Novo Nordisk

PRODUCT INFORMATION

Norditropin® cartridges

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

Rx Only

DESCRIPTION

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

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

Each **Norditropin cartridge** contains the following:

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

CLINICAL PHARMACOLOGY

a. Tissue Growth

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

1. Skeletal growth – the measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGF). The somatomedins, among them IGF-I, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-I levels are low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, but its presence can be demonstrated after treatment with somatropin.

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

3. Organ growth – somatropin influences the size of internal organs, and it also increases red cell mass.

b. Protein Metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention which can be quantitated by observing the decline in urinary nitrogen excretion and blood urea nitrogen following the initiation of somatropin therapy.

c. Carbohydrate Metabolism

Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, large doses of somatropin may impair glucose tolerance. Although the precise mechanism of the diabetogenic effect of somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase. Administration of human growth hormone to normal adults and patients with growth hormone deficiency results in increases in mean serum fasting and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A_{1C} levels remain in the normal range.

d. Lipid Metabolism

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

e. Mineral Metabolism

Administration of somatropin results in the retention of total body potassium and phosphorus and to a lesser extent sodium. This retention is thought to be the result of cell growth. Serum levels of phosphate increase in patients with growth hormone deficiency after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

f. Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

g. Pharmacokinetics

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

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

Norditropin cartridge formulation is bioequivalent to Norditropin vial formulation.

CLINICAL STUDIES

Adult Growth Hormone Deficiency (GHD)

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

CLINICAL STUDIES

Adult Growth Hormone Deficiency (GHD)

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

Study 1

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

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

Table 1 – Lean Body Mass (kg) by TBP

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

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

Table 2 – Total Body Fat (%) by TBP

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

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

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

Study 2

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

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

Table 3 – Lean Body Mass (kg) by TBP

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

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

Table 4 – Total Body Fat (%) by TBP

	Norditropin (n=36)	Placebo (n=13)

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

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

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

INDICATIONS AND USAGE

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

Adult Patients:
Norditropin is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

1. Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma;

or

2. Childhood Onset: Patients who were growth hormone deficient during childhood should have growth hormone deficiency confirmed as an adult before replacement therapy with Norditropin is started.

In both of these patient populations, growth hormone deficiency should be confirmed by an appropriate growth hormone stimulation test.

CONTRAINDICATIONS

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

In general, somatropin is contraindicated in the presence of active neoplasia. Any pre-existing neoplasia should be inactive and its treatment complete prior to instituting therapy with Norditropin. Norditropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Norditropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial space-

occupying lesion. Available information suggests that the rate of tumor recurrence is not increased by growth hormone therapy.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions 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).

Norditropin is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.

Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see WARNINGS). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Norditropin is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

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

WARNINGS

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

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure. The safety of continuing growth hormone 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 growth hormone in patients experiencing acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with growth hormone 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 growth hormone. If, during treatment with growth hormone, 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 growth hormone should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (see CONTRAINDICATIONS). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Norditropin is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

PRECAUTIONS

General

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

Because somatropin may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Somatropin products should be used with caution in patients with diabetes mellitus or a family history of diabetes mellitus. In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated.

Hypothyroidism may develop during Norditropin therapy. Untreated hypothyroidism will jeopardize the response to growth hormone. Therefore, thyroid hormone determinations should be performed periodically during Norditropin administration and thyroid hormone replacement therapy should be initiated when indicated.

In patients with hypopituitarism and multiple hormone deficiencies, standard hormonal replacement therapy should be monitored closely when Norditropin therapy is initiated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. IH has been reported more frequently after treatment with IGF-I. Symptoms usually occur within the first eight weeks after the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved rapidly after temporary suspension or termination of therapy. Funduscopic examination should be performed routinely before initiating treatment with Norditropin to exclude preexisting papilledema and periodically during the course of Norditropin therapy. If papilledema is observed by funduscopy during Norditropin treatment, treatment should be stopped. If idiopathic IH is confirmed, treatment with Norditropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved.

Patients with growth hormone deficiency secondary to an intracranial lesion should be evaluated frequently in order to detect progression or recurrence of the underlying disease process.

When growth hormone is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site. As is the case with any protein product, local or systemic allergic reactions may occur. Parents/Patient should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Pediatric Patients (see General Precautions)

Bone age should be monitored periodically during Norditropin administration, especially in patients who are pubertal and/or receiving concomitant thyroid hormone replacement therapy. Under these circumstances, epiphyseal maturation may progress rapidly.

Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Norditropin. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully monitored to avoid an inhibitory effect on growth.

Patients with endocrine disorders, including growth hormone deficiency may have an increased incidence of slipped capital femoral epiphysis. Any child who develops a limp or complains of hip or knee pain during growth hormone therapy should be evaluated.

Progression of scoliosis can occur in children who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis.

Adult Patients (see General Precautions)
Patients with epiphyseal closure who were treated with growth hormone replacement therapy in childhood should be reevaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the reduced dose level recommended for growth hormone deficient adults. Fluid retention during growth hormone replacement therapy in adults may occur. Clinical manifestations of fluid retention are usually transient and dose dependent (see ADVERSE REACTIONS).

Experience with prolonged treatment in adults is limited.

Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, and IGF-I may increase after Norditropin therapy.

Drug Interactions
Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Norditropin. Published *in vitro* data indicate that growth hormone may be an inducer of cytochrome P450 3A4. When growth hormone is administered in combination with drugs known to be metabolized by cytochrome P450 3A4 hepatic enzymes, it is advisable to monitor the clinical effectiveness of such drugs. However, formal drug interaction studies have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin.

