A similar dose response was observed for the increase in height SDS from baseline to Year 2 (Table 4).

Overall mean height velocity at baseline was 5.4 cm/y (SD 1.2; n=29). Height velocity was greatest during the first year of Norditropin treatment and was significantly greater after treatment with Dose B (mean 11.1 cm/y [SD 1.9; n=19]) compared with Dose A (mean 9.7 cm/y [SD 1.3; n=10]).

Table 4 – Study 1: Results for Final Height SDS and Change from Baseline to Final Height in Height SDS Using National Standard After Long-Term Treatment of SGA Children with Norditropin

	Raw Mean ± SD (N)		
	Dose A 0.033 mg/kg/day	Dose B 0.067 mg/kg/day	Total
Baseline Height SDS	-3.2 ± 0.7 (26)	-3.2 ± 0.7 (27)	-3.2 ± 0.7 (53)
Adjusted least-squares mean ± standard error (N) and [95% confidence intervals]			
Height SDS: Change from Baseline at Year 2[2]	1.4 ± 0.1 (26) [1.1, 1.6]	1.8 ± 0.1 (26) [1.5, 2.0]	Treatment Diff = 0.4 [0.2, 0.7] p-value = 0.002
Height SDS: Change from Baseline at Final Height[1]	1.4 ± 0.2 (19) [0.9, 1.8]	1.8 ± 0.2 (19) [1.4, 2.2]	Treatment Diff = 0.5 [0.0, 0.9] p-value = 0.045
Final Height SDS[1]	-1.8 ± 0.2 (19) [-2.2, -1.4]	-1.3 ± 0.2 (19) [-1.7, -0.9]	
Final Height SDS > -2	13/19 (68%)	11/19 (58%)	24/38 (63%)

SDS: Standard deviation score.
[1]Adjusted (least-squares) means based on an ANCOVA model including terms for treatment, gender, age at baseline, bone age at baseline, height SDS at baseline, duration of treatment, peak GH after stimulation and baseline IGF-1.
[2] Adjusted (least-squares) means based on an ANCOVA model including terms for treatment, gender, age at baseline, height SDS at baseline, and pubertal status.

Study 2

In this study, 84 randomized, prepubertal, non-GHD, Japanese children (age 3-8) with short stature born SGA with no catch-up growth were treated for 2 years with 0.033 or 0.067 mg/kg/day of Norditropin subcutaneously daily at bedtime or received no treatment for 1 year. Additional inclusion criteria included birth length or weight SDS ≤ -2 or < 10th percentile for gestational age, height SDS for chronological age ≤ -2, and height velocity SDS for chronological age < 0 within one year prior to Visit 1. Exclusion criteria included diabetes mellitus, history or presence of active malignancy, and serious co-morbid conditions.

As seen in Table 5, for boys and girls combined, there was a dose-dependent increase in height SDS at Year 1 and Year 2. The increase in height SDS from baseline to Year 2 (0.033 mg/kg/day, 0.8 vs. 0.067 mg/kg/day, 1.4) was significantly greater after treatment with 0.067 mg/kg/day. In addition, the increase in height SDS at Year 1 was significantly greater in both active treatment groups compared to the untreated control group.

Table 5 – Study 2: Results for Change from Baseline in Height SDS At Year 1 and Year 2 Using National Standard After Short-Term Treatment of SGA Children with Norditropin

	Raw Mean ± SD (N)			
	No Treatment	0.033 mg/kg/day	0.067 mg/kg/day	Total
Height SDS: Baseline	-2.9 ± 0.5 (15)	-3.0 ± 0.6 (35)	-2.9 ± 0.7 (34)	-2.9 ± 0.6 (84)
Height SDS: Year 1	-2.8 ± 0.5 (15)	-2.4 ± 0.6 (33)	-2.0 ± 0.8 (34)	-2.3 ± 0.7 (82)
Height SDS: Year 2	NA	-2.2 ± 0.7 (33)	-1.4 ± 0.7 (32)	-1.8 ± 0.8 (65)
Adjusted least-squares mean ± standard error (N) and [95% confidence intervals]				
Height SDS: Change from Baseline at Year 1[1]	0.1 ± 0.1 (15) [-0.1, 0.2]	0.6 ± 0.1 (33) [0.5, 0.7]	0.9 ± 0.1 (34) [0.8, 1.0]	

	0.033 vs. No Treatment: Treatment Diff = 0.5, [0.3, 0.7], p < 0.0001 0.067 vs. No Treatment: Treatment Diff = 0.8, [0.6, 1.0], p < 0.0001 0.067 vs. 0.033: Treatment Diff = 0.3, [0.2, 0.5], p-value < 0.0001			
Height SDS: Change from Baseline at Year 2[1]	NA	0.8 ± 0.1 (33) [0.7, 0.9]	1.4 ± 0.1 (32) [1.3, 1.6]	
	0.067 vs. 0.033: Treatment Diff = 0.6, [0.5, 0.8], p-value < 0.0001			

SDS: Standard deviation score.
[1]Adjusted (least-squares) means based on an ANCOVA model including terms for treatment, gender, age at baseline, and height SDS at baseline. All children remained prepubertal during the study.

14.4 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 6).

Table 6 – 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 7).

Table 7 – 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 8).

Table 8 – Lean Body Mass (kg) by TBP

	Norditropin	Placebo

	(n=36)	(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 9).

Table 9 – 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

- Norditropin Cartridges 5 mg/1.5 mL (orange) NDC 0169-7768-11
- Norditropin Cartridges 15 mg/1.5 mL (green) NDC 0169-7770-11

Unused Norditropin cartridges must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

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

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

Norditropin NordiFlex prefilled pens *[somatropin (rDNA origin) injection] 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL and 30 mg/3 mL:*

Norditropin NordiFlex is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL or 30 mg/3 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
- Norditropin NordiFlex 30 mg/3 mL (purple) NDC 0169-xxxx-xx

Unused Norditropin NordiFlex prefilled pens must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

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 (2-8ºC/36-46ºF) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25ºC (77ºF). Discard unused portion.

15 mg/1.5 mL (green) and 30 mg/3 mL (purple) prefilled pens:

After the initial injection, a Norditropin NordiFlex (15 mg/1.5 mL or 30 mg/3 mL) prefilled pen must be stored in the refrigerator (2-8ºC/36-46ºF) and used within 4 weeks. Discard unused portion after 4 weeks.

Table 10 – Storage Options

Norditropin Product Formulation	**Before Use**	**In-use (After 1st injection)**	
	Storage requirement	**Storage Option 1 (Refrigeration)**	**Storage Option 2 (Room temperature)**
5 mg	2-8 ºC/ 36-46 ºF Until exp date	2-8 ºC/36-46 ºF 4 weeks	Up to 25ºC/77ºF 3 weeks
10 mg		2-8 ºC/36-46 ºF 4 weeks	Up to 25ºC/77ºF 3 weeks
15 mg		2-8 ºC/36-46 ºF 4 weeks	Does Not Apply
30 mg		2-8 ºC/36-46 ºF 4 weeks	Does Not Apply

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Patients being treated with Norditropin Cartridges or Norditropin NordiFlex prefilled pens (and/or their parents) should be informed about the potential risks and benefits associated with somatropin treatment *[in particular, see Adverse Reactions (6.1) for a listing of the most serious and/or most frequently observed adverse reactions associated with somatropin treatment in children and adults]*. 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 or Norditropin NordiFlex prefilled pens should receive appropriate training and instruction on proper use from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used 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. This information is intended to aid in the safe and effective administration of the medication.

