HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all 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·····

- Warnings and Precautions, Neoplasms (5.3) 9/2014

·····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 to 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 to 0.034 mg/kg/day, 6 to 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 to 0.30 mg/day) increased gradually every 1 to 2 months by increments of approximately 0.1 to 0.2 mg/day (2.2)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

·····DOSAGE FORMS AND STRENGTHS·····

Norditropin is preloaded in the Norditropin FlexPro pens (3):

- 5 mg/1.5 mL (orange): FlexPro pen
- 10 mg/1.5 mL (blue): FlexPro pen
- 15 mg/1.5 mL (green): FlexPro pen
- 30 mg/3 mL (purple): FlexPro pen

·····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)
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain. (5.14)

·····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 (1-888-668-6444) 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/Injectable Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2015

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 pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH).

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

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

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

Patients who were treated with somatropin for GHD in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for GHD adults. According to current standards, confirmation of the diagnosis of adult GHD 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 to 0.034 mg/kg/day, 6 to 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 to 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/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)

Either of two approaches to Norditropin dosing may be followed: a non-weight-based regimen or a weight-based regimen.

Non-weight based — based on published consensus guidelines, 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 to 2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor I (IGF-I) concentrations. The dose should be decreased as necessary on the basis of adverse events and/or serum IGF-I concentrations above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person, and between male and female patients.

Weight-based — based on the dosing regimen used in the original adult GHD registration trials, the recommended dosage at the start of treatment 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 concentrations should be used as guidance in dose titration.

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® FlexPro® 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 FlexPro 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

Norditropin is available preloaded in the Norditropin FlexPro pens:

- 5 mg/1.5 mL (orange): Norditropin FlexPro pen
- 10 mg/1.5 mL (blue): Norditropin FlexPro pen
- 15 mg/1.5 mL (green): Norditropin FlexPro pen
- 30 mg/3 mL (purple): Norditropin FlexPro pen

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
In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence [*see Contraindications* (4.3)]. Monitor all patients with a history of GHD secondary to an intracranial neoplasm routinely while on somatropin therapy for progression or recurrence of the tumor.

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms.

Monitor patients on somatropin therapy carefully for increased growth, or potential malignant changes, of preexisting nevi.

5.4 Impaired Glucose Tolerance and Diabetes Mellitus
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. New onset type 2 Diabetes Mellitus has been reported in patients. 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/injectable agents) may require adjustment when somatropin therapy is instituted in these patients.

5.5 Intracranial Hypertension
Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose.

Funduscopic examination should be performed routinely before initiating treatment with 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.

5.14 Pancreatitis

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops persistent severe abdominal pain.

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)]*
- Pancreatitis *[see Warnings and Precautions (5.14)]*

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 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.

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

In clinical trials, GHD pediatric patients receiving Norditropin for up to 12 months were tested for induction of antibodies, and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Amongst these patients, 165 had previously been treated with other somatropin formulations, and 193 were previously untreated naive patients.

6.3 Post-Marketing Experience

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 and adults *[see Warnings and Precautions (5.14)]*).

New-onset type 2 diabetes mellitus has been reported.

7 DRUG INTERACTIONS

7.1 Inhibition of 11β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1)

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH and somatropin inhibit 11βHSD-1. Consequently, individuals with untreated GHD have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. As a consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment; 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 11βHSD-1.

7.2 Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment

Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement dosing should be carefully adjusted in children receiving concomitant somatropin and glucocorticoid treatments 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

Because oral estrogens may reduce the serum IGF-1 response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages *[see Dosage and Administration (2.2)]*.

7.5 Insulin and/or Oral/Injectable Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable 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 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 is supplied as a sterile solution for subcutaneous injection in ready-to-administer 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/3 mL
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.

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 $\geq 3^{rd}$ 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 $< 3^{rd}$ percentile for gestational age, and height velocity (cm/year) for chronological age $< 50^{th}$ 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 $\leq$ -2 or $< 10^{th}$ percentile for gestational age, height SDS for chronological age $\leq$ -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 (n=36)	Placebo (n=13)
Baseline (mean)	48.18	48.90
Change from baseline at 6 months (mean)	2.06	0.70
Treatment difference (mean) 95% confidence interval p-value	1.40 (0.39, 2.41) p=0.0079	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0048) in the Norditropin-treated groups (pooled data) compared to the placebo group (Table 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 FlexPro 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 FlexPro is individually cartoned as 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL or 30 mg/3 mL prefilled pens.