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

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

Geriatric Use

The safety and effectiveness of Norditropin in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of Norditropin, and may be more prone to develop adverse reactions.

Information For Patients

Patients being treated with Norditropin and/or their caregivers should be informed about the potential benefits and risks associated with treatment. If home use is determined to be desirable by the physician, instructions on appropriate use should be given. This information is intended to aid in the safe and effective administration of the medication. It is not a disclosure of all possible adverse or intended effects.

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

If home use is prescribed, a puncture resistant container for the disposal of used needles should be recommended to the patient. Patients and/or caregivers should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles.

ADVERSE REACTIONS

Growth Hormone Deficient Pediatric Patients

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

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

Fluid retention and peripheral edema may occur.

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

Growth Hormone Deficient Adult Patients

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

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

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

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

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

OVERDOSAGE

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

Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

DOSAGE AND ADMINISTRATION

Pediatric Patients

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

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

Adult Patients

For adult growth hormone deficient patients, the recommended dosage at the start of therapy is not more than 0.004 mg/kg/day. The dosage may be increased as tolerated to not more than 0.016 mg/kg/day after approximately 6 weeks. In addition to adverse effects, determination of age- and gender-adjusted serum IGF-I levels and clinical response (e.g., body composition assessments) may be used to help guide dose titration. This approach will tend to result in doses that are larger for women compared with men, and smaller for AO growth hormone deficient patients compared with CO growth hormone deficient patients as well as older and obese patients.

All Patients

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

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

Measuring The Prescribed Dose

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

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

STABILITY AND STORAGE

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

Norditropin cartridges retain their biological potency until the date of expiry indicated on the label. After a Norditropin cartridge has been inserted into the NordiPen injector, it must be stored in the pen in the refrigerator and used within 4 weeks. Discard unused portion after 4 weeks.

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

The Norditropin NordiFlex prefilled pens retain their biological potency until the date of expiry indicated on the label. After the initial injection, Norditropin NordiFlex prefilled pens must be stored in the refrigerator and used within 4 weeks. Discard unused portion after 4 weeks.

HOW SUPPLIED

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

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

mg/1.5 mL, and 15 mg/1.5 mL:
Norditropin NordiFlex is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL prefilled pens.

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

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Novo Nordisk

PATIENT INFORMATION

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
15 mg/1.5 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. Do not freeze it or expose it to heat.

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 6 air shots before the first injection.

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

What is Norditropin NordiFlex®?

Norditropin® is a clear and colorless solution used to treat children with growth failure caused by very low or no production of growth hormone, as well as adults who lack growth hormone.

Norditropin® is injected using the Norditropin NordiFlex®, a multi-dose disposable 1.5 mL pre-filled pen. Norditropin NordiFlex® contains several doses of growth hormone solution. A dose is injected into the thigh in the evening 6-7 times a week.

Norditropin NordiFlex® is available in three strengths: 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL (i.e. 3.3 mg/mL, 6.7 mg/mL and 10.0 mg/mL respectively).

Throw away the Norditropin NordiFlex® when the cartridge is empty.

Medicines are sometimes prescribed for purposes other than those listed in a patient guide. Patients should ask their doctor about any concerns and refer to the professional labeling for additional information.

What does Norditropin NordiFlex® contain?

The cartridge in Norditropin NordiFlex® contains human growth hormone called somatropin (so-ma-tro-pin) made through biotechnology. It is identical to the growth hormone produced in the human body.

The cartridge contains other ingredients: Histidine, Poloxamer 188, Phenol, Mannitol and Water for Injection.

Who should not take 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
- allergic to phenol or any other ingredients in the medicine
- had a kidney transplant
- pregnant
- breast-feeding
- cancer or other forms of tumor
- acute critical illness

What should you consider if you are pregnant or breast-feeding?
If you become pregnant while you are receiving Norditropin NordiFlex®, you are recommended to stop the treatment and discuss this with your doctor.

You are recommended not to take Norditropin NordiFlex® while you are breast-feeding because somatropin might pass into your milk.

Be sure to tell your doctor if you:

- have diabetes mellitus
- had cancer or other forms of tumor

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

How should I take Norditropin NordiFlex®?

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

You should inject Norditropin NordiFlex® in the thigh in the evening just before bedtime. You should change the injection area on the thigh 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: 0.024 to 0.034 mg/kg body weight, 6-7 times a week.

Adults: 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.

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 if you want to stop taking Norditropin®.

What should I avoid while taking Norditropin NordiFlex®?

Be sure to tell your doctor about all of the medication you are taking especially if you are taking:
a glucocorticoid medication such as hydrocortisone or cortisone acetate
thyroid hormone
insulin

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, your insulin dose may need to be adjusted.

What are the possible or reasonably likely side effects of Norditropin NordiFlex®?

The following side effects are usually mild and temporary:

- headaches
- muscle pain
- joint stiffness
- weakness
- 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, you may need to reduce your dose. Discuss this with your doctor.

In rare cases you may develop antibodies to growth hormone or suffer raised pressure within the brain. If you get headaches, eyesight problems, feel sick or vomit, contact your doctor as these complaints could be signs of raised pressure within your brain.

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 somatropin have experienced pain in the hip or knee or a limp. These symptoms may be caused by slipped capital femoral epiphysis (the end of the bone slips from the cartilage).

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.

Patients should have periodic thyroid function tests.

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

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

How to store Norditropin NordiFlex®?

Store non-injected/unused Norditropin NordiFlex® in a refrigerator (2°C - 8°C/36°F - 46°F). Do not freeze or expose it to heat. Avoid direct light.

