PRODUCT MONOGRAPH

[Pr]Norditropin® SimpleXx®

Somatropin solution for injection

Cartridge

5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL

[Pr]Norditropin NordiFlex®

Somatropin solution for injection

Pre-filled disposable pen

5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL

Growth Hormone

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Solution: 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL	*For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Norditropin® contains 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. Recombinant human growth hormone (hGH) contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone.

INDICATIONS AND CLINICAL USE

Norditropin® SimpleXx® (somatropin) and **Norditropin NordiFlex®** (somatropin) are indicated in pediatric patients for:

- The long-term treatment of children with growth failure due to an inadequate secretion of endogenous growth hormone (Growth Hormone Deficiency). Children below the age of 3 have not been studied in the pivotal clinical studies.

- The treatment of growth disturbance (current height Standard Deviation Score (SDS) < -2) in short children born small for gestational age (SGA) with a birth weight and/or length below -2 standard deviations (SD), who failed to show catch-up growth (Height Velocity SDS < 0 during the last year) by 2 years of age or later.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Growth hormone should not be initiated in patients with acute critical illness due to complications following cardiac or abdominal surgery, multiple accident traumas or to patients having acute respiratory failure. Clinical studies demonstrated that high doses of growth hormone were associated with a significantly increased morbidity and mortality in those patients (see WARNINGS AND PRECAUTIONS, General).
- 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. There have been reports of sudden death when somatropin was used in such patients. **Norditropin®** is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome (See Serious Warnings and Precautions).
- Growth hormone should not be used or should be discontinued when there is any evidence of neoplastic activity. Anti-tumour therapy should be completed before growth hormone therapy is initiated.
- Intracranial tumour must be inactive and anti-malignancy treatment must be completed with evidence of remission prior to the institution of growth hormone therapy. Patients should be examined frequently for progression or recurrence of the underlying process.
- Growth hormone should not be used for growth promotion in pediatric patients with closed epiphyses. Growth hormone has no effect on cartilaginous growth areas of the long bone. Treatment of pediatric growth disorders with growth hormone should be discontinued when the patient has reached satisfactory adult height, or the epiphyses are closed.
- Growth hormone should not be administered in patients with proliferative or

preproliferative diabetic retinopathy.
- Treatment with **Norditropin®** should be discontinued at the time of renal transplantation.

WARNINGS AND PRECAUTIONS

Treatment with somatropin should be directed by specialists experienced in the diagnosis and management of growth disorders.

Any transfer of growth hormone products should be made cautiously and only under medical supervision.

There have been reports of fatalities associated with the use of growth hormone in pediatric patients with Prader-Willi syndrome who have one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea or unidentified [i.e., previously undiagnosed/ mildly symptomatic] respiratory infections (See CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Congenital Disorders).

General

- The maximum recommended daily dose should not be exceeded (see DOSAGE AND ADMINISTRATION).
- It is recommended that Insulin-like Growth Factor-I (IGF-I) concentrations be monitored regularly and maintained within the normal range for age and sex (see Monitoring and Laboratory Tests).
- A significant increase in mortality was reported among growth hormone treated patients with acute critical illnesses in intensive care units due to complications following open heart surgery or abdominal surgery, multiple accidental trauma or acute respiratory failure compared with those receiving placebo (see CONTRAINDICATIONS and ADVERSE REACTIONS).
- As **Norditropin®** is injected subcutaneously, the injection site should be rotated to minimize the risk of lipoatrophy occurring.
- To avoid transmission of disease, **Norditropin® SimpleXx®** cartridges and **Norditropin NordiFlex®** prefilled pens should not be used by more than one person.
- For instructions on proper use of **Norditropin®** refer to Patient Information and PART III: CONSUMER INFORMATION**.**

Growth hormone has not been shown to increase the incidence of scoliosis. Progression of scoliosis can occur in pediatric patients 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.

Concomitant glucocorticoid therapy may inhibit the response to growth hormone and should not exceed 10-15 mg hydrocortisone equivalent/m^2 body surface area during growth hormone therapy.

Patients being treated with growth hormone should be informed of the potential benefits and risks associated with treatment. Patients should be instructed to contact their physician should they experience any side effects or discomfort during treatment with growth hormone (see Patient Information and PART III: CONSUMER INFORMATION).

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 doses of somatropin (5.3 – 8 mg/day). 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 compared to those receiving placebo (see CONTRAINDICATIONS).

The safety of continuing somatropin treatment in patients receiving replacement doses 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.

Carcinogenesis and Mutagenesis
Carcinogenicity and mutagenicity studies have not been conducted with **Norditropin®**.

Leukemia has been reported in a small number of growth hormone deficient patients, treated with growth hormone. Based on the current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences. Analysis of somatropin treatment in 54,996 children monitored over a period of 20 years, revealed no increased risk of leukemia.

Neoplasms:
Treatment with growth hormone may have an increased risk of developing neoplasm.

There is no evidence for increased risk of *de novo* malignancy in patients treated with somatropin. There is no evidence for increased risk of recurrence of malignancies in patients treated with somatropin.

Secondary Neoplasm in Survivors of Childhood Cancer:
In childhood cancer survivors, an increased risk of a second neoplasm (benign and malignant) has been reported in patients treated with growth hormone. Intracranial tumours, in particular meningiomas in patients treated with radiation to the head for their first neoplasm, were the most

common of the second neoplasms. However, in childhood cancer survivors, no increased risk of primary cancer recurrence has been reported in patients treated with growth hormone.

Patients with previous malignant disease should be monitored carefully for recurrence of malignant disease. Somatropin treatment should be interrupted in case of any development or reoccurrence of malignant disease.

Cardiovascular

Fluid retention (edema, arthralgia, carpal tunnel syndrome) may occur (see ADVERSE REACTIONS/ General). Clinical manifestations of fluid retention are usually transient and dose-dependent. A dose reduction may be necessary.

Congenital Disorders

Prader-Willi Syndrome (PWS):

There have been reports of sleep apnea and 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 (i.e., previously undiagnosed/mildly symptomatic) 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 of sleep apnea, treatment should be interrupted and the patients should be treated as indicated.

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).

Dependence/Tolerance

Inappropriate use of growth hormone by individuals who do not have indications for which growth hormone is approved, may result in clinically significant negative health consequences (see ADVERSE REACTIONS).

Growth hormone is not a drug of dependence.

Endocrine and Metabolism

Patients with diabetes mellitus or glucose intolerance should be monitored closely during therapy with growth hormone as an adjustment of their anti-diabetic therapy may be required (see Monitoring and Laboratory Tests).