If patients are prescribed Norditropin Cartridges (to be inserted into color-coded NordiPen delivery systems), physicians should instruct patients to read the NordiPen INSTRUCTION booklet provided with the NordiPen delivery systems.

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

Date of Issue: October 31, 2008

Version: 10

For information contact:
Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540, USA
1-888-NOVO-444

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

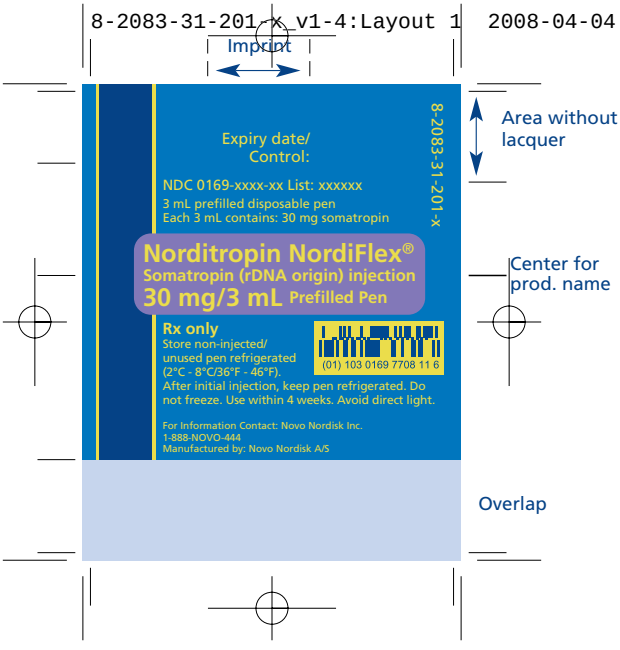
RA Labelling & Graphics

Label: 48x61-203
Current: 2.0

Lacquer area:
Lacquerform: 20005-1

Colour:
PMS 280C + PMS 285C +
PMS 2655C + White

White tintground under blue band and Product Name
White colour indicated by yellow



RA Labelling & Graphics

Carton: 22-505-10
NordiFlex 3 ml
Current x.0

Colour:
PMS 280C + PMS 2655C

Code centre line
Code: 100% Direction →
Length Max 29 mm (100%)

Novo Nordisk®

PATIENT INFORMATION

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
30 mg/3.0 mL Prefilled Pen

Your doctor will discuss with you the benefits and risks of Norditropin NordiFlex® (pronounced Nor-dee-tro-pin Nor-dee-flex). Read all of the information in this patient guide because it contains important information for you. If you have further questions, please ask your doctor or your pharmacist.

Norditropin NordiFlex has been prescribed for you and you must not pass it on to others.

What is the most important information I should know about Norditropin NordiFlex?

Store Norditropin NordiFlex in a refrigerator before use. Do not freeze it or expose it to heat.

For specific information on storage conditions please see the section How to store Norditropin NordiFlex.

Do not use Norditropin NordiFlex if the solution in the cartridge does not appear clear and colorless. Check this by turning the pen upside down once or twice.

Norditropin NordiFlex is for use by one person only.

Do not use Norditropin NordiFlex if you need to make more than 4 air shots before the first injection.

Your doctor may measure your height, weight and your ability to produce growth hormone before you are prescribed Norditropin NordiFlex.

Norditropin NordiFlex 30 mg/3.0 mL cannot be used with the NordiFlex PenMate® auto-insertion accessory.

What is Norditropin NordiFlex?

Norditropin® is a clear and colorless solution. It contains a human growth hormone called somatropin (so-ma-tro-pin) made through biotechnology. It is identical to the growth hormone produced in the human body.

Norditropin is used to treat the following:

- children with growth failure caused by very low or no production of growth hormone
- short stature in children with Noonan syndrome

- short stature in children with Turner syndrome
- Children with short stature born small for gestational age (SGA) with no catch-up growth by age 2-4 years
- adults who do not make sufficient growth hormone

Norditropin is injected using Norditropin NordiFlex, a multi-dose disposable 1.5 mL or 3.0 mL pre-filled pen. Norditropin NordiFlex contains several doses of growth hormone solution. A dose is injected under the skin in the evening 6 times a week or daily.

Norditropin NordiFlex is available in several delivery pens, sizes, and strengths as outlined in the table below,

Strength	Size	Concentration
5 mg/1.5 mL	1.5 mL	3.3 mg/mL
10 mg/1.5 mL	1.5 mL	6.7 mg/mL
15 mg/1.5 mL	1.5 mL	10 mg/mL
30 mg/3.0 mL	3 mL	10 mg/mL

Throw away Norditropin NordiFlex when the cartridge is empty.

Medicines are sometimes prescribed for purposes other than those listed in a patient guide. You should ask your doctor about any concerns and refer to the prescriber information for additional information.

What does Norditropin NordiFlex contain?

The cartridge in Norditropin NordiFlex contains human growth hormone.
The cartridge also contains other ingredients: Histidine, Poloxamer 188, Phenol, Mannitol and Water for Injection.

Who should not use Norditropin NordiFlex?

Do not use Norditropin NordiFlex if you have any of the following conditions:

- child with closed epiphyses (closed bone growth plates)
- child with Prader-Willi syndrome who is also severely obese or has significant respiratory impairment
- allergic to phenol or any other ingredients in the medicine
- had a kidney transplant
- pregnant
- breast-feeding
- active cancer or other forms of tumor
- acute critical illness due to certain types of heart or abdomen surgery, trauma or acute respiratory failure

What should you consider if you are pregnant or breast-feeding?

If you become pregnant while you are using Norditropin NordiFlex, you are recommended to stop the treatment and discuss this with your doctor.

You are recommended not to use Norditropin NordiFlex while you are breast-feeding because growth hormone might pass into your milk.

Be sure to tell your doctor if you:

- have diabetes mellitus
- had cancer or other forms of tumor
- are pregnant, planning to be pregnant or breastfeeding
- had a kidney transplant

If any of the above applies to you, Norditropin NordiFlex may not be suitable. Your doctor will give you advice.

How should I use Norditropin NordiFlex?

Carefully follow the "Instructions for Use" on the other side of this patient guide.

You should inject Norditropin NordiFlex under the skin in the evening just before bedtime. You should change the injection area so you do not harm your skin.

NovoFine® disposable needles are designed to be used with Norditropin NordiFlex.

How much Norditropin should you take?

Your doctor will tell you how much Norditropin you should take. In children it depends on the body weight.

General guidelines for dosages are shown below.