After the initial injection, Norditropin NordiFlex® 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 excessive temperatures.

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

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

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

Date of issue: October/2004

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

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

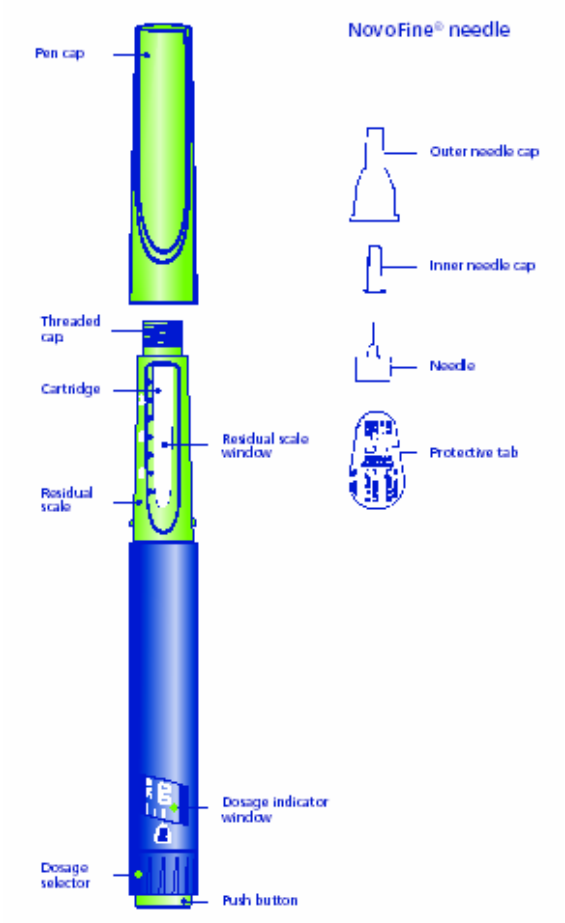
INSTRUCTIONS FOR USE

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
15 mg/1.5 mL Prefilled Pen

Using the disposable Norditropin NordiFlex® 15 mg/1.5 mL Prefilled Pen

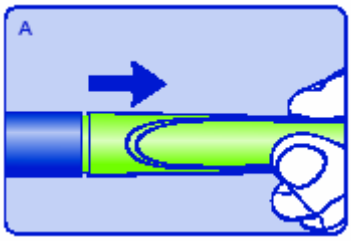
Norditropin NordiFlex® 15 mg/1.5 mL is a disposable dial-a-dose growth hormone delivery system able to deliver doses from 0.075 to 4.5 mg. The dose can be adjusted in increments of 0.075 mg. Your doctor will determine the correct dose for you. Norditropin NordiFlex® prefilled pen is designed to be used 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 the Norditropin NordiFlex®.

Please read these instructions carefully before using this device

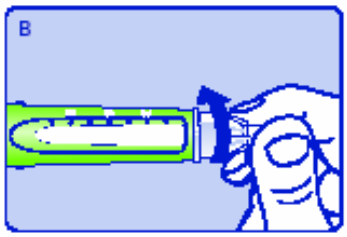


1 Preparing Norditropin NordiFlex® 15 mg/1.5 mL for injection

A. Wash hands well. Pull off the pen cap and wipe the front rubber stopper on the threaded plastic cap with an alcohol swab. **DO NOT use Norditropin NordiFlex® if the growth hormone solution is cloudy or contains particles. Use it only if it is clear and colorless.** Check this by turning the Norditropin NordiFlex® upside down once or twice and view the solution through the residual scale window.

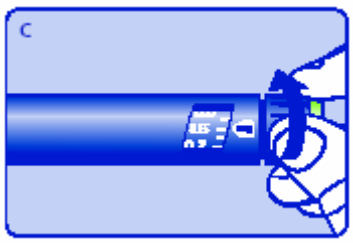


B. Place the NovoFine® needle onto the Norditropin NordiFlex® immediately before use. Remove the protective tab from the disposable needle and screw the needle tightly onto Norditropin NordiFlex®. Pull off the outer and inner needle caps. Never place a disposable needle on your Norditropin NordiFlex®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

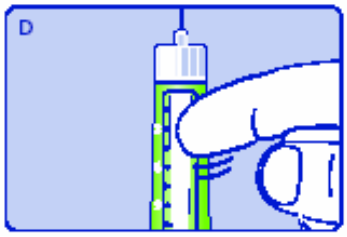


C. Do an air shot before each injection as follows:
Small amounts of air may collect in the needle and cartridge during normal use. To avoid injecting air and ensure proper dosing, set the dosage selector to 0.15 mg. Each line between labeled dosages is 0.075 mg.

Dial 0.15 mg

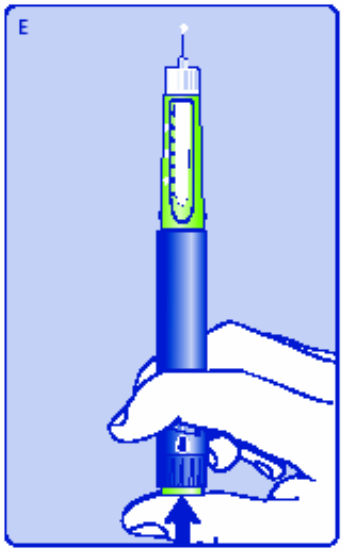


D. Hold Norditropin NordiFlex® with the needle pointing up, tap the cartridge gently with your finger a few times to raise any air bubbles to the top of the cartridge.