In adults with risk factors for insulin resistance or glucose intolerance, such as obesity, a family history of diabetes mellitus and those on high dose corticosteroid therapy, growth hormone therapy may induce Type II Diabetes Mellitus if the insulin secretory capacity is impaired.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when growth hormone therapy is administered (see Monitoring and Laboratory Tests).

Hypothyroidism may develop during treatment with growth hormone (see ADVERSE REACTIONS).

Growth hormone can affect the metabolism of thyroid hormones by increasing the extrathyroidal conversion of T4 to T3 and this lowering effect on T4 may unmask incipient central hypothyroidism in hypopituitary patients.

Thyroid function should be evaluated before starting growth hormone therapy and regularly assessed during treatment, not less frequently than annually (see Monitoring and Laboratory Tests).

In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during growth hormone treatment. If hypothyroidism is diagnosed in the course of growth hormone therapy, it should be corrected according to clinical practice.

Patients with endocrine disorders, including growth hormone deficiency have a higher incidence of slipped capital femoral epiphyses. Any child with the onset of a limp or complaining of hip or knee pain during growth hormone therapy should be evaluated (see Monitoring and Laboratory Tests).

Note:

- Growth hormone therapy can be followed by a transient phase of hypoglycemia, then by an increase in blood glucose levels despite high insulin concentrations. To detect insulin resistance, patients should be monitored for evidence of glucose intolerance.
- Growth hormone therapy may affect the metabolism of glucocorticoids, by inhibiting the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) which is required for the conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Individuals with untreated growth hormone deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of growth hormone therapy may result in inhibition of

11βHSD-1 and reduced serum cortisol concentrations. In consequence, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required in patients treated with growth hormones.

- Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of therapy; 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.
- Growth hormone also enhances the activity of CYP3A4, a cytochrome P450 enzyme involved in glucocorticoid catabolism. Therefore, growth hormone therapy may both unmask unsuspected adrenocorticotropic hormone (ACTH) deficiencies and negate low replacement glucocorticoid doses used in secondary adrenal insufficiency (AI) by decreasing the availability of cortisol. Patients starting growth hormone therapy may require adjustments in their glucocorticoid replacement doses, and stress doses.

Immune

Local Allergic Reactions:
With growth hormone therapies patients may experience redness, swelling, pain, inflammation, or itching at the site of injection (see ADVERSE REACTIONS). Most of these minor reactions usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the growth hormone or any excipients (see CONTRAINDICATIONS).

Rarely, subcutaneous administration of growth hormone products can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their physician if they notice any of these conditions.

Continuous rotation of the injection site within a given area may help reduce or prevent these reactions. On rare occasion, injection site reactions may require discontinuation of therapy.

Systemic Reactions:
Systemic allergic reactions have rarely occurred with growth hormone therapy. These reactions may be characterized by generalized rash (with pruritus), shortness of breath, wheezing, angioneurotic edema and drop of blood pressure (see ADVERSE REACTIONS). Severe cases of generalized allergy including anaphylactic reaction may be life threatening (see CONTRAINDICATIONS). If any serious hypersensitivity or allergic reactions occur, growth hormone therapy should be discontinued immediately and appropriate therapy initiated as per general guidelines.

Antibody Production:
As with all protein pharmaceuticals, a small percentage of patients may develop antibodies

during treatment with growth hormone. Patients who have demonstrated an allergic reaction to other growth hormone products may demonstrate an allergic reaction to **Norditropin®** (see ADVERSE REACTIONS).

If growth deceleration is observed that is not attributable to another cause, the physician should consider testing the patient for antibodies to growth hormone (see Monitoring and Laboratory Tests).

Intracranial Hypertension (IH)

Very rare cases of benign intercranial hypertension have been reported. If appropriate, growth hormone treatment should be discontinued.

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

Funduscopic examination of patients is recommended at the initiation, and periodically during the course of growth hormone therapy.

Musculoskeletal

Increased tissue turgor (non-edematous swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with growth hormone (see ADVERSE REACTIONS). These symptoms may resolve spontaneously, with analgesic therapy, or after reducing the dosage (see DOSAGE AND ADMINISTRATION).

Carpal tunnel syndrome may occur during treatment with growth hormone (see ADVERSE REACTIONS). If the symptoms of carpal tunnel syndrome do not resolve by decreasing the dosage of growth hormone, it is recommended that treatment be discontinued.

Pancreatitis in Children

Children treated with growth hormone may have an increased risk of developing pancreatitis compared to adults. Although rare, pancreatitis should be considered in growth hormone-treated children who develop abdominal pain.

Renal / Hepatic / Biliary / Pancreatic Impairments

The safety of **Norditropin®** has not been established in patients with renal, hepatic, biliary or pancreatic impairments.

Growth hormone requirements may need to be adjusted in patients with renal and/or hepatic and/or biliary and/or pancreatic impairments.

Reproduction Studies
No adequate and well-controlled studies with **Norditropin®** in reproduction studies have been performed. For animal data, see TOXICOLOGY.

Drug Interactions
Caution is recommended when administering growth hormone with compounds that are metabolized by the CP450 or CY3A4 liver enzymes (e.g. corticosteroids, sex steroids, anticonvulsants, cyclosporine and others) (see DRUG INTERACTIONS).

Careful monitoring is advisable when growth hormone is administered in combination with other drugs known to be metabolized by CP450 or CYP3A4 liver enzymes.

Concomitant glucocorticoid treatment may inhibit the growth promoting effect of growth hormone. Growth hormone deficient children with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

High doses of androgens, estrogens or anabolic steroids can accelerate bone maturation and inhibit an increase in growth.

The physician should be consulted when using other medications in addition to growth hormone products (see Patient Information and PART III: CONSUMER INFORMATION).

Information for Patients
Patients and/or their parents should be informed about potential advantages and disadvantages of growth hormone therapy including the possible side effects. If home use is determined to be desirable by the physician, patients should also be offered instruction for use of injection devices, storage, travelling and other pertinent information (see PART III: CONSUMER INFORMATION).

Female patients should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring, as well as general health is essential in pregnant patients (see Special Populations and PART III: CONSUMER INFORMATION).

Special Populations

Pediatric Patients:
The stimulation of longitudinal growth in children can only be expected until the epiphysial discs are closed. Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any pediatric patient with onset of a limp during growth hormone therapy should be evaluated.