Children with growth failure caused by very low or no growth hormone: 0.024 to 0.034 mg/kg body weight, 6-7 times a week

Children with short stature and Noonan syndrome: Up to 0.066 mg/kg/day

Children with short stature and Turner syndrome: Up to 0.067 mg/kg/day

Children with short stature born small for gestational age (SGA) with no catch-up growth by age 2-4 years: Up to 0.067 mg/kg/day

Adults: Not more than 0.004 mg/kg/day at start of therapy. Dosage may be increased as tolerated to not more than 0.016 mg/kg/day after approximately 6 weeks, or

Alternative dose for adults:

Approximately 0.2 mg/day (range, 0.15-0.30 mg/day) at start of therapy. Dosage can be increased gradually every 1-2 months by steps of approximately 0.1-0.2 mg/day, based on your doctor's recommendations.

If you forget to take a dose, take the next dose as usual - do not double your dose.

What should you do if you inject too much growth hormone using Norditropin NordiFlex?

If you inject too much growth hormone, contact your doctor.

How long should you continue to take Norditropin?

Discuss with your doctor how long you should take Norditropin.

What should I avoid while using Norditropin NordiFlex?

Be sure to tell your doctor about all of the medications you are taking especially if you are taking:

- a glucocorticoid medication (for example, hydrocortisone or cortisone acetate)
- thyroid hormone
- insulin and/or oral diabetes medicine
- drugs metabolized by the liver (for example, corticosteroids, sex steroids, anticonvulsants, cyclosporine)
- oral estrogen replacement

Adult height can be influenced if you are on Norditropin NordiFlex for growth failure and using glucocorticoids or thyroid hormone at the same time.

If you are treated with insulin and/or oral diabetes medicine, your insulin/oral diabetes medicine dose may need to be adjusted.

What are the possible side effects of Norditropin NordiFlex?

The following side effects are usually mild and temporary:

- headaches
- muscle pain
- joint stiffness
- high blood sugar (hyperglycemia)
- sugar in your urine (glucosuria)
- swollen hands and feet due to fluid retention
- redness and itching in the area you inject

If you experience any of these symptoms, discuss this with your doctor.

In rare cases you may develop antibodies to growth hormone.

If you have symptoms of headaches, eyesight problems, nausea and/or vomiting, these may be symptoms of raised pressure in the brain. Contact your doctor immediately.

Be sure to tell your doctor if you have any other side effects not mentioned here.

Special warnings

In very rare cases children treated with growth hormone have experienced pain in the hip or knee or a limp. These symptoms may be caused by a slippage of the growth plate in the hip (slipped capital femoral epiphysis).

Scoliosis (curvature of the spine) can occur in children who experience rapid growth. Because growth hormone increases growth rate, patients should be monitored for progression of scoliosis.

Thyroid function tests should be performed periodically.

Patients with Turner syndrome have an increased risk of ear or hearing disorders. They should be carefully evaluated for middle ear infection (otitis media) and other ear disorders.

Skin lesions should be checked carefully for any cancerous changes.

The following tumors have been reported in patients treated with growth hormone: Leukemia in children, relapse of brain tumors in children and adults. However, there is no evidence that growth hormone is responsible for causing these diseases.

Talk to your doctor if you think you have any of these conditions.

How to store Norditropin NordiFlex?

Store unused Norditropin NordiFlex in a refrigerator (2ºC - 8ºC/36ºF - 46ºF). Do not freeze or expose it to heat. Avoid direct light.

After the initial injection, Norditropin NordiFlex 30 mg/3.0 mL must be kept in a refrigerator and used within 4 weeks. Discard unused portion after 4 weeks.

Do not use Norditropin NordiFlex which has been frozen or exposed to temperatures higher than 25ºC (77ºF).

Always use a new NovoFine needle for each injection. Do not keep the needle screwed onto Norditropin NordiFlex when you are not using it.

Always keep the pen cap closed on Norditropin NordiFlex when you are not using it.

Never use Norditropin NordiFlex after the expiration date printed on the pen and on the carton.

Date of issue:
Version:

US Patent Nos. 6,235,004; 6,004,297; 5,849,704 and 6,582,404

For assistance or further information, write to:
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540, USA
1-888-NOVO-444
norditropin-us.com

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Novo Nordisk®

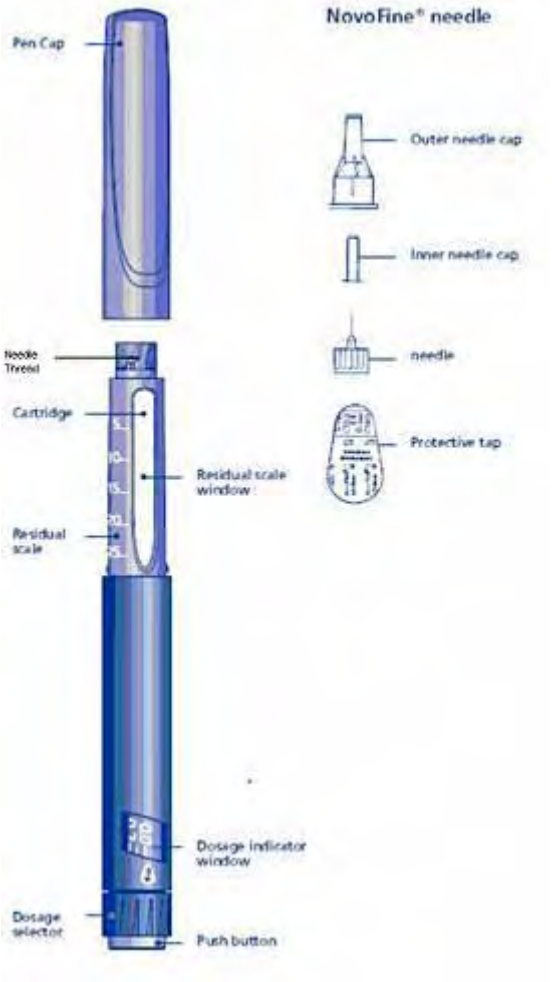
INSTRUCTIONS FOR USE

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
30 mg/3.0 mL Prefilled Pen

Using the disposable Norditropin NordiFlex® 30 mg/3.0 mL Prefilled Pen

Norditropin NordiFlex 30 mg/3.0 mL is a multi-dose, disposable, prefilled pen with liquid growth hormone able to deliver doses from 0.1 to 6.0 mg. The dose can be adjusted in increments of 0.1 mg. Your doctor will determine the correct dose for you. Norditropin NordiFlex prefilled pen is designed to be used with NovoFine® disposable needles (sold separately). Norditropin NordiFlex prefilled pen is not recommended for people who are blind or have trouble seeing unless they have the help of a sighted individual trained to use Norditropin NordiFlex.