E. Still holding Norditropin NordiFlex® with the needle up, press the push button all the way in. A drop of growth hormone should appear at the needle tip. If not, repeat the procedure, no more than 6 times.

IF A DROP OF GROWTH HORMONE STILL DOES NOT APPEAR, CALL 1-888-NOVO-HGH FOR HELP.

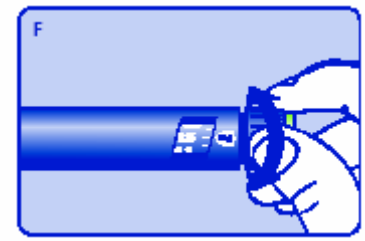


2 Setting the dose

F. Check that the dose selector is set at **0.0**. Dial the number of mg that you need to inject. 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 growth hormone liquid will come out.
DO NOT use the clicking sound as a guide for selecting 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 GROWTH HORMONE 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.

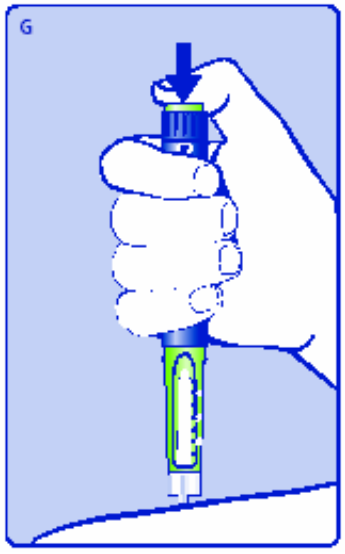


3 Giving the injection

Use the injection procedure recommended by your doctor or health care professional.

G. This product is for subcutaneous use only. Insert the needle into your thigh and deliver the dose by pressing the push button all the way in. Press the push button only when injecting.

AFTER THE INJECTION, THE NEEDLE SHOULD REMAIN UNDER THE SKIN FOR AT LEAST 6 SECONDS. KEEP THE PUSH BUTTON FULLY DEPRESSED UNTIL THE NEEDLE IS REMOVED FROM THE SKIN. THIS WILL ENSURE THAT THE FULL DOSE HAS BEEN DELIVERED. VARY THE INJECTION SITE ON THE THIGH USING THE INJECTION PROCEDURE RECOMMENDED BY YOUR DOCTOR.



4 Removing the 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. HEALTH CARE PROFESSIONALS, RELATIVES AND OTHER CAREGIVERS SHOULD FOLLOW GENERAL PRECAUTIONARY MEASURES FOR REMOVAL AND DISPOSAL OF NEEDLES TO ELIMINATE THE RISK OF UNINTENDED NEEDLE STICK.

When the cartridge is empty, throw away the Norditropin NordiFlex® without the needle attached.

5 Maintenance

Norditropin NordiFlex® should be handled with care. Protect Norditropin NordiFlex® from dust, dirt, and direct sunlight.

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

6 Important Notes

- Store non-injected/unused Norditropin NordiFlex® pens in a refrigerator (2ºC-8ºC/36ºF-46ºF). After the initial injection, keep the pen refrigerated and use within 4 weeks.
- Remember to perform an air shot before each injection. See diagrams **C, D** and **E**.
- If you need to perform more than 6 air shots before the first use of the Norditropin NordiFlex® to get a droplet of growth hormone at the needle tip, **DO NOT** use the Norditropin NordiFlex®. *Call 1-888-NOVO-HGH for help.*
- Take care not to drop the Norditropin NordiFlex®.
- **DO NOT** leave the 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 NovoFine® needle on the Norditropin NordiFlex® until you are ready to use it. Remove the needle right after use without recapping.
- **Throw away used needles properly, so people will not be harmed.**
- Throw away the 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.**

7 Warranty

If your Norditropin NordiFlex® is defective in materials or workmanship, Novo Nordisk Pharmaceuticals, Inc. will replace it at no charge if you mail the defective unit, postage prepaid to:

Novo Nordisk Pharmaceuticals, Inc.
Product Safety
100 College Road West
Princeton, NJ 08540, USA

Novo Nordisk

PATIENT INFORMATION

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
10 mg/1.5 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. Do not freeze it or expose it to heat.

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 6 air shots before the first injection.

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

What is Norditropin NordiFlex®?

Norditropin® is a clear and colorless solution used to treat children with growth failure caused by very low or no production of growth hormone, as well as adults who lack growth hormone.

Norditropin® is injected using the Norditropin NordiFlex®, a multi-dose disposable 1.5 mL pre-filled pen. Norditropin NordiFlex® contains several doses of growth hormone solution. A dose is injected into the thigh in the evening 6-7 times a week.

Norditropin NordiFlex® is available in three strengths: 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL (i.e. 3.3 mg/mL, 6.7 mg/mL and 10.0 mg/mL respectively).

Throw away the Norditropin NordiFlex® when the cartridge is empty.

Medicines are sometimes prescribed for purposes other than those listed in a patient guide. Patients should ask their doctor about any concerns and refer to the professional labeling for additional information.

What does Norditropin NordiFlex® contain?

The cartridge in Norditropin NordiFlex® contains human growth hormone called somatropin (so-ma-tro-pin) made through biotechnology. It is identical to the growth hormone produced in the human body.

The cartridge contains other ingredients: Histidine, Poloxamer 188, Phenol, Mannitol and Water for Injection.

Who should not take 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
- allergic to phenol or any other ingredients in the medicine
- had a kidney transplant
- pregnant
- breast-feeding
- cancer or other forms of tumor
- acute critical illness

What should you consider if you are pregnant or breast-feeding?
If you become pregnant while you are receiving Norditropin NordiFlex®, you are recommended to stop the treatment and discuss this with your doctor.