Pregnant Women:
There are no adequate and well controlled studies in pregnant women. Therefore, **Norditropin®** should be used during pregnancy only if clearly indicated and under medical supervision.

For effects in animal reproductive studies see TOXICOLOGY.

Reproduction studies have not been conducted. It is not known whether growth hormones can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Growth hormones should only be given to a pregnant woman if the benefits outweigh the risks.

Patients should inform their doctor if they are pregnant or are contemplating pregnancy.

Nursing Women:
It is not known whether growth hormones are excreted in human milk. There are no adequate and well-controlled studies in nursing women. Therefore, growth hormones should be used with caution in nursing women.

Due to the large molecular weight, it is unlikely that somatropin would be passed intact into the maternal milk, and absorption of intact protein from the gastrointestinal tract of the infant is also unlikely. However, secretion of breakdown products of the drug in breast milk has not been studied. Because many drugs are excreted in human milk, caution should be exercised when growth hormone is administered to a nursing mother.

Geriatrics:
The safety and effectiveness of **Norditropin®** in patients aged 65 and over has not been evaluated in clinical studies.

Elderly patients may be more prone to develop adverse reactions.

Obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen.

Monitoring and Laboratory Tests
With growth hormone therapy the need for regular IGF-1 monitoring should be considered to maintain IGF-1 within the normal range for age and sex.

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 of 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.

Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Patients with diabetes or glucose intolerance should be monitored closely during therapy with growth hormone.
In patients with hypopituitarism (multiple hormonal deficiencies) standard hormonal replacement therapy should be monitored closely when growth hormone therapy is administered.

Hypothyroidism may develop during treatment with growth hormone. Inadequate treatment of hypothyroidism may prevent optimal response to growth hormone. Thyroid function should be evaluated before starting growth hormone therapy and regularly assessed during treatment and should be treated with thyroid hormone when indicated.

Serum levels of inorganic phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) may increase with growth hormone therapy.

Patients on growth hormone therapy should be monitored for the emergence of any new malignancy and the treatment discontinued if a new tumour or signs of relapse are detected.

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

Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Patients with an intra or extracranial neoplasia in remission who are receiving treatment with growth hormone should be examined carefully and at regular intervals by the physician. Patients developing neoplasia should be reported to Health Canada by the treating physician.

In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

For SGA patients, it is recommended to measure IGF-I level before start of treatment and twice a year thereafter. If on repeated measurements IGF-I levels exceed +2 SD compared to references for age and pubertal status, the IGF-I / IGFBP-3 ratio could be taken into account to consider dose adjustment.

Experience in initiating treatment in SGA patients near onset of puberty is limited. It is therefore not recommended to initiate treatment near onset of puberty. Experience with SGA patients with Silver-Russel syndrome is limited.

Some of the height gain obtained with treating short children born SGA with somatropin may be lost if treatment is stopped before final height is reached.

In case of persistent edema or severe paresthesia the dosage should be decreased in order to avoid the development of carpal tunnel syndrome. Growth hormone deficiency in the adult is a lifelong condition and should be treated accordingly, however experience with patients over sixty years and experience with prolonged treatment is limited.

Growth hormone administration is followed by a transient phase of hypoglycemia of approximately 2 hours, then from 2-4 hours onward by an increase in blood glucose levels despite high insulin concentrations. To detect insulin resistance, patients should be monitored for evidence of glucose intolerance.

Idiopathic intracranial hypertension has been recognized as a complication (early in treatment usually) of growth hormone treatment. The diagnosis is made on the basis of clinical symptoms such as severe, persistent or recurrent headache, visual problems, nausea and/or vomiting, papilledema and temporal relationship to growth hormone. Physicians and parents should be attentive to relevant symptoms such as headache and visual problems in patients under growth hormone therapy. Fundoscopic examination should be performed routinely before initiating treatment with growth hormones to exclude pre-existent papilledema and repeated if there is any clinical suspicion. If papilledema is confirmed by fundoscopy, growth hormone treatment should be stopped. It can be restarted at a lower dose after idiopathic-intracranial hypertension has resolved which occurs rapidly when treatment is withdrawn. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary, and treatment should be discontinued if intracranial hypertension recurs. At present, there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension.

Legg-Calvé-Perthes disease may occur more frequently in patients with short stature.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events in the two key pediatric studies in GHD were childhood infections of mild/moderate severity normally seen in children. The most frequent adverse events in the 2 key pediatric trials in SGA were common infections of childhood, such as bronchitis, pharyngitis, gastroenteritis, otitis media, influenza and upper respiratory tract infection.

General

Growth hormone deficient patients are characterized by extracellular volume deficit. When treatment with somatropin is initiated, this deficit is corrected. Fluid retention with peripheral edema may occur especially in adults. Mild arthralgia, muscle pain and paresthesia may also occur, but is usually self-limiting. The symptoms are usually transient, dose dependant and may require transient dose reduction.

Adverse reactions in children are uncommon or rare.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Clinical Trials in Pediatric Growth Hormone Deficiency (GHD)

The safety population in GHD consisted of 697 children, of which 150 children were from the two key trials, and 547 children were from the supportive trials in GHD. The two key trials provided treatment up to two years with **Norditropin®** at doses up to 0.10 mg/kg/day. For a list of Adverse Drug Reactions refer to Table 1-1.

Table 1-1: Summary of Adverse Drug Reactions Occurring at a Frequency of ≥ 1% in Pediatric GHD Trials