Please read these instructions carefully before using this pen

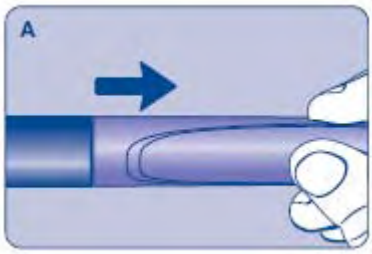


1 Preparing Norditropin NordiFlex 30 mg/3.0 mL for Injection

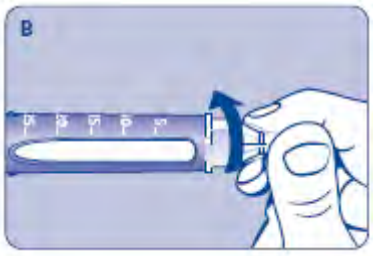
A. Pull off the pen cap and check if the growth hormone solution is clear and colorless by turning the Norditropin NordiFlex upside down once or twice and view the solution through the residual scale window. **DO NOT use Norditropin NordiFlex if the growth hormone solution is cloudy or contains particles. Use it only if it is clear and colorless.**

Wash hands well and dry completely.

Wipe the front rubber stopper on the needle thread with an alcohol swab.



B. Place a new NovoFine disposable needle onto Norditropin NordiFlex immediately before use. Remove the protective tab from the disposable needle and screw the needle tightly onto Norditropin NordiFlex. Pull off the outer and inner needle caps. Never place a disposable needle on your Norditropin NordiFlex until you are ready to give an injection. Remove the needle immediately after use. If the needle is not removed, some liquid may be expelled from Norditropin NordiFlex.



2 Performing an Air Shot

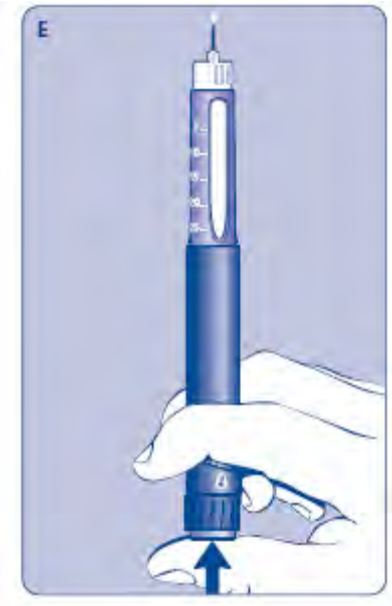
Do an air shot before starting a new Norditropin NordiFlex as follows:
Small amounts of air may collect in the needle and cartridge. To ensure proper dosing and to avoid injecting air, you must perform an air shot before administering your first injection.

C. Dial the dosage selector to 0.1 mg. Each line between labeled dosages is 0.1 mg.

D. Hold Norditropin NordiFlex with the needle pointing up, tap the cartridge gently with your finger a few times to make any air bubbles rise to the top of the cartridge.

E. Still holding Norditropin NordiFlex with the needle up, press the push button all the way in. A drop of liquid should appear at the needle tip. If not, repeat the above steps, no more than 4 times.

If a drop of liquid still does not appear, call 1-888-NOVO-444 for help.



3 Setting the Dose

F. Check that the dose selector is set at **0.0**. Dial the number of mg (milligram) that you need to inject. If you dial more than your dose, the dose can be changed up or down by turning the dose selector in either direction. When dialing back, be careful not to press the push button as liquid will come out.
Use dosage indicator, NOT the clicking sound, as a guide for selecting the dose.

The numbers on the residual scale can be used to estimate the mg left in the cartridge. **DO NOT use these numbers to measure the dose.**

You cannot set a dose higher than the number of mg left in the cartridge. Use a new Norditropin NordiFlex pen to inject the remaining amount of your dose. Be sure to remember the dose already received with the first dose. For example, if your dose is 0.6 mg and you can only set the dose selector to 0.3 mg. You will need to inject an additional 0.3 mg with a new Norditropin NordiFlex pen.

4 Giving the Injection

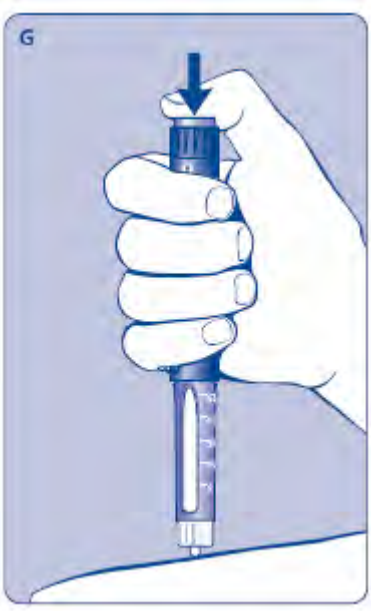
Use the injection technique recommended by your healthcare professional.

G. This product is for subcutaneous use only. Insert the needle under the skin and press the push button as far as it goes to deliver the dose. To ensure that the full dose is injected keep the needle in the skin for at least 6 seconds after injection with your thumb on the push button. Keep the push button fully pushed in until after the needle has been removed from the skin.

After the injection, check the dosage indicator window to make sure it shows zero (0.0).

If zero does not appear, you did not receive the full dose. Call 1-888-NOVO-444 for assistance.

Note:
Always **press** the push button to inject the dose. **Turning** the dosage selector will **not** inject the dose.



5 Removing the NovoFine Disposable Needle

H. After the injection, remove the needle **without recapping** and dispose of it in a puncture-resistant container. Used needles should be placed in sharps container (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

It is important that you use a new needle for each injection. Healthcare professionals, relatives and other caregivers should follow general precautionary measures for removal and disposal of needles to reduce the risk of unintended needle stick injuries.

When the cartridge is empty, dispose of Norditropin NordiFlex without the needle attached.

6 Maintenance

Handle Norditropin NordiFlex with care. Protect Norditropin NordiFlex from dust, dirt, and direct sunlight.

You can clean the outside of Norditropin NordiFlex by wiping it with a soft cloth moistened with water. Do not soak Norditropin NordiFlex in alcohol, wash, or lubricate it.

7 Important Things to Know

- Norditropin NordiFlex 30 mg/3.0 mL cannot be used with the NordiFlex PenMate auto-insertion accessory.
- Store unused Norditropin NordiFlex pens in a refrigerator (2ºC - 8ºC/36ºF - 46ºF). After the initial injection, keep Norditropin NordiFlex 30 mg/3.0 mL refrigerated and use within 4 weeks.
- Remember to perform an air shot before starting a new Norditropin NordiFlex or before the injection if you dropped or knocked the pen against a hard surface. See diagrams **C, D** and **E**.
- If you need to perform more than 4 air shots before the first use of Norditropin NordiFlex to get a droplet of liquid at the needle tip, **DO NOT** use Norditropin NordiFlex. *Call 1-888-NOVO-444 for help.*
- Take care not to drop Norditropin NordiFlex or knock it against a hard surface.
- **DO NOT** leave Norditropin NordiFlex in a car or other location where it can get too hot or too cold.
- Always have a spare Norditropin NordiFlex disposable pen in order to avoid running out of this product.
- Norditropin NordiFlex is designed to be used with NovoFine disposable needles.
- **NEVER** place a needle on Norditropin NordiFlex until you are ready to use it. Remove the needle right after use without recapping.
- **Dispose of used needles properly, so people will not be harmed.**
- Dispose of used Norditropin NordiFlex, without the needle attached.
- To avoid spread of disease, do not let anyone else use your Norditropin NordiFlex, even if you attach a new needle.
- Keep the Norditropin NordiFlex out of the reach of children.
- **Novo Nordisk is not responsible for harm due to using the Norditropin NordiFlex with products that are not recommended by Novo Nordisk.**

8 Customer Satisfaction

Customer service and satisfaction are our top concerns. If you have any questions about Norditropin NordiFlex prefilled pens please call Novo Nordisk Inc. at 1-888-NOVO-444.