You are recommended not to take Norditropin NordiFlex® while you are breast-feeding because somatropin might pass into your milk.

Be sure to tell your doctor if you:

- have diabetes mellitus
- had cancer or other forms of tumor

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

How should I take Norditropin NordiFlex®?

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

You should inject Norditropin NordiFlex® in the thigh in the evening just before bedtime. You should change the injection area on the thigh 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: 0.024 to 0.034 mg/kg body weight, 6-7 times a week.

Adults: 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.

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 if you want to stop taking Norditropin®.

What should I avoid while taking Norditropin NordiFlex®?

Be sure to tell your doctor about all of the medication you are taking and especially if you are taking:
a glucocorticoid medication such as hydrocortisone or cortisone acetate
thyroid hormone
insulin

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, your insulin dose may need to be adjusted.

What are the possible or reasonably likely side effects of Norditropin NordiFlex®?

The following side effects are usually mild and temporary:

- headaches
- muscle pain
- joint stiffness
- weakness
- 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, you may need to reduce your dose. Discuss this with your doctor.

In rare cases you may develop antibodies to growth hormone or suffer raised pressure within the brain. If you get headaches, eyesight problems, feel sick or vomit, contact your doctor as these complaints could be signs of raised pressure within your brain.

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 somatropin have experienced pain in the hip or knee or a limp. These symptoms may be caused by slipped capital femoral epiphysis (the end of the bone slips from the cartilage).

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.

Patients should have periodic thyroid function tests.

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

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

How to store Norditropin NordiFlex®?

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

After the initial injection, Norditropin NordiFlex® 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 excessive temperatures.

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

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

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

Date of issue: October/2004

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

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

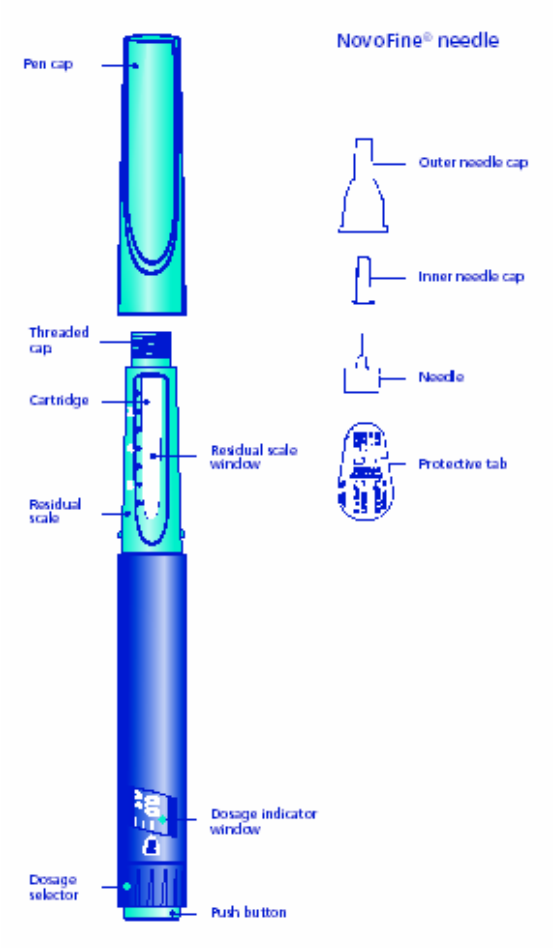
INSTRUCTIONS FOR USE

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
10 mg/1.5 mL Prefilled Pen

Using the disposable Norditropin NordiFlex® 10 mg/1.5 mL Prefilled Pen

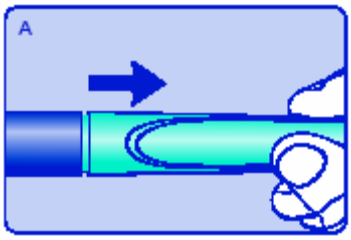
Norditropin NordiFlex® 10 mg/1.5 mL is a disposable dial-a-dose growth hormone delivery system able to deliver doses from 0.05 to 3.0 mg. The dose can be adjusted in increments of 0.05 mg. Your doctor will determine the correct dose for you. Norditropin NordiFlex® prefilled pen is designed to be used 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 the Norditropin NordiFlex®.

Please read these instructions carefully before using this device



1 Preparing Norditropin NordiFlex® 10 mg/1.5 mL for injection

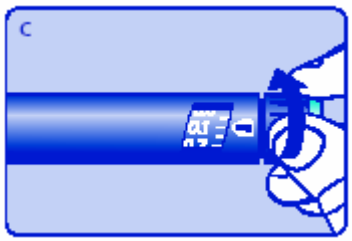
A. Wash hands well. Pull off the pen cap and wipe the front rubber stopper on the threaded plastic cap with an alcohol swab. **DO NOT use Norditropin NordiFlex® if the growth hormone solution is cloudy or contains particles. Use it only if it is clear and colorless.** Check this by turning the Norditropin NordiFlex® upside down once or twice and view the solution through the residual scale window.



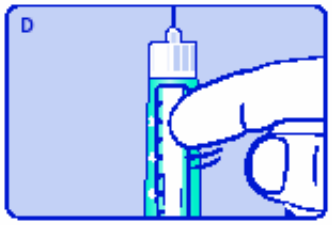
B. Place the NovoFine® needle onto the Norditropin NordiFlex® immediately before use. Remove the protective tab from the disposable needle and screw the needle tightly onto Norditropin NordiFlex®. Pull off the outer and inner needle caps. Never place a disposable needle on your Norditropin NordiFlex®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

C. Do an air shot before each injection as follows:
Small amounts of air may collect in the needle and cartridge during normal use. To avoid injecting air and ensure proper dosing, set the dosage selector to 0.1 mg. Each line between labeled dosages is 0.05 mg.