	Study 1 (GHD)			Study 2 (GHD)		
	0.025 mg/kg/day	**0.050 mg/kg/day**	**0.100 mg/kg/day**	**IGF-I dosing [-0.5 to +0.5]**	**IGF-I dosing [+1.5 to +2.5]**	**Conventional 0.040 mg/kg/day**
Number of Subjects	31	35	31	26	18	9
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Adverse Reaction	5 (16.1)	9 (25.7)	5 (16.1)	12 (46.2)	9 (50.0)	3 (33.3)
Application Site						
Injection Site Abscess	-	-	-	1 (3.8)	-	-
Injection Site Atrophy	-	-	-	1 (3.8)	-	-
Injection Site Hematoma	-	-	-	3 (11.5)	3 (16.7)	1 (11.1)
Injection Site Inflammation	1 (3.2)	2 (5.7)	-	-	-	-
Injection Site Pain	-	2 (5.7)	-	2 (7.7)	1 (5.6)	-
Injection Site Reaction	-	-	-	1 (3.8)	-	-
Body As A Whole						
Face Edema	-	-	-	1 (3.8)	1 (5.6)	-
Chest Pain	-	-	-	-	1 (5.6)	-
Leg Pain	-	-	-	-	1 (5.6)	1 (11.1)
Pain	1 (3.2)	1 (2.9)	-	1 (3.8)	-	-
Fever	-	-	1 (3.2)	-	-	-
Endocrine System						
Gynecomastia	1 (3.2)	1 (2.9)	-	-	-	-
Hypothyroidism	1 (3.2)	-	-	-	-	-
Fetal						
Nevus	-	-	-	-	2 (11.1)	-
Gastro-Intestinal System						
Vomiting	-	-	-	-	1 (5.6)	1 (11.1)
Metabolic And Nutritional						
Periorbital Edema	1 (3.2)	-	1 (3.2)	-	-	-
Cachexia	-	1 (2.9)	-	-	-	-
Hyperglycemia	-	-	-	-	1 (5.6)	-
Musculo-Skeletal System						
Arthralgia	-	1 (2.9)	-	1 (3.8)	-	-
Bone Disorder	-	-	1 (3.2)	-	1 (5.6)	-
Skeletal Pain	-	-	-	1 (3.8)	-	-
Nervous System						
Headache	-	-	-	4 (15.4)	3 (16.7)	1 (11.1)
Cramps Legs	-	-	-	1 (3.8)	-	-
Hyperkinesia	-	1 (2.9)	-	-	-	-
Intracranial Hypertension	-	1 (2.9)	-	-	-	-
Psychiatric						
Nervousness	-	-	-	1 (3.8)	-	-
Resistance Mechanism						
Viral Infection	-	-	1 (3.2)	-	-	-

	Study 1 (GHD)			Study 2 (GHD)		
	0.025 mg/kg/day	**0.050 mg/kg/day**	**0.100 mg/kg/day**	**IGF-I dosing [-0.5 to +0.5]**	**IGF-I dosing [+1.5 to +2.5]**	**Conventional 0.040 mg/kg/day**
Respiratory System						
Pharyngitis	-	-	1 (3.2)	-	-	-
Rhinitis	-	-	1 (3.2)	-	-	-
Secondary Terms						
Medication Error	-	-	-	2 (7.7)	-	-
Other Events	-	-	-	1 (3.8)	-	1 (11.1)
Skin And Appendages						
Skin Disorder	1 (3.2)	-	-	-	-	-
Rash	-	1 (2.9)	-	-	-	-
Alopecia	-	-	-	-	-	1 (11.1)
White Cell and Res.						
Lymphadenopathy	-	-	-	-	1 (5.6)	-

N: Number of subjects with an adverse reaction
%: Proportion of subjects having an adverse reaction

The overall safety profile of **Norditropin®** in short children with GHD was similar across trials. **Norditropin®** was safe and well tolerated. The most common adverse events were childhood infections of mild/moderate severity normally seen in children. The majority of adverse events were unlikely to be related to the trial drug. There were no indications of a dose relationship on adverse events in the dose range tested. Most children recovered from their adverse events.

Clinical Trials in Children Born Small for Gestational Age (SGA)

The safety population in SGA consisted of 151 children from 2 clinical trials. The first trial was a long term study in 53 non-GHD children with short stature born SGA and the second trial was conducted in 98 Japanese non-GHD children with short stature born SGA. For a list of Adverse Drug Reactions refer to Table 1-2.

Table 1-2: Summary of Adverse Drug Reactions Occurring at a Frequency of ≥ 1% in Pediatric SGA Trials

	Study 1 (Long-Term SGA)		Study 2 (Short-Term SGA)		
	40/33*	80/67*	Untreated Control	33 µg/kg/day	67 µg/kg/day
	N (%)	N (%)	N (%)	N (%)	N (%)
Adverse Reaction	4 (15.4)	5 (18.5)	-	6 (15.8)	15 (39.5)
Congenital, Familial and Genetic	-	-	-	-	1 (2.6)
Multiple Epiphyseal Dysplasia	-	-	-	-	1 (2.6)
General Disorders and Administration Site Conditions	-	1 (3.7)	-	2 (5.3)	2 (5.3)
Pain	-	1 (3.7)	-	-	-
Application Site Papules	-	-	-	-	1 (2.6)
Face Edema	-	-	-	1 (2.6)	-
Injection Site Erythema	-	-	-	-	1 (2.6)
Injection Site Pruritus	-	-	-	-	1 (2.6)
Injection Site Swelling	-	-	-	1 (2.6)	-
Injection Site Urticaria	-	-	-	-	1 (2.6)
Hepatobiliary System	-	-	-	-	1 (2.6)
Hepatic Function Abnormal	-	-	-	-	1 (2.6)
Injury, Poisoning and Procedural Complications	-	-	-	1 (2.6)	-
Joint Dislocation	-	-	-	1 (2.6)	-
Investigations	-	-	-	-	3 (7.9)
Antibody Test Positive	-	-	-	-	2 (5.3)
White Blood Cell Count Increased	-	-	-	-	1 (2.6)
Metabolism and Nutritional	-	-	-	-	2 (5.3)
Glucose Tolerance Impaired	-	-	-	-	2 (5.3)
Musculoskeletal and Connective tissue	1 (3.8)	3 (11.1)	-	2 (5.3)	6 (15.8)
Arthralgia	-	1 (3.7)	-	-	4 (10.5)
Bone Disorder	1 (3.8)	1 (3.7)	-	-	-
Pain in Extremity	-	1 (3.7)	-	2 (5.3)	1 (2.6)
Growing Pains	-	-	-	-	1 (2.6)
Nervous System	-	-	-	1 (2.6)	1 (2.6)
Headache	-	-	-	1 (2.6)	-
Hypoesthesia	-	-	-	-	1 (2.6)
Reproductive System and Breast	2 (7.7)	2 (7.4)	-	-	-
Gynecomastia	2 (7.7)	2 (7.4)	-	-	-

	Study 1 (Long-Term SGA)		Study 2 (Short-Term SGA)		
	40/33*	80/67*	Untreated Control	33 µg/kg/day	67 µg/kg/day
	N (%)	N (%)	N (%)	N (%)	N (%)
Skin and Subcutaneous Tissue	1 (3.8)	-	-	1 (2.6)	3 (7.9)
Hyperhidrosis	1 (3.8)	-	-	-	-
Alopecia Areata	-	-	-	1 (2.6)	-
Hemorrhage Subcutaneous	-	-	-	-	1 (2.6)
Pruritis	-	-	-	-	1 (2.6)
Urticaria	-	-	-	-	1 (2.6)

N: Number of subjects with an adverse reaction
%: Proportion of subjects having an adverse reaction
*: When calculating the exact doses in µg/kg/day, the children received approximately 40 µg/kg/day and 80 µg/kg/day for the first two years, and hereafter the doses decreased to about 33 µg/kg/day and 67 µg/kg/day during the remainder of the trial.