RA
Labelling & Graphics

Carton: 23-262-05-313-dev
Current: 5.0

Lacquer free area:
Lacquerform: 30016-1-dev

Colour:
PMS 280C + CMYK

Licensed under US Patent 5980491 and US Patent 6537252.
Designed and intended for use with
Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL
prefilled Pens and NovoFine® disposable needles.
Norditropin®, Norditropin NordiFlex® and NordiFlex PenMate®
are trademarks of Novo Nordisk Health Care AG.
NovoFine® is a trademark of Novo Nordisk A/S.

3 01697 71011 2

For information contact:

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
1-888-NOVO-444

Manufactured in Denmark for:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

novo nordisk®

NordiFlex PenMate®

List: 771011

NordiFlex PenMate®

Auto-insertion accessory only
for Norditropin NordiFlex 5 mg/1.5 mL,
10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens

List: 771011

23-262-05

NordiFlex PenMate®

List: 771011

LOT

NordiFlex PenMate®

novo nordisk®

NordiFlex PenMate®

Auto-insertion accessory only for Norditropin NordiFlex 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens

**Contains One
NordiFlex PenMate®**
List: 771011

8-4240-31-301-2

NordiFlex PenMate®

List: 771011

Auto-insertion accessory only
for Norditropin NordiFlex 5 mg/1.5 mL,
10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens

Designed and intended for use with
NovoFine® disposable needles.
Norditropin NordiFlex® prefilled pens
and needles sold separately.

NordiFlex PenMate®

Auto-insertion accessory for Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens

User Manual

Please read this manual carefully before using NordiFlex PenMate®

Novo Nordisk®

Introduction
Dear NordiFlex PenMate® User:

NordiFlex PenMate® is an auto-insertion accessory designed to be used with Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens. NordiFlex PenMate helps you to insert the needle and to give injections easily and conveniently.

This manual includes everything you need to know about using NordiFlex PenMate. Read it carefully before using NordiFlex PenMate for the first time.

NordiFlex PenMate is designed for use with:

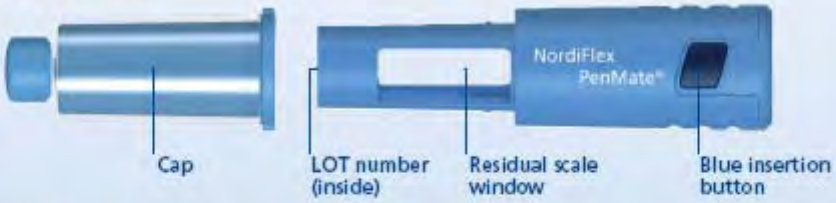
- Norditropin NordiFlex® (somatropin [rDNA origin] injection) 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens
- NovoFine® disposable needles

Customer service and satisfaction are our top concern. If you have any questions about NordiFlex PenMate or Norditropin NordiFlex prefilled pens please call
Novo Nordisk Inc. at 1-888-NOVO-444.
Thank you for choosing NordiFlex PenMate.

(See **Important Things to Know** and **Important Notes** on pages 19-20)

Open this flap for a drawing of NordiFlex PenMate and Norditropin NordiFlex.

NordiFlex PenMate®



Norditropin NordiFlex® Prefilled Pen 5 mg/1.5 mL

NovoFine® disposable needles

NordiFlex PenMate® is designed for use with NovoFine® disposable needles and Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens.

! How to use this manual

This manual gives you step-by-step instructions for using NordiFlex PenMate in combination with Norditropin NordiFlex 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL. A Norditropin NordiFlex 5 mg/1.5 mL prefilled pen (orange) is used to show the correct use of NordiFlex PenMate. Norditropin NordiFlex is also available as a 10 mg/1.5 mL prefilled pen (blue), 15 mg/1.5 mL prefilled pen (green) and 30 mg/3 mL prefilled pen (purple). Do not use Norditropin NordiFlex 30 mg/3 mL pens with the NordiFlex PenMate® auto-insertion accessory.

Begin by reviewing the drawings of the parts of NordiFlex PenMate, Norditropin NordiFlex prefilled pen and NovoFine disposable needle. The inside front cover opens out so you have a handy reference while you read the rest of the manual.

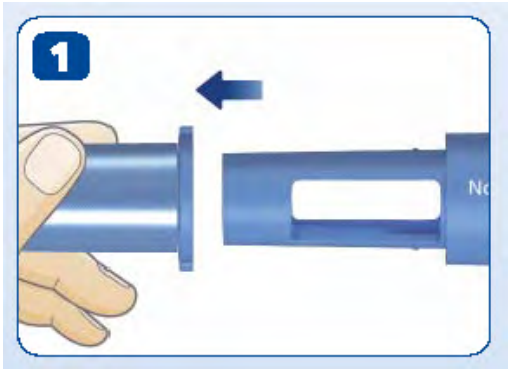
Most pages contain drawings with numbered instructions.
Important additional information is given below the instructions.

Read the text carefully and look at the drawings to make sure that you understand each step well.

Table of Contents **Page**

4 Section 1: Assembling NordiFlex PenMate

!Note:
Do not use Norditropin NordiFlex 30 mg/3 mL pens with the NordiFlex PenMate® auto-insertion accessory.



1. Remove NordiFlex PenMate cap.

2. A. Pull off the cap of Norditropin NordiFlex. You will not need it with NordiFlex PenMate. **DO NOT use Norditropin NordiFlex if the liquid is cloudy or contains particles. Use it only if it is clear and colorless.** Check this by turning Norditropin NordiFlex upside down once or twice and view the liquid through the residual scale window.

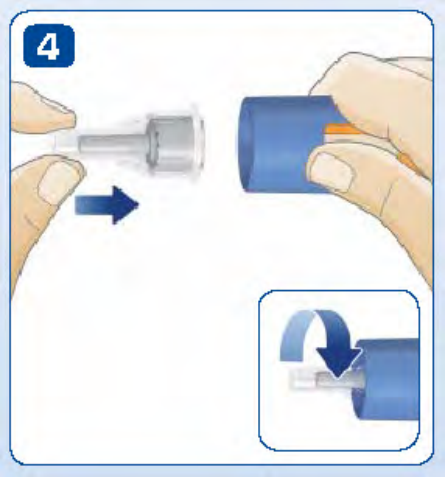
B. Wash hands well and dry completely.

C. Wipe the front rubber stopper on the threaded plastic cap with an alcohol swab.

! Note:
You must wipe the front rubber stopper with an alcohol swab before each injection even if you are still using the same Norditropin NordiFlex.