Dial 0.1 mg

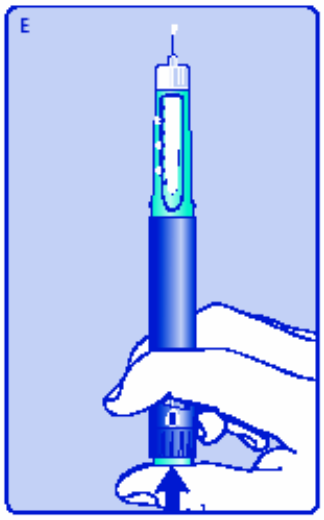


D. Hold Norditropin NordiFlex® with the needle pointing up, tap the cartridge gently with your finger a few times to raise any air bubbles to the top of the cartridge.



E. Still holding Norditropin NordiFlex® with the needle up, press the push button all the way in. A drop of growth hormone should appear at the needle tip. If not, repeat the procedure, no more than 6 times.

IF A DROP OF GROWTH HORMONE STILL DOES NOT APPEAR, CALL 1-888-NOVO-HGH FOR HELP.



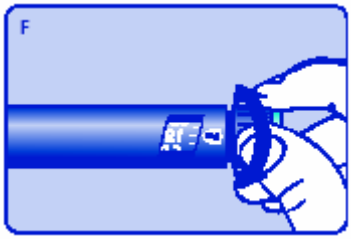
2 Setting the dose

F. Check that the dose selector is set at **0.0**. Dial the number of mg that you need to inject. 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 growth hormone liquid will come out.
DO NOT use the clicking sound as a guide for selecting 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 GROWTH HORMONE 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 0.4 mg. You will need to inject an additional 0.2 mg with a new Norditropin NordiFlex® pen.

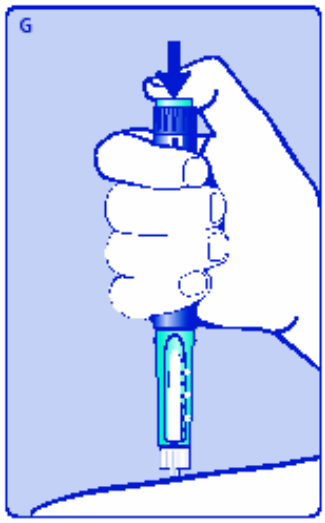


3 Giving the injection

Use the injection procedure recommended by your doctor or health care professional.

G. This product is for subcutaneous use only. Insert the needle into your thigh and deliver the dose by pressing the push button all the way in. Press the push button only when injecting.

AFTER THE INJECTION, THE NEEDLE SHOULD REMAIN UNDER THE SKIN FOR AT LEAST 6 SECONDS. KEEP THE PUSH BUTTON FULLY DEPRESSED UNTIL THE NEEDLE IS REMOVED FROM THE SKIN. THIS WILL ENSURE THAT THE FULL DOSE HAS BEEN DELIVERED. VARY THE INJECTION SITE ON THE THIGH USING THE INJECTION PROCEDURE RECOMMENDED BY YOUR DOCTOR.



4 Removing the 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. HEALTH CARE PROFESSIONALS, RELATIVES AND OTHER CAREGIVERS SHOULD FOLLOW GENERAL PRECAUTIONARY MEASURES FOR REMOVAL AND DISPOSAL OF NEEDLES TO ELIMINATE THE RISK OF UNINTENDED NEEDLE STICK.

When the cartridge is empty, throw away the Norditropin NordiFlex® without the needle attached.

5 Maintenance

Norditropin NordiFlex® should be handled with care. Protect Norditropin NordiFlex® from dust, dirt, and direct sunlight.

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

6 Important Notes

- Store non-injected/unused Norditropin NordiFlex® pens in a refrigerator (2ºC-8ºC/36ºF-46ºF). After the initial injection, keep the pen refrigerated and use within 4 weeks.
- Remember to perform an air shot before each injection. See diagrams **C, D** and **E**.
- If you need to perform more than 6 air shots before the first use of the Norditropin NordiFlex® to get a droplet of growth hormone at the needle tip, **DO NOT** use the Norditropin NordiFlex®. *Call 1-888-NOVO-HGH for help.*
- Take care not to drop the Norditropin NordiFlex®.
- **DO NOT** leave the 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 NovoFine® needle on the Norditropin NordiFlex® until you are ready to use it. Remove the needle right after use without recapping.
- **Throw away used needles properly, so people will not be harmed.**
- Throw away the 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.**

7 Warranty

If your Norditropin NordiFlex® is defective in materials or workmanship, Novo Nordisk Pharmaceuticals, Inc. will replace it at no charge if you mail the defective unit, postage prepaid to:

Novo Nordisk Pharmaceuticals, Inc.
Product Safety
100 College Road West
Princeton, NJ 08540, USA

Novo Nordisk

PATIENT INFORMATION

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
5 mg/1.5 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. Do not freeze it or expose it to heat.

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 6 air shots before the first injection.

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

What is Norditropin NordiFlex®?

Norditropin® is a clear and colorless solution used to treat children with growth failure caused by very low or no production of growth hormone, as well as adults who lack growth hormone.