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

Norditropin FlexPro 5 mg/1.5 mL (orange),10 mg/1.5 mL (blue), 15mg/1.5 mL (green), and 30 mg/3 mL (purple) prefilled pens:

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

After the initial injection, a Norditropin FlexPro prefilled pen may be **EITHER** stored in the refrigerator (2°C-8ºC/36°F-46ºF) and used within 4 weeks **OR** stored for up to 3 weeks at room temperature not more than 25ºC (77ºF). Discard unused portion.

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			
15 mg			
30 mg			

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Patients being treated with Norditropin FlexPro 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 FlexPro 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 FlexPro, physicians should instruct patients to read the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflets provided with the Norditropin FlexPro prefilled pens.

17.1 Never Share a Norditropin Pen Between Patients

Counsel patients that they should never share a Norditropin pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

For information contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536, USA
1-888-668-6444

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

INSTRUCTIONS FOR USE

Norditropin® (Nor-dee-tro-pin) **FlexPro**®
(somatropin [rDNA origin] injection)
Prefilled Pen with PenMate®

Read this Instructions for Use before you start using your Pen with PenMate.

- PenMate hides the needle when you inject your Norditropin growth hormone with Norditropin FlexPro 5 mg, 10 mg, and 15 mg Pens so that you cannot see it. Use your PenMate only after you have been trained by a healthcare provider.

- Blind people or people with severe vision problems should only use the PenMate and Pen with help from another person with good eyesight who is trained to use the PenMate and Pen.

- The figures in these instructions show PenMate being used with a Norditropin FlexPro 5 mg Pen and a NovoFine needle that is **8 mm** long. Even if you are using a 10 mg or 15 mg Pen or a different needle that is **8 mm** long the instructions are the same.

- **Do not** share your Norditropin Pen and needles with another person. You may give another person an infection or get an infection from them.

Supplies you will need to use your Pen with PenMate:

- 1 PenMate. **See figure A.**
- 1 Norditropin FlexPro Pen. **See figure B.** PenMate does not work with other injection devices.
- 1 disposable needle up to a length of **8 mm. See figure C.** Needles are not included with your PenMate or Pen.
- 2 alcohol swabs. **See figure C.**
- a sharps disposal container. **See figure C.** See **"How should I dispose of my Pen and needles"** at the end of these instructions for information on how to dispose of used needles.

PenMate:

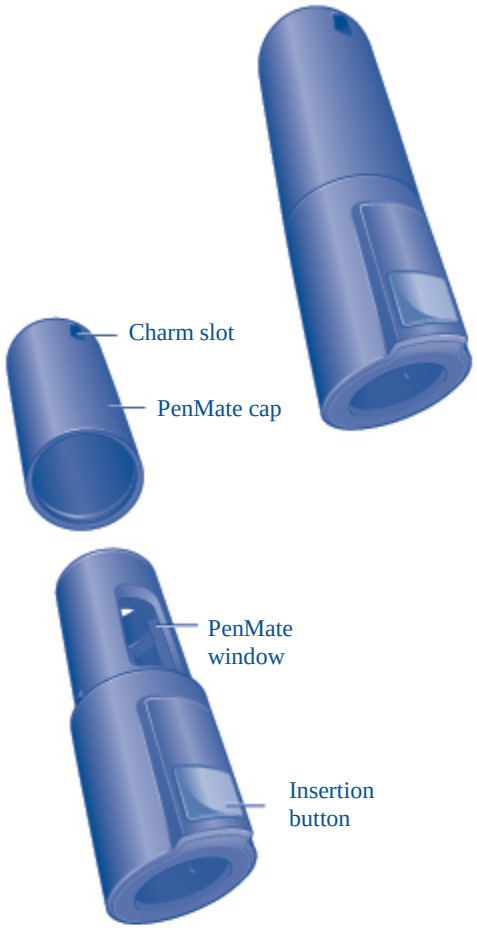

Figure A

Norditropin FlexPro 5 mg, 10 mg or 15 mg Pen:

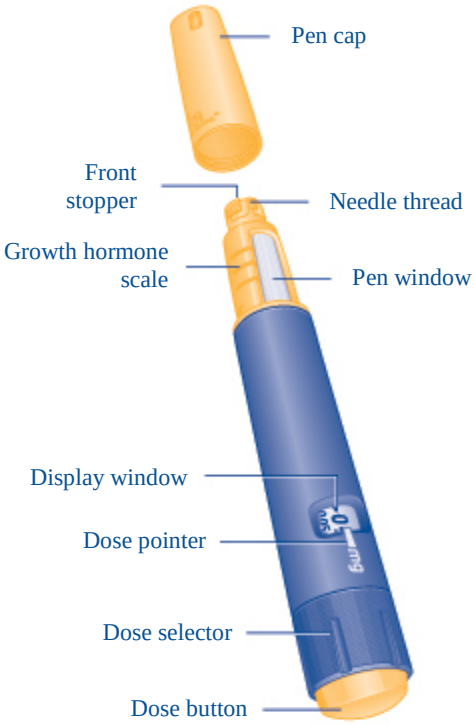

Figure B

Needle parts:

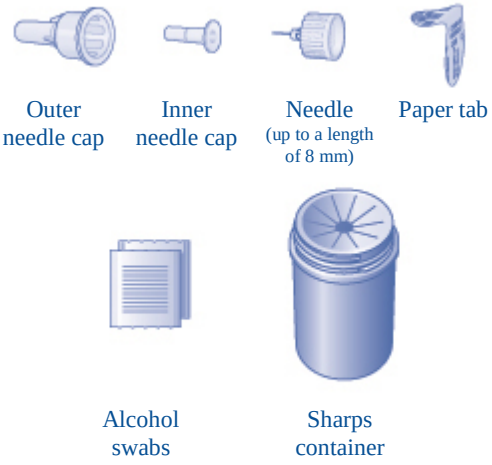

Figure C

Pen case:

Pen and needles are not included in the case.

Figure D

Step 1: Preparing your Pen with PenMate:

Wash your hands with soap and water and dry them. Check the name and the colored label on your Pen to make sure it contains the growth hormone strength prescribed by your healthcare provider.

Pull off the PenMate cap.
See figure E.

Figure E

Pull off the Pen cap and throw it away.
See figure F.

You will not need the Pen cap with your PenMate.

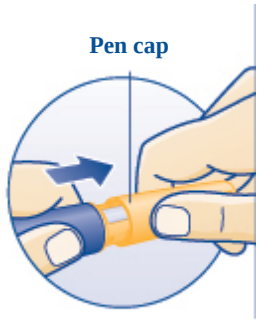

Figure F

Look in the Pen window. Check that the liquid medicine in your Pen is clear and colorless by tipping it upside down 1 or 2 times.
See figure G.

If the liquid looks cloudy or unclear, do not use the Pen.

Figure G

Wipe the front stopper on the needle thread of the Pen with an alcohol swab.
See figure H.

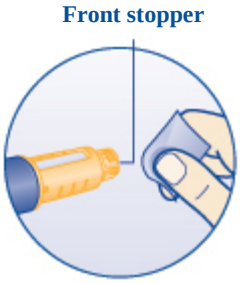

Figure H

Insert the Pen into the PenMate. Twist the Pen clockwise until you hear or feel a click.
See figure I.

The Pen is correctly attached in your PenMate when the display window on the Pen lines up with the insertion button on your PenMate.

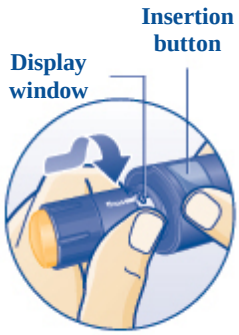

Figure I

Step 2. Attaching the needle to your Pen:

- **Do not** place a needle on your Pen until you are ready to give an injection.
- Always use a new needle for each injection.
- **Do not** use a bent or damaged needle.

Take a new disposable needle and tear off the paper tab.
See figure J.