3. Grasp the body of Norditropin NordiFlex and insert Norditropin NordiFlex into NordiFlex PenMate and turn Norditropin NordiFlex clockwise until you feel a "click", the dose indicator window should be set at "0.0" after assembly. **The dosage indicator window on Norditropin NordiFlex must align with the insertion button on NordiFlex PenMate.**

6 Section 1 (cont.): Assembling NordiFlex PenMate



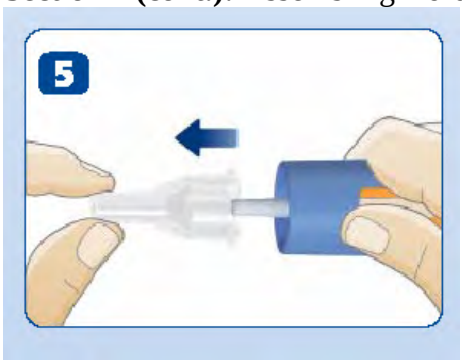
4. Place a new NovoFine disposable needle onto Norditropin NordiFlex immediately before use. Remove the protective tab off the needle and screw the needle tightly onto Norditropin NordiFlex prefilled pen.

! Note:

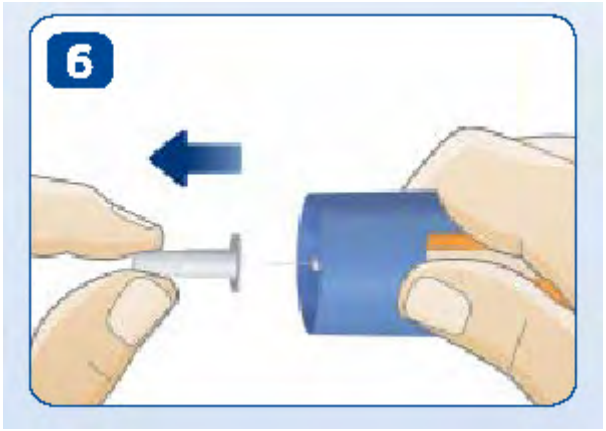
- Never place a NovoFine disposable needle on Norditropin NordiFlex until you are ready to give an injection. If the NovoFine disposable needle is “left on” Norditropin NordiFlex, some liquid may leak out.

- NovoFine needles have an inner and outer cap that must be removed prior to injection.

! Note:
Always use a new NovoFine disposable needle for each injection.



5. Pull off the **outer** needle cap and keep it within reach.



6. Carefully remove the inner needle cap and dispose of it properly.

! Note:
To minimize the risks of unintended needle stick injuries never replace the inner needle cap once it has been removed.

8 Section 2: Performing an Air Shot

Small amounts of air may collect in the needle and cartridge. To ensure proper dosing and to avoid injecting air, you must perform an air shot before administering your first injection with a new Norditropin NordiFlex.

1. Dial the dosage selector to the first line after 0.0.

Each line between labeled dosages is 0.025 mg for a Norditropin NordiFlex 5 mg/1.5 mL, 0.05 mg for a Norditropin NordiFlex 10 mg/1.5 mL and 0.075 mg for a Norditropin NordiFlex 15 mg/1.5 mL.

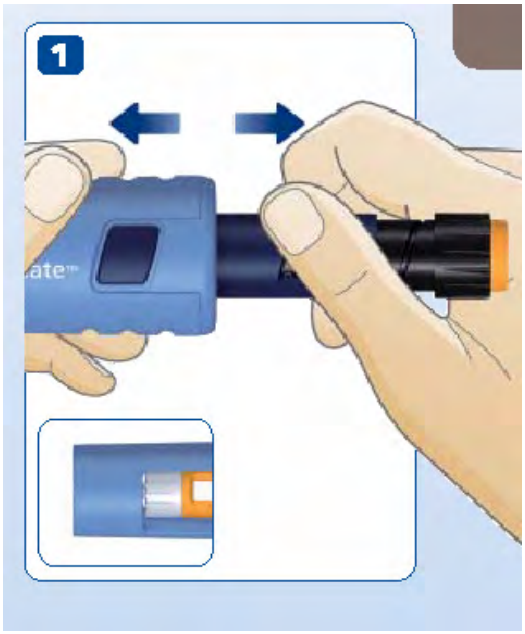
2. Hold NordiFlex PenMate with the NovoFine disposable needle pointing upwards and tap NordiFlex PenMate gently with your finger a few times to make any air bubbles rise to the top of the cartridge.

3. Still holding NordiFlex PenMate with the needle up, press the push button all the way in. A drop of liquid should appear at the needle tip. If not, repeat steps 1-3, no more than 4 times.

   If Norditropin NordiFlex or NordiFlex PenMate has been dropped or knocked against hard surfaces, perform an airshot before your next injection

If a drop of liquid still does not appear or if you have any questions, call 1-888-NOVO-444 for help.

10 Section 3: Preparing NordiFlex PenMate for Injection



1. Preparing NordiFlex PenMate

To prepare NordiFlex PenMate, grip both NordiFlex PenMate and Norditropin NordiFlex firmly and pull in opposite directions until you hear a click.

Now the needle is hidden in NordiFlex PenMate.

Setting the Dose

Check that the dosage indicator on Norditropin NordiFlex is set at 0.0.

1. Dial the number of mg you need to inject.

If you dial more than your dose, the dose can be corrected up or down by turning the dosage selector in either direction. When turning the dosage selector backwards, be careful not to press the push button as liquid will come out. **Use the dosage indicator not the clicking sound as a guide for selecting the dose** The numbers on the residual scale can be used to estimate the mg left in the cartridge. **DO NOT use these numbers to measure the dose.**

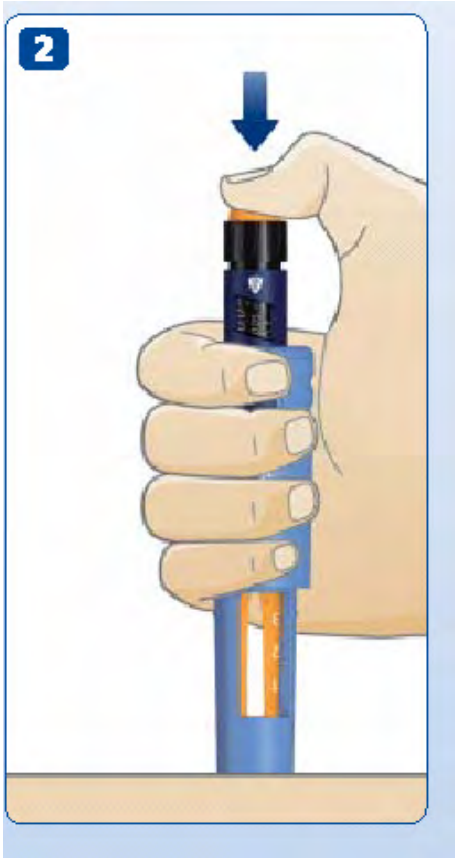
You cannot select a dose larger than the number of mg left in the cartridge. Use a new Norditropin NordiFlex pen to inject the remaining amount of your dose. Be sure to remember the dose already received with the first dose. For example, if your dose is 0.6 mg and you can only set the dose selector to 0.4 mg. You will need to inject an additional 0.2 mg with a new Norditropin NordiFlex pen. See page 14 for detailed instructions.