Study 1 (Long Term**):**
The most frequent adverse events were common infections of childhood, such as bronchitis, gastroenteritis, otitis media, and upper respiratory tract infection. Other common adverse events included arthralgia, abdominal pain, influenza-like illness, pain, and headache. Adverse Drug Reactions to **Norditropin®** were gynecomastia, bone disorders/pain, and increased sweating. No apparent differences between dose groups were observed. A dose-dependent increase in mean IGF-I SDS within the reference range was seen with **Norditropin®** treatment.

Study 2 (Short Term):
The most common adverse events were common infections of childhood, such as pharyngitis, upper respiratory tract infection, bronchitis, gastroenteritis, influenza, and otitis media. Frequent Adverse Drug Reactions were arthralgia and pain in extremity. Arthralgia and impaired glucose tolerance were only reported in the 0.067 mg/kg/day group. The proportions of subjects with adverse events as well as serious adverse events were comparable among the three treatment groups, but the number of adverse events per subject tended to increase in the active treatment groups and with the higher dose.

Abnormal Hematologic and Clinical Chemistry Findings
No clinically relevant changes were observed in glucose metabolism (HbA_{1c}, fasting glucose and insulin) during two years of **Norditropin®** treatment. The changes to baseline were minor for all treatment groups. There were no major differences between dose groups. There were no trends for development of diabetes and no cases of diabetes were reported.

IGF-I levels normalised during the 2-years of **Norditropin®** treatment. IGF-I SDS was at the lower border or below the reference population at baseline in both trials. **Norditropin®** treatment led to clear initial increases in IGF-I SDS within the reference range (-2 to 2). The new higher levels were maintained hereafter. The increases in IGF-I SDS were dose dependent, with the greater increases on the higher dose levels.

Post-Market Adverse Drug Reactions

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

Adverse events that have been observed during the post-marketing period are similar to those seen in clinical trials with **Norditropin®**. In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported and are by an overall judgement considered possibly related to Norditropin treatment.

Blood Disorders

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.

Ear Disorders: Otitis media.

Endocrine Disorders: Hypothyroidism; decrease in serum thyroxin (T4) levels.

Very rare cases of decrease in serum thyroxin levels have been reported during treatment with **Norditropin®** (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). Increase in blood alkaline phosphatase level may be seen during the treatment with **Norditropin®**.

Immune System Disorders: Generalized hypersensitivity reactions (e.g. anaphylactic reactions) have been reported in rare cases (less than 1 in 1000).

Formation of antibodies directed against somatropin has been rarely observed during **Norditropin®** therapy. The titres and binding capacities of these antibodies have been very low and have not interfered with the growth response to **Norditropin®** administration.

Investigations: Increase in blood alkaline phosphatase level.

Metabolism Disorders: Hyperglycemia.

Musculoskeletal and Connective Tissue Disorders: Slipped capital femoral epiphysis; Legg-Calvé-Perthes disease.

Nervous System Disorders: Benign intracranial hypertension.

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

(children).

Table 1-3: Summary of Post-marketing Reports in GHD

	Spontaneous			Solicited Report			Literature			Total		
	N	%	E	N	%	E	N	%	E	N	%	E
No. of Subjects	117			6			9			132		
All adverse events	117	100	169	6	100	9	9	100	17	132	100	195
Mild	3	2.6	3	2	33.3	4	0	0.0	0	5	3.8	7
Moderate	5	4.3	6	2	33.3	2	0	0.0	0	7	5.3	8
Severe	18	15.4	26	0	0.0	0	0	0.0	0	18	13.6	26
Missing severity	96	82.1	134	2	33.3	3	9	100	17	107	81.1	154
Probable	7	6.0	18	0	0.0	0	1	11.1	1	8	6.1	19
Possible	57	48.7	71	1	16.7	1	3	33.3	4	61	46.2	76
Unlikely	40	34.2	52	3	50.0	4	0	0.0	0	43	32.6	56
Impossible to assess	3	2.6	3	2	33.3	4	0	0.0	0	5	3.8	7
Unknown relation	12	10.3	25	0	0.0	0	6	66.7	12	18	13.6	37
Recovered	44	37.6	62	2	33.3	2	5	55.6	12	51	38.6	76
Stabilized	1	0.9	1	0	0.0	0	0	0.0	0	1	0.8	1
Recovered with sequelae	5	4.3	5	0	0.0	0	0	0.0	0	5	3.8	5
Not yet recovered	43	36.8	62	2	33.3	2	3	33.3	4	48	36.4	68
Died	11	9.4	13	0	0.0	0	0	0.0	0	11	8.3	13
Unknown	24	20.5	26	2	33.3	5	1	11.1	1	27	20.5	32

5 events with reporting type= Regulatory Auth. were not reported. Event number is used for counting due to missing subject numbers.

Table 1-4: Post-marketing Adverse Events in SGA

Type of Report	Preferred Term	Relationship	Outcome
Clinical Trial	Osteochondrosis	Possible/Possible	Recovered with sequelae
Clinical Trial	Nephrotic syndrome	Unlikely/Unlikely	Stabilized
Clinical Trial	Glomerulonephritis proliferative	Possible/Unlikely	Not recovered
Clinical Trial	Tonsillar hypertrophy	Possible/Unlikely	Recovered
Spontaneous	Retinal vascular disorder	Unlikely/Unlikely	Not yet recovered
Spontaneous	Diabetes mellitus insulin-dependent	Unlikely/Unlikely	Not recovered
Spontaneous	Injection site swelling	Possible/Possible	Recovered

DRUG INTERACTIONS

Overview

Concomitant treatment with glucocorticoids inhibits the growth promoting effects of somatropin containing products. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on somatropin. If glucocorticoid replacement therapy is required, glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth promoting effects.

In patients treated with somatropin, previously undiagnosed secondary hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses.

Growth hormone therapy may increase CP450 and CYP3A4 mediated antipyrine clearance in man. Limited published data in growth hormone deficient adults, suggests that somatropin administration may increase the clearance of compounds known to be metabolized by cytochrome P450 isoenzymes. The clearance of compounds metabolized by cytochrome P450 3A4 (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

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.