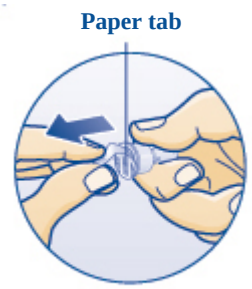

Figure J

Holding the Pen with 1 hand, firmly press the needle onto the needle thread of the Pen. Screw the needle in a clockwise direction until the needle will not turn anymore.
See figure K.

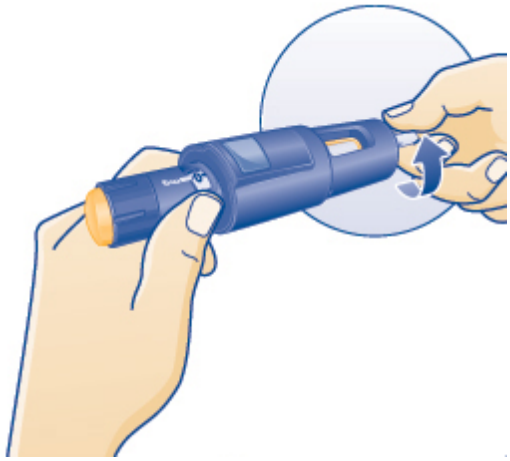

Figure K

Pull off the outer needle cap and save it.
See figure L.

You will need the outer needle cap after the injection so you can safely remove the needle from the Pen.

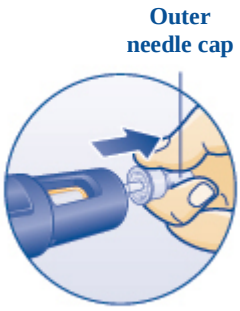

Figure L

Pull off the inner needle cap and throw it away.
See figure M.

A drop of liquid may appear at the needle tip. This is normal.

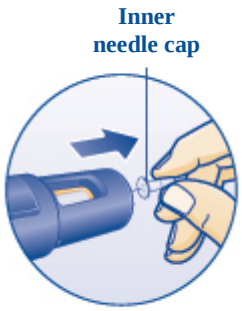

Figure M

Step 3. Priming a new Pen:

Checking the growth hormone flow in the Pen (priming) is not needed for a Pen you have used before. If the Pen has already been primed, go to Step 4.

Before you use a new Pen you must prepare it for use. Hold the Pen with 1 hand and turn the dose selector clockwise 1 tick mark to select the **minimum dose.**
See figure N.

You may hear or feel a click when you turn the dose selector.

Figure N

When you turn the dose selector 1 tick mark, you select the smallest amount of medicine for a dose.
See figure O.

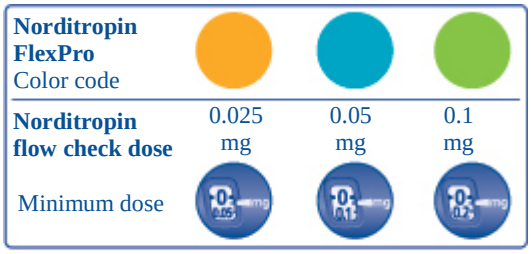

Figure O

This lowest dose will be used for your Norditropin flow check dose.

Hold your Pen with PenMate with the needle pointing up. You may see air bubbles in the PenMate window. Gently tap the top of PenMate a few times to let any air bubbles rise to the top.
See figure P.

Figure P

Press the dose button until the dose pointer lines up with the **“0”** in the display window on the Pen and a drop of liquid appears at the needle tip.
See figure Q.

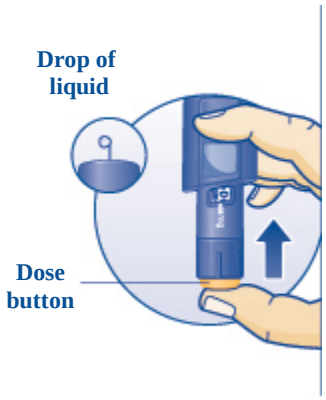

Figure Q

If no drop of liquid appears at the needle tip, repeat Step 3 again up to 6 times.

If there is still no drop of liquid at the needle tip, **change the needle** and repeat Step 3 again.