12 Section 4 (cont.): Giving the Injection

Giving the Injection

Use the injection technique recommended by your healthcare professional. This product is for subcutaneous injection only.

1. Hold NordiFlex PenMate against your skin. Press the blue insertion button with your finger. The needle will automatically enter your skin.



2. Press the push button **as far as it will go** to deliver the dose. **To ensure that the full dose is injected keep the needle in the skin for at least 6 seconds after injection with your thumb on the push button.** Keep the push button fully pushed in until after the needle has been removed from the skin. Vary the injection site using the injection procedure recommended by your healthcare professional.

3. After the injection check the dosage indicator window to make sure it shows zero (0.0).

   If zero does not appear, you did not receive the full dose. Call 1-888-NOVO-444 for assistance.

! Note:
Always **press** the push button to inject the dose. **Turning** the dosage selector will **not** inject the dose.

14 Section 4 (cont.): Giving the Injection

With Norditropin NordiFlex it is not possible to select a dose that is larger than the mg left in the cartridge. If you need a dose more than the mg left in the cartridge, you must spread your dose over two injections. Follow the steps below:

To get the remaining part of your dose:

a. Inject the dose left in the cartridge, making a note of the number of mg you inject. For example, if your dose is 0.6 mg and you can only set the dose selector to 0.4 mg. You will need to inject an additional 0.2 mg with a new Norditropin NordiFlex pen.
b. Remove the NovoFine disposable needle from Norditropin NordiFlex (see Section 5).
c. Remove the empty Norditropin NordiFlex (see Section 6).
d. Insert a new Norditropin NordiFlex (see Section 1 and 6).
e. Attach a new NovoFine disposable needle (see Section 1, pages 6 and 7).
f. Perform an air shot (see Section 2).
g. Dial the number of mg still needed to complete your dose.
h. Give the injection.

Need Help? Call 1-888-NOVO-444

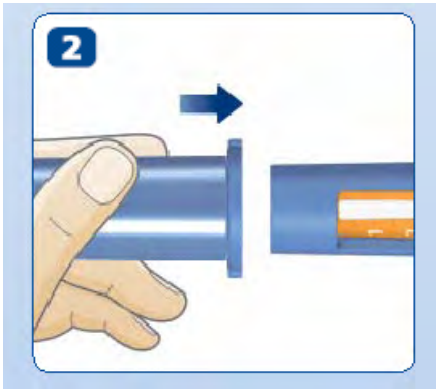
Remove the NovoFine Disposable Needle

1. Carefully replace the **outer** needle cap onto the needle immediately after the injection.

Follow the instructions you received for removal and disposal of needles to reduce the risk of needle stick injuries.

Hold NordiFlex PenMate firmly while you unscrew the NovoFine disposable needle.

Place the NovoFine disposable needle in a puncture-resistant disposal container. Used needles should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.



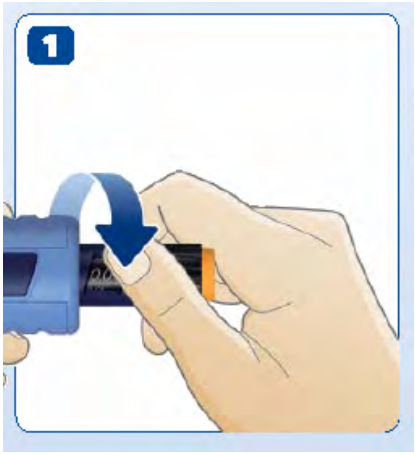
2. Replace NordiFlex PenMate cap.

! Note:
The NovoFine disposable needle must be removed immediately after each injection. If the NovoFine disposable needle is not removed, some liquid may leak out of Norditropin cartridge.

It is important that you use a new needle for each injection. **Healthcare professionals, relatives and other caregivers should follow general precautionary measures for removal and disposal of needles to reduce the risk of unintended needle stick injuries**.

16 Section 6: Replacing an Empty Norditropin NordiFlex

You will need to remove Norditropin NordiFlex prefilled pen when it is empty.



1. When Norditropin NordiFlex is empty, turn Norditropin NordiFlex counterclockwise until you feel a “click” and gently pull it out of NordiFlex PenMate. Dispose of Norditropin NordiFlex properly without the needle attached.

Screw a new Norditropin NordiFlex and NordiFlex PenMate together as described on pages 4 to 5.

To prepare for a new injection continue as described on pages 6 to10.

Guidelines for storing NordiFlex PenMate and Norditropin NordiFlex

- Always remove the NovoFine disposable needle and replace NordiFlex PenMate cap after use.
- When Norditropin NordiFlex is inserted in NordiFlex PenMate, store NordiFlex PenMate as described in the leaflet in Norditropin NordiFlex pack.
- When using a NordiFlex PenMate with a Norditropin NordiFlex 5 mg/1.5 mL or a Norditropin NordiFlex 10 mg/1.5 mL **EITHER** keep refrigerated (2-8°C/36-46°F) for 4 weeks **OR** store not above 25°C (77°F) for 3 weeks.
- When using a NordiFlex PenMate with a Norditropin NordiFlex 15 mg/1.5 mL keep refrigerated (2-8°C/36-46°F) for 4 weeks.
- Do not freeze. Norditropin **MUST NOT BE INJECTED** if the liquid is cloudy or contains particulate matter. Use it only if it is clear and colorless.
- Keep NordiFlex PenMate and Norditropin NordiFlex in the supplied case whenever possible. Inside the case you can also keep 3 extra NovoFine disposable needles.

18 Maintenance

Guidelines for maintaining NordiFlex PenMate and Norditropin NordiFlex:

Be sure to:

- Clean the outside surface by wiping it with a soft cloth moistened with a mild detergent.

- Protect NordiFlex PenMate and Norditropin NordiFlex from dust, dirt, and direct sunlight when not in its case.

Make certain that you:

- Handle NordiFlex PenMate and Norditropin NordiFlex with care. Do not drop it and avoid knocking it against hard surfaces.

- Do not soak NordiFlex PenMate and/or Norditropin NordiFlex in alcohol, wash, or lubricate it.