In insulin treated patients, adjustment of insulin dose may be needed after initiation of somatropin treatment (see WARNINGS AND PRECAUTIONS).

Drug-Drug Interactions

Table 1-5: Established or Potential Drug-Drug Interactions

Proper Name	Effect	Clinical Comment
Cortisone acetate/ Prednisone	Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1 (11ßHSD-1)	May require an increase in the maintenance or stress doses of glucocorticoid; Conversion of cortisone acetate and prednisone to their biologically active metabolites is dependent on the activity of the 11βHSD-1 enzyme.
Glucocorticoid therapy	Attenuate the growth promoting effects of somatropin	In children with concomitant GH and glucocorticoid deficiency careful monitoring both treatments to avoid hypoadrenalism and an inhibitory effect on growth.
Oral estrogen	Reduce efficacy of somatropin	Women on oral estrogen replacement may require a larger dose of somatropin to achieve the defined treatment goal
Insulin and/or Oral Hypoglycemic Agents	May decrease effectiveness of insulin and/or hypoglycemic agents	Dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Therapy with **Norditropin®** (somatropin) should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with short stature associated with GHD, or SGA.
- The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the injection (see WARNINGS AND PRECAUTIONS; Allergic Reactions).
- The **Norditropin®** dosage and administration schedule should be individualized based on the body weight and growth response of each patient.
- Generally, daily subcutaneous administration in the evening is recommended.
- 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, under nutrition, advanced bone age and antibodies to recombinant human GH (rhGH).
- Treatment with **Norditropin®** for short stature should be discontinued when the epiphyses are closed.
- Because oral estrogens may reduce the serum IGF-I response to somatropin treatment, girls and women receiving oral estrogen replacement may require greater somatropin dosages.

Recommended Dose and Dosage Adjustment

Pediatric Growth Hormone Deficiency (GHD):
A daily dosage up to 0.043 mg/kg/day is recommended.

Pediatric Patients Born Small for Gestational Age (SGA):
A daily dosage of up to 0.067 mg/kg/day is recommended.

Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.067 mg/kg/day), especially in very short children (i.e. HSDS < -3), and/or older/early pubertal children, and that a reduction in dosage (e.g., gradually towards 0.033 mg/kg/day) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger SGA children (e.g. approximately < 4 years), who respond the best in general, with less severe short stature (i.e. baseline HSDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g. 0.033 mg/kg/day), and titrating the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the rhGH dose as necessary.

Missed Dose
For patients who miss a dose, it is not recommended to double the next dose. Administer the regular dose at the next scheduled dosage time.

Administration
For subcutaneous injection. Injection site should be rotated each time **Norditropin®** is administered in order to prevent lipoatrophy.

Norditropin® SimpleXx® cartridges contain a solution ready for injection. No reconstitution or preparation is required. The product is for multiple uses in one patient only. **Norditropin® SimpleXx®** cartridges must be used with the matching colour coded **NordiPen®** to give the correct dose (Refer to DOSAGE FORMS, COMPOSITION AND PACKAGING). Detailed injection instructions are included in the **NordiPen®** Instruction Manual that is enclosed with the **NordiPen®**. Patients should be advised to read these instructions very carefully.

Norditropin NordiFlex® is a pre-filled pen designed to be used with **NovoFine®, NovoFine® Plus,** or **NovoTwist®** needles (8 mm 30 G or smaller). The product is for multiple uses in one patient only. Detailed injection instructions for **Norditropin NordiFlex®** are included in PART III of the Product Monograph, and in the **Norditropin NordiFlex®** package insert. Patients should be advised to read these instructions very carefully.

OVERDOSAGE
The maximum generally recommended dosage should not be exceeded due to the potential risk of side effects.

Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, 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 growth hormone.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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).

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 A1C 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.

Pharmacokinetics

Subcutaneous injection of **Norditropin®** (2.5 mg/m^2 (0.085 mg/kg)) to 31 healthy subjects (with endogenous somatropin suppressed by continuous infusion of somatostatin) resulted in a maximal concentration of human growth hormone of 42-46 ng/mL after approximately 4 hours. The area under the drug concentration-time curve from time zero to 24 hours was 397-408 ng/mL. The human growth hormone declined with a half-life of approximately 2.6 hours.

Subcutaneous injection of **Norditropin®** (5 mg (0.054-0.082 mg/kg)) to 23 healthy subjects (with endogenous somatropin suppressed by continuous infusion of somatostatin) resulted in a maximal concentration of human growth hormone of 39-43 ng/mL after 4-4.5 hours. The area under the drug concentration-time curve from time zero to 24 hours was approximately 396-433 ng/mL. The human growth hormone declined with a half-life of approximately 3 hours.

The substantially longer half-life with s.c. compared to i.v. administration reflects the so-called "flip-flop" kinetics of s.c. administered Norditropin®. That is, since the absorption process is slow relative to the elimination process, the terminal half-life after s.c. administration is related to the absorption rate.

Special Populations and Conditions

Pediatrics: No information is available concerning **Norditropin®** for this population.

Gender: Differences in PK response between genders were investigated in a clinical trial. There were no significant differences between males or females for the parameters AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} or $t_{½}$ for hGH.

Race: A study was conducted to evaluate the PK of **Norditropin®** in healthy Japanese subjects as compared to Caucasian subjects. A single dose (0.055–0.096 mg/kg) of **Norditropin®** was administered to each subject. Both the Japanese and Caucasian subjects appeared to be comparable with respect to AUC_{0-24h} and C_{max}, as well as T_{max} and the half-life. No interaction between ethnic groups, dose or BMI was observed. The maximum hGH concentration was measured 4 to 6 hours after the time of the **Norditropin®** injection and approached zero at 24 hours. The mean $t_{½}$ was 3.6 and 3.2 hours for Japanese and Caucasian subjects, respectively.

STORAGE AND STABILITY

Norditropin® SimpleXx® (somatropin)
Unused **Norditropin® SimpleXx®** cartridges must be stored at 2-8°C (refrigerate. Do not freeze.) Avoid direct light.

After a **Norditropin® SimpleXx®** cartridge has been inserted into its **NordiPen®** delivery system it may be **EITHER** stored in the pen in the refrigerator (2-8ºC) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25ºC. Discard unused portion.

Norditropin NordiFlex® (somatropin)
Unused **Norditropin NordiFlex®** prefilled pens must be stored at 2-8°C (refrigerate. Do not freeze.) Avoid direct light.