Norditropin® is injected using the Norditropin NordiFlex®, a multi-dose disposable 1.5 mL pre-filled pen. Norditropin NordiFlex® contains several doses of growth hormone solution. A dose is injected into the thigh in the evening 6-7 times a week.

Norditropin NordiFlex® is available in three strengths: 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL (i.e. 3.3 mg/mL, 6.7 mg/mL and 10.0 mg/mL respectively).

Throw away the Norditropin NordiFlex® when the cartridge is empty.

Medicines are sometimes prescribed for purposes other than those listed in a patient guide. Patients should ask their doctor about any concerns and refer to the professional labeling for additional information.

What does Norditropin NordiFlex® contain?

The cartridge in Norditropin NordiFlex® contains human growth hormone called somatropin (so-ma-tro-pin) made through biotechnology. It is identical to the growth hormone produced in the human body.

The cartridge contains other ingredients: Histidine, Poloxamer 188, Phenol, Mannitol and Water for Injection.

Who should not take 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
- allergic to phenol or any other ingredients in the medicine
- had a kidney transplant
- pregnant
- breast-feeding
- cancer or other forms of tumor
- acute critical illness

What should you consider if you are pregnant or breast-feeding?
If you become pregnant while you are receiving Norditropin NordiFlex®, you are recommended to stop the treatment and discuss this with your doctor.

You are recommended not to take Norditropin NordiFlex® while you are breast-feeding because somatropin might pass into your milk.

Be sure to tell your doctor if you:

- have diabetes mellitus
- had cancer or other forms of tumor

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

How should I take Norditropin NordiFlex®?

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

You should inject Norditropin NordiFlex® in the thigh in the evening just before bedtime. You should change the injection area on the thigh 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: 0.024 to 0.034 mg/kg body weight, 6-7 times a week.

Adults: 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.

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 if you want to stop taking Norditropin®.

What should I avoid while taking Norditropin NordiFlex®?

Be sure to tell your doctor about all of the medications you are taking especially if you are taking:
a glucocorticoid medication such as hydrocortisone or cortisone acetate
thyroid hormone
insulin

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, your insulin dose may need to be adjusted.

What are the possible or reasonably likely side effects of Norditropin NordiFlex®?

The following side effects are usually mild and temporary:

- headaches
- muscle pain
- joint stiffness
- weakness
- 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, you may need to reduce your dose. Discuss this with your doctor.

In rare cases you may develop antibodies to growth hormone or suffer raised pressure within the brain. If you get headaches, eyesight problems, feel sick or vomit, contact your doctor as these complaints could be signs of raised pressure within your brain.

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 somatropin have experienced pain in the hip or knee or a limp. These symptoms may be caused by slipped capital femoral epiphysis (the end of the bone slips from the cartilage).

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.

Patients should have periodic thyroid function tests.

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

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

How to store Norditropin NordiFlex®?

Store non-injected/unused Norditropin NordiFlex® in a refrigerator (2°C - 8°C/36°F - 46°F). Do not freeze or expose it to heat. Avoid direct light.

After the initial injection, Norditropin NordiFlex® 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 excessive temperatures.

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

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

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

Date of issue: October/2004

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

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

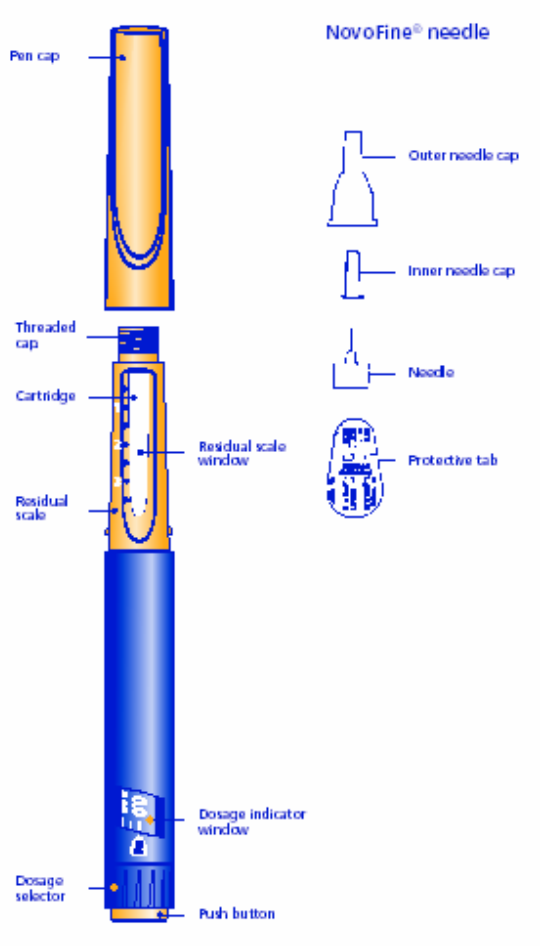
INSTRUCTIONS FOR USE

Norditropin NordiFlex®
Somatropin (rDNA origin) injection
5 mg/1.5 mL Prefilled Pen

Using the disposable Norditropin NordiFlex® 5 mg/1.5 mL Prefilled Pen

Norditropin NordiFlex® 5 mg/1.5 mL is a disposable dial-a-dose growth hormone delivery system able to deliver doses from 0.025 to 1.5 mg. The dose can be adjusted in increments of 0.025 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 the Norditropin NordiFlex®.