If a drop of liquid still does not appear at the needle tip after repeating Step 3 and changing the needle, call Novo Nordisk at 1-888-668-6444 for assistance.

Step 4. Selecting the correct dose of Norditropin:

Use the dose selector on your Pen to make sure you have the exact dose selected. Your dose will be in a certain number of mg (milligrams).

To start, check that the dose pointer on the Pen is set at **"0".**

Select the dose you need by turning the dose selector clockwise. If you go beyond your dose, turn the dose selector counterclockwise until the right number of mg lines up with the dose pointer. **See figure R.**

Figure R

To guide you, the dose selector click sound is different when turned clockwise (softer click) or counterclockwise (louder click). You will hear a click for every single unit dialed.

When dialing counterclockwise, be careful not to press the dose button as liquid will come out.

You can use the growth hormone scale on the side of the Pen to see approximately how much growth hormone is left in the Pen. You can also use the dose selector to see exactly how much growth hormone is left in the Pen.

If the Pen contains less than 2 mg, 4 mg, or 8 mg (depending on whether you use a 5 mg, 10 mg, or 15 mg Pen), turn the dose selector until it stops. The number that lines up with the dose pointer shows how many mg are left in the Pen. You cannot set a dose higher than the number of mg left in the Pen.

If there is not enough Norditropin left in the Pen for your full dose, use a new Norditropin FlexPro Pen to inject the remaining amount of your dose or contact your healthcare provider.

Remember to subtract the dose already received. For example, if the dose is 0.7 mg and you can only set the dose selector to 0.35 mg, you should inject another 0.35 mg with a new Norditropin FlexPro Pen.

Important:

Do not use the Pen clicks to count the number of mg you select. Only the display window and dose pointer will show the exact number.

Do not use the growth hormone scale to measure how much liquid to inject. Only the display window and dose pointer will show the exact number.

Step 5. Selecting your injection site and injecting the dose of Norditropin:

Change your injection site every day. Select the injection site and wipe your skin with an alcohol swab as your healthcare provider showed you.

Norditropin can be injected under your skin (subcutaneously) of your hips, stomach area (abdomen), upper legs (thighs), upper arms, or as otherwise instructed by your healthcare provider.
See Figure S.

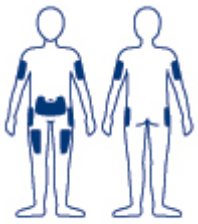

Figure S

Hold onto both the PenMate and your Pen without touching the insertion button on the PenMate **or** the dose button on the Pen.

Do not press the insertion button on the PenMate before you are ready to inject your dose. This lowers the risk of hurting yourself with the needle.

Hold the PenMate firmly with 1 hand and pull the Pen out with your other hand until you hear and feel a click. **See figure T.**

The needle is now hidden in PenMate.

Figure T

Norditropin is for use under your skin only (subcutaneous). Hold the PenMate against your skin. Press the insertion button on the PenMate until you hear or feel a click.
When you hear or feel the click, the needle has been inserted automatically into your skin. **See figure U.**

You are now ready to inject your dose.

Figure U

Press the dose button on the Pen to inject your dose. Do not turn the dose button while you are pressing it. If you turn the dose button, you will not inject growth hormone.

Make sure you can see the display window. **Do not** cover it with your fingers.
Press and hold down the dose button on the Pen until the display window returns to "0".

The **"0"** must line up with the dose pointer. You may then hear or feel a firm click.
See figure V.

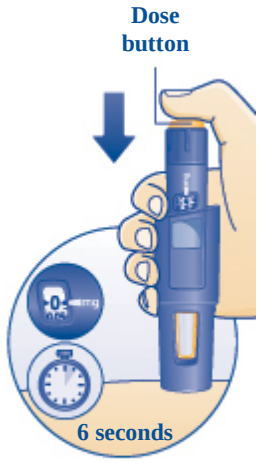

Figure V

If the dose button cannot be pushed in completely or "0" does not appear in the display window, you did not receive the full dose. Call Novo Nordisk at 1-888-668-6444 for assistance. You may need a new Pen.

After the display window has returned to "0", leave the needle under your skin for at least 6 seconds to make sure you get your full dose.
See figure V.

Let go of the dose button while you wait.