After the initial injection, a **Norditropin NordiFlex®** prefilled pen may be **EITHER** stored in the refrigerator (2-8ºC) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25ºC. Discard unused portion.

Table 1-6: Storage Options

Norditropin® SimpleXx® or Norditropin NordiFlex®	Before Use	In-Use (After 1st Injection)	
	Storage Requirement	Storage Option 1 (Refrigeration)	Storage Option 2 (Room Temperature)
5 mg/1.5 mL	2-8 ºC Until expiry date	2-8 ºC 4 weeks	Up to 25ºC 3 weeks
10 mg/1.5 mL			
15 mg/1.5 mL			

SPECIAL HANDLING INSTRUCTIONS

Norditropin® SimpleXx® (somatropin) and **Norditropin NordiFlex®** (somatropin) should not be shaken vigorously at any time.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Norditropin® SimpleXx®(somatropin)

- **Norditropin® SimpleXx®** cartridges MUST be used with the matching colour coded **NordiPen®** to give the correct dose:
  - **Norditropin® SimpleXx®** 5 mg (orange) MUST be used with **NordiPen®** 5 mg (orange).
  - **Norditropin® SimpleXx®** 10 mg (blue) MUST be used with **NordiPen®** 10 mg (blue).
  - **Norditropin® SimpleXx®** 15 mg (green) MUST be used with **NordiPen®** 15 mg (green).
- Detailed injection instructions are included in the **NordiPen®** Instruction Manual that is enclosed with the **NordiPen®**. Patients should be advised to read these instructions very carefully.

Norditropin NordiFlex® (somatropin)

- **Norditropin NordiFlex®** is a pre-filled pen designed to be used with **NovoFine®, NovoFine® Plus,** or **NovoTwist®** needles (8 mm 30 G or smaller).
- Detailed injection instructions for **Norditropin NordiFlex®** are included in PART III of the Product Monograph, and in the **Norditropin NordiFlex®** package insert. Patients should be advised to read these instructions very carefully.

Listing of Non-Medicinal Ingredients
A list of ingredients for each **Norditropin® SimpleXx® and Norditropin NordiFlex®** presentation is given below.

Ingredient	**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	As needed	As needed	As needed
Water for Injection	Up to 1.5 mL	Up to 1.5 mL	Up to 1.5 mL

Packaging
Norditropin® SimpleXx® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens are available individually packaged in a carton or in pack sizes of 3 cartridges per carton.

Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL prefilled pens are individually packaged in a carton

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

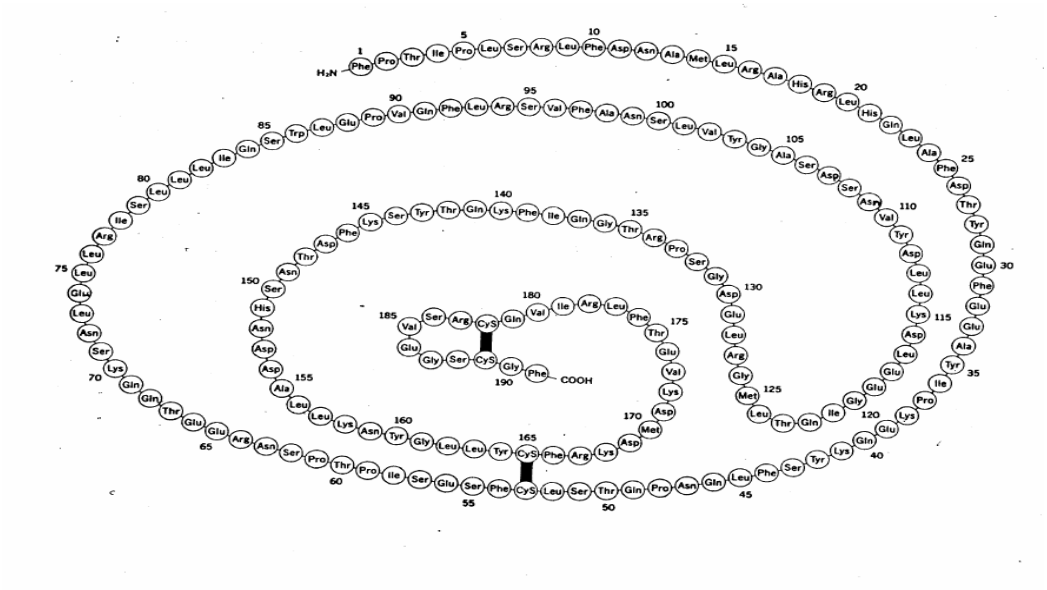
Drug Substance

Proper name: Norditropin® SimpleXx® and Norditropin NordiFlex®

Chemical name: somatropin

Molecular formula and molecular mass: $C_{990}H_{1528}N_{262}O_{300}S_7$ (22,125 Da)

Structural formula:



Physicochemical properties: Somatropin, produced by recombinant DNA methods, is a white, or almost white, powder. It dissolves readily in water or isotonic solutions.

Product Characteristics

Somatropin is a polypeptide hormone consisting of 191 amino acid residues and its structure is identical to that of growth hormone extracted from human pituitary glands. Somatropin is a four-helical bundle protein with an up-up down-down topology. The structure contains two disulfide bridges, Cys53-Cys165 and Cys182-CyS189.

CLINICAL TRIALS

Clinical Trials in Pediatric Growth Hormone Deficiency (GHD)

Study Demographics and Trial Design (GHD)

Table 2-1: Summary of Patient Demographics for Clinical Trials in GHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1	Randomised, multi-centre, three arm dose-response	Three dose levels (0.025, 0.05 and 0.1 mg/kg/day) Subcutaneous injection Study duration: 2 years	97	7.5 (2.7)	68% boys and 32% girls
Study 2	Randomised, multi-centre, three arm dose-response	IGF-I based: IGF-SDS of either a) [-0.5 to +0.5] or b) [+1.5 to +2.5] Conventional Dose: 0.04 mg/kg/day Subcutaneous injection Study duration: 2 years	53	7.0 (2.3)	75% boys and 25% girls

Study Results (GHD)

Study 1
The primary objective of this study was to evaluate and compare the safety and growth velocity effectiveness of graded **Norditropin®** dose levels after administration to growth hormone deficient children for two years. A secondary objective of this study was to determine the safety and effectiveness of chronic **Norditropin®** administration in patients until they reach adult height. Efficacy endpoints included: growth velocity, sitting height, bone age, BMI and weight, and growth factor panel (i.e., IGF-1, IGF-2, and IGFBP-3).