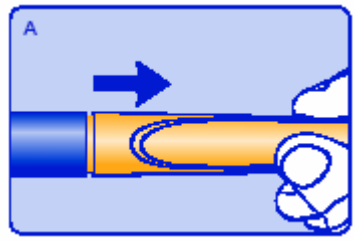
Please read these instructions carefully before using this device



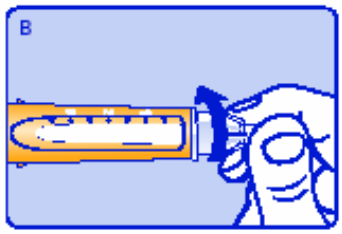
1

Preparing Norditropin NordiFlex® 5 mg/1.5 mL for injection

A. Wash hands well. Pull off the pen cap and wipe the front rubber stopper on the threaded plastic cap with an alcohol swab. **DO NOT use Norditropin NordiFlex® if the growth hormone solution is cloudy or contains particles. Use it only if it is clear and colorless.** Check this by turning the Norditropin NordiFlex® upside down once or twice and view the solution through the residual scale window.



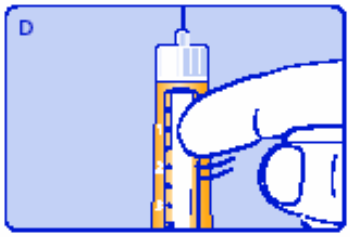
B. Place the NovoFine® needle onto the Norditropin NordiFlex® immediately before use. Remove the protective tab from the disposable needle and screw the needle tightly onto Norditropin NordiFlex®. Pull off the outer and inner needle caps. Never place a disposable needle on your Norditropin NordiFlex®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



C. Do an air shot before each injection as follows:
Small amounts of air may collect in the needle and cartridge during normal use. To avoid injecting air and ensure proper dosing, set the dosage selector to 0.05 mg. Each line between labeled dosages is 0.025 mg.

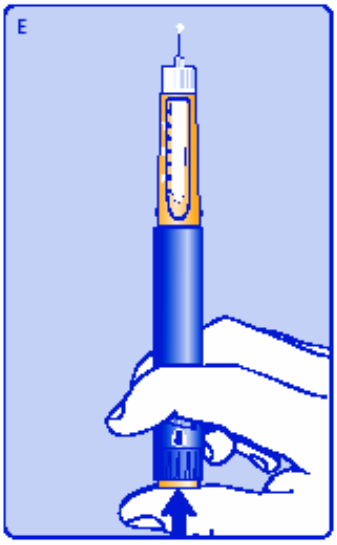
Dial 0.05 mg

D. Hold Norditropin NordiFlex® with the needle pointing up, tap the cartridge gently with your finger a few times to raise any air bubbles 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 growth hormone should appear at the needle tip. If not, repeat the procedure, no more than 6 times.

IF A DROP OF GROWTH HORMONE STILL DOES NOT APPEAR, CALL 1-888-NOVO-HGH FOR HELP.



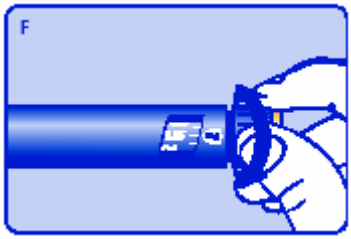
2 Setting the dose

F. Check that the dose selector is set at **0.0**. Dial the number of mg that you need to inject. 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 growth hormone liquid will come out.
DO NOT use the clicking sound as a guide for selecting 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 GROWTH HORMONE 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 0.4 mg. You will need to inject an additional 0.2 mg with a new Norditropin NordiFlex® pen.

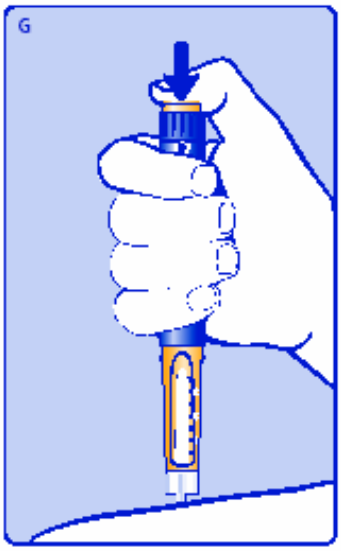


3 Giving the injection

Use the injection procedure recommended by your doctor or health care professional.

G. This product is for subcutaneous use only. Insert the needle into your thigh and deliver the dose by pressing the push button all the way in. Press the push button only when injecting.

AFTER THE INJECTION, THE NEEDLE SHOULD REMAIN UNDER THE SKIN FOR AT LEAST 6 SECONDS. KEEP THE PUSH BUTTON FULLY DEPRESSED UNTIL THE NEEDLE IS REMOVED FROM THE SKIN. THIS WILL ENSURE THAT THE FULL DOSE HAS BEEN DELIVERED. VARY THE INJECTION SITE ON THE THIGH USING THE INJECTION PROCEDURE RECOMMENDED BY YOUR DOCTOR.



4 Removing the 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. HEALTH CARE PROFESSIONALS, RELATIVES AND OTHER CAREGIVERS SHOULD FOLLOW GENERAL PRECAUTIONARY

MEASURES FOR REMOVAL AND DISPOSAL OF NEEDLES TO ELIMINATE THE RISK OF UNINTENDED NEEDLE STICK.

When the cartridge is empty, throw away the Norditropin NordiFlex® without the needle attached.

5 Maintenance

Norditropin NordiFlex® should be handled with care. Protect Norditropin NordiFlex® from dust, dirt, and direct sunlight.

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

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- If you need to perform more than 6 air shots before the first use of the Norditropin NordiFlex® to get a droplet of growth hormone at the needle tip, **DO NOT** use the Norditropin NordiFlex®. *Call 1-888-NOVO-HGH for help.*
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