Important:
Always press the dose button to inject the dose. Turning the dose selector will not inject the dose.

Do not touch the display window when you inject, as this can block the injection.

Carefully lift the Pen to remove the needle from the skin.
See figure W.

Figure W

Step 6. What to do after your injection is completed:

Carefully put the outer needle cap back on the needle.
Remove the needle from the Pen after each injection.
See figure X.

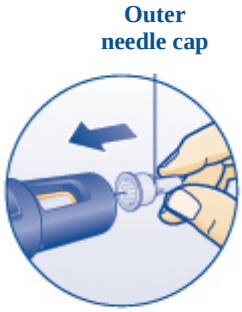

Figure X

Unscrew the needle by turning it counterclockwise. Do not touch the needle. Hold the Pen with 1 hand and carefully remove the needle from the Pen with your other hand.
See figure Y.

Dispose of the needle as directed by a healthcare provider. See **"How should I dispose of my Pen and needles?"** at the end of these instructions.

Figure Y

Put the PenMate cap back on your PenMate after each use to protect the growth hormone from light.
See figure Z.

Figure Z

Important safety information to remember:

- Be careful not to drop your PenMate and Pen or knock them against a hard surface. If this happens you will need to check the growth hormone flow.
- **Do not** try to put the inner needle cap back on the needle. You may stick yourself with the needle. Be careful when handling used needles to avoid needle stick injuries.
- After each use always remove and dispose of the needle from your Pen.
- **Do not** share your Pen or needles with other people.
- If your PenMate is damaged or lost, you can still use your Pen without your PenMate.
- Always keep your Pen and needles out of reach of others, especially children.

How should I replace an empty Pen?

PenMate is reusable and should not be disposed of. Reuse your PenMate by replacing your Pen when it is empty.

When your Pen is empty, **twist the Pen** until you hear or feel a click.
See figure AA.

Figure AA

Gently pull the Pen out of PenMate.
See figure BB.

Before disposing of your empty Pen, make sure the needle has been removed. Dispose of the empty Pen as recommended by your healthcare provider. See **"How should I dispose of my Pen and needles?"** at the end of these instructions.

Figure BB

Insert the new Pen into your PenMate.
See figure CC.

Figure CC

Twist the Pen until you hear or feel a click.
See figure DD.

The Pen is correctly attached in your PenMate when the display window on the Pen lines up with the insertion button on your PenMate.

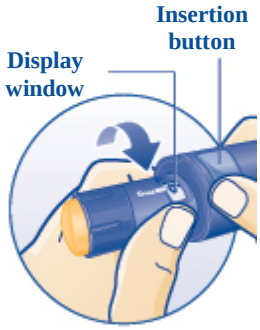

Figure DD

How should I store my PenMate and Pen?

- Do not expose your PenMate or Pen to dust, dirt, or any kind of liquid.
- Store your PenMate and Pen in their case. See figure D at the beginning of these instructions.
- When your Pen is inserted in PenMate, store it as described in the Patient Information Leaflet that comes with your Pen.

How should I care for and clean my Pen with PenMate?

- **Do not** try to refill your Pen. It is prefilled.
- **Do not** try to repair your PenMate or your Pen.
- Only clean your PenMate or Pen with a mild detergent on a moistened cloth.
- **Do not** wash, soak, or lubricate your PenMate or Pen. Do not use products containing bleaching agents, such as chlorine, iodine, or alcohol to clean your PenMate or Pen. These products may damage them.
- If there is liquid growth hormone on the outside of your PenMate or Pen, clean it with a mild detergent on a moistened cloth **before it dries up.**

How should I dispose of my Pen and needles?

- Put your used needles and Pens in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and Pens in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,

  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and Pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Need help?

PenMate must only be used according to the instructions provided. The manufacturer cannot be held responsible for any problems with PenMate if these instructions have not been followed.

If you find that your PenMate or case is defective, make sure to have Novo Nordisk replace it. Call the number below to order a new PenMate or case and arrange return of the defective item for inspection.

For assistance or further information, write to:

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

Visit norditropin-us.com

Or call: 1-888-668-6444

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Issued: [Month] [Year]

Norditropin® FlexPro® PenMate®

INSTRUCTIONS FOR USE