- Do not use Norditropin NordiFlex 30 mg/3 ml pens with the NordiFlex PenMate® auto-insertion accessory.
- Always screw Norditropin NordiFlex and NordiFlex PenMate tightly together.
- NordiFlex PenMate and Norditropin NordiFlex are not recommended for people who are blind or who have trouble seeing unless they have the help of a sighted individual trained to use NordiFlex PenMate and Norditropin NordiFlex.
- If your NordiFlex PenMate becomes lost or damaged, you can still use your Norditropin NordiFlex without NordiFlex PenMate.
- Keep Norditropin NordiFlex, NordiFlex PenMate and NovoFine disposable needles out of the reach of children.
- With Norditropin NordiFlex it is not possible to select a dose larger than the number of mg left in the cartridge.
- When using a NordiFlex PenMate with a Norditropin NordiFlex 5 mg/1.5 mL or a Norditropin NordiFlex 10 mg/1.5 mL **EITHER** keep refrigerated (2-8°C/36-46°F) for 4 weeks **OR** store not above 25°C (77°F) for 3 weeks.
- When using a NordiFlex PenMate with a Norditropin NordiFlex 15 mg/1.5 mL keep refrigerated (2-8°C/36-46°F) for 4 weeks. Do not freeze.
- NordiFlex PenMate and Norditropin NordiFlex are designed for use with NovoFine disposable needles.
- Novo Nordisk is not responsible for harm due to using NordiFlex PenMate and Norditropin NordiFlex with products that are not recommended by Novo Nordisk.

20 Important Notes

The following is a review of some important information about the use and care of your NordiFlex PenMate and Norditropin NordiFlex.

Before using a new Norditropin NordiFlex, be certain to:

- Always perform an air shot with the NovoFine disposable needle pointing upward.

Be sure to:

- Remove the NovoFine disposable needle immediately after each injection.
- Select your dose only by using the number in the dosage indicator window.
- Perform an air shot before injection if you dropped Norditropin NordiFlex or knocked it against a hard surface.

Make certain you:

- **NEVER** place a needle on Norditropin NordiFlex until you are ready to use it. Remove the needle immediately after each injection. If the NovoFine disposable needle is not removed, some liquid may leak out of Norditropin NordiFlex.
- Do not use the clicking sound to set your dose.
- Avoid dropping Norditropin NordiFlex or knocking it against hard surfaces.
- **DO NOT** leave Norditropin NordiFlex in a car or other location where it can get too hot or too cold.
- Always have a spare Norditropin NordiFlex in order to avoid running out of this product.
- Do not use the same Norditropin NordiFlex for more than one person, even if you attach a new NovoFine disposable needle for each injection. This will prevent the spread of disease. Each Norditropin NordiFlex is for single-person use only.

Here are the answers to some questions you might ask when using NordiFlex PenMate.

Question	Answer
No liquid appears at the needle tip when I perform an air shot	**The NovoFine disposable needle may not be securely attached.** • Put the plastic **outer** cap back on the NovoFine disposable needle. • Turn the plastic **outer** cap in a clock-wise direction to tighten the NovoFine disposable needle. **The needle may be blocked.** • Screw on a new NovoFine disposable needle and perform one or more air shots until a drop of liquid appears at the needle tip (see pages 8 to 9). **Norditropin NordiFlex may be damaged.** • Remove the NovoFine disposable needle carefully (see page 15). Unscrew Norditropin NordiFlex and replace it with a new Norditropin NordiFlex (see page 16). Attach a new NovoFine disposable needle, and perform an air shot (see page 8).
I want to change the selected dose before injection.	• Turn the dosage selector forwards or backwards until the number of milligrams you need lines up with the dosage indicator.
You think the needle has not entered the skin.	• Make sure the needle caps are removed. • Check that the needle is not bent. • Check NordiFlex PenMate for damage (that it is not broken or cracked) and that it works normally.

Question	Answer
I turn the dosage selector but Norditropin NordiFlex does not release any liquid.	**This is normal.** Always press the push button to inject the dose. Turning the dosage selector will not inject the dose.
The push button stops during the injection, before 0.0 lines up with the dosage indicator.	**The needle may be blocked.** You did not receive the selected dose. To complete your dose you must inject the remaining number of milligrams as described below: • Check the dosage indicator window. The number that lines up with the dosage indicator is the number of milligrams that you need to inject to complete your dose. Make a note of this number. • Turn the dosage selector until 0.0 lines up with the dosage indicator. • Screw on a new needle and perform an air shot as described on pages 6 to 9. • Select the number of milligrams you need to complete your dose. This is the number that you made a note of. Prepare NordiFlex PenMate as described on page 10. Inject as described on pages 11 to 14.

Question	Answer
When selecting a dose the dosage selector stops before I have selected the required number of milligrams.	**Either**, you are trying to select a dose larger than there is left in NordiFlex prefilled pen **or** you are trying to select a dose larger than the maximum dose for one injection. • If you need a dose larger than the number of milligrams left in the cartridge, follow the instructions on page 14. • If you need a dose larger than the maximum dose for one injection you must spread the dose over two injections.

24 What to do if…

Question	Answer
My Norditropin NordiFlex and/or my NordiFlex PenMate has been dropped or knocked.	• Unscrew Norditropin NordiFlex and pull it gently out of NordiFlex PenMate. Check that Norditropin NordiFlex is intact. • Make sure that the cartridge is intact, e.g. no cracks. • Screw NordiFlex PenMate and Norditropin NordiFlex together as described on page 5. • Screw on a new NovoFine disposable needle (see pages 6 to 7). • Perform an air shot (see pages 8 to 9).

If you have any questions, please call 1-888-NOVO-444.

Customer service and satisfaction are our top concerns. If you have any questions about NordiFlex PenMate or Norditropin NordiFlex prefilled pens please call Novo Nordisk Inc. at 1-888-NOVO-444.

Licensed under US Patents 5980491 and 6537252.

Designed and intended for use with Norditropin NordiFlex 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens, NordiFlex PenMate and NovoFine disposable needles.

If you need the LOT number of your NordiFlex PenMate it is located as illustrated in the diagram inside the cover.

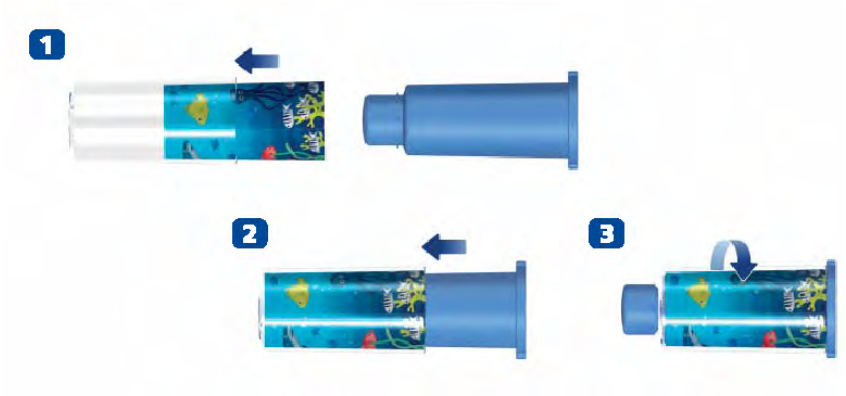
Inside Cover

- **Making your NordiFlex PenMate personal**

Making NordiFlex PenMate® Personal

Between the outer cap and the inner cap you can place a drawing or picture to give your NordiFlex PenMate a personal look.

You can cut out the illustration placed on the page to the right, create the drawing yourself or find illustrations on www.norditropin-us.com to print out.



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For assistance or further information,
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Princeton, NJ 08540
Visit norditropin-us.com
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