In this study, 97 short children with GHD were randomised (0.025 mg/kg: 31 children; 0.05 mg/kg: 35 children; 0.10 kg/mg: 31 children). A total of 86 children completed 2-years of the trial (0.025 mg/kg: 27 children; 0.05 mg/kg: 32 children; 0.10 kg/mg: 27 children). Up to 2 years results are presented. Mean age was 7.5 (2.7) years. More boys than girls were evaluated (68% boys and 32% girls). The children were naïve to GH therapy.

The mean baseline HSDS were -3.3, -3.1 and -2.9 in the 0.025, 0.050 and 0.10 mg/kg/day groups, respectively. The estimated mean HSDS after **Norditropin®** treatment were -2.39, -1.65 and -1.49 in the three dose groups, respectively. The majority of the children thus achieved a height within normal range. The estimated mean gains in HSDS over the 2-year periods were 0.81, 1.57 and 1.73 in the three dose groups, respectively. All gains in HSDS were statistically significantly different from zero (both years). Statistically significant differences in estimated mean HSDS and change in HSDS were observed between the low and the high dose groups (0.025 versus 0.05 and 0.10 mg/kg/day). There was no statistically significant difference between the two higher dose groups (0.05 and 0.10 mg/kg/day).

Study 2
The primary objective of this study was to evaluate and compare treatment outcomes with **Norditropin®** in children with GHD who were treated by dose titration to achieve a serum IGF-I SDS of either [-0.5 to +0.5] or [+1.5 to +2.5]. A comparison group dosed according to body weight was included. Secondary objectives for this study included: an assessment of the relationship between the administered GH dose and resultant serum IGF-I concentration; evaluation of potential gender specific differences in dose response; determination of the effect of GH dosing protocols on bone age development. The primary efficacy endpoint was the change from baseline in height SDS. The secondary endpoints included IGF-I, IGFBP3, free IGF-I, and bone age.

In Study 2, 53 children with short stature and documented GHD were randomised. The children in the IGF-I based dosing arms were treated to achieve an IGF-SDS of either [-0.5 to +0.5] (referred to as the RRC1 group) or an IGF-SDS of [+1.5 to +2.5] (referred to as the RRC2 group). The children in the conventional arm were dosed with 0.04 mg/kg/day. A total of 49 children with GHD completed the 2-year trial. Up to 2 years results are presented. Mean age was

7.0 (2.3) years. More boys than girls were included (40 boys and 13 girls). The children were naïve to GH therapy.

At the end of trial, HSDS increased as compared to baseline in all three treatment groups. The RCC2 group had the greatest increase in HSDS. The mean baseline HSDS were -2.6, -2.7 and -2.5 in the conventional, RCC1 and RCC2 groups, respectively. The estimated mean HSDS after **Norditropin®** treatment were -1.48, -1.23 and -0.77 in the conventional, RCC1 and RCC2 groups, respectively. The majority of the children thus achieved a height within normal range. The estimated mean gains in HSDS over the 2-year periods were 1.15, 1.39 and 1.85 in the conventional, RCC1 and RCC2 groups, respectively. All gains in HSDS were statistically significantly different from zero (both years). Statistically significant differences in estimated mean HSDS and change in HSDS were observed between the RCC1 and RCC2 dose groups and between the conventional group and the RCC2 dose group. There was no statistically significant difference between the conventional group and the RCC1 group.

Clinical Trials in Children Short for Gestational Age (SGA)

Study Demographics and Trial Design (SGA)

Table 2-2: Summary of Patient Demographics for Clinical Trials in SGA

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study 1	Multi-centre, double-blind, randomised, two-arm trial investigating **Norditropin®** in treatment of children after Intrauterine Growth Retardation	40/33 or 80/67 µg/kg/day Up to 13 years Subcutaneous injection	53	7.1 (2.3)	28% girls and 72% boys
Study 2	Multi-centre, randomised, double-blind, parallel-group trial investigating the efficacy and safety of **Norditropin®** in short children born SGA.	33 or 67 µg/kg/day Up to 2 years Subcutaneous injection	98 randomised 84 included in efficacy analysis	5.3 (1.3)	39% girls and 61% boys

Study Results (SGA)

Study 1

The primary objective of this trial was to assess the effect of GH therapy on linear growth (height, standardised height, height velocity and final height), bone maturation, and pubertal development in short children born SGA. Secondary objectives included assessment of the additional effects of GH therapy on glucose and lipid metabolism, blood pressure, and plasma IGF-I and IGF binding protein 3 (IGFBP-3).

The pivotal study included 53 (38 male, 15 female, 38 male) non-GHD Dutch children 3-11 years of age with short stature born SGA with no catch-up growth. No catch-up growth was defined as not 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 9 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 2-3, for boys and girls combined, both mean final height SDS (0.033 mg/kg/day, -1.8 vs. 0.067 mg/kg/day, -1.3), and increase in height SDS from baseline to final height, (0.033 mg/kg/day, 1.4 vs. 0.067 mg/kg/day, 1.8), were significantly greater after treatment with 0.067 mg/kg/day (0.067 mg/kg/day). A similar dose response was observed for the increase in height SDS from baseline to Year 2 (Table 2-3).

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 Nortidropin treatment and was significantly greater after treatment with 0.067 mg/kg/day (mean 11.1 cm/y [SD 1.9; n=19]) compared with 0.033 mg/kg/day (mean 9.7 cm/y [SD 1.3; n=10]).

Table 2-3: 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	Mean
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

The primary objective of this trial was to evaluate the efficacy of the two dose levels of **Norditropin®** (0.033 mg/kg/day and 0.067 mg/kg/day) compared with untreated controls (one year) as assessed by change in HSDS from baseline to Year 1 (52-week) treatment in short children born SGA. A secondary objective was to compare the efficacy of the two dose levels as assessed by the change in HSDS after 2 years of treatment.

In this study, eighty-four (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 and weight SDS ≤ -2 or < 10th percentile for gestational age, height SDS for chronological age ≤ -2 and height velocity SDS for chronological age < 0 within one year prior to Visit 1. Exclusion criteria included diabetes mellitus, history or presence of active malignancy, and serious co-morbid conditions.

As seen in Table 2-4, 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 was significantly greater after treatment with 0.067 mg/kg/day (0.8 with 0.033 mg/kg/day versus 1.4 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 2-4: 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	Mean
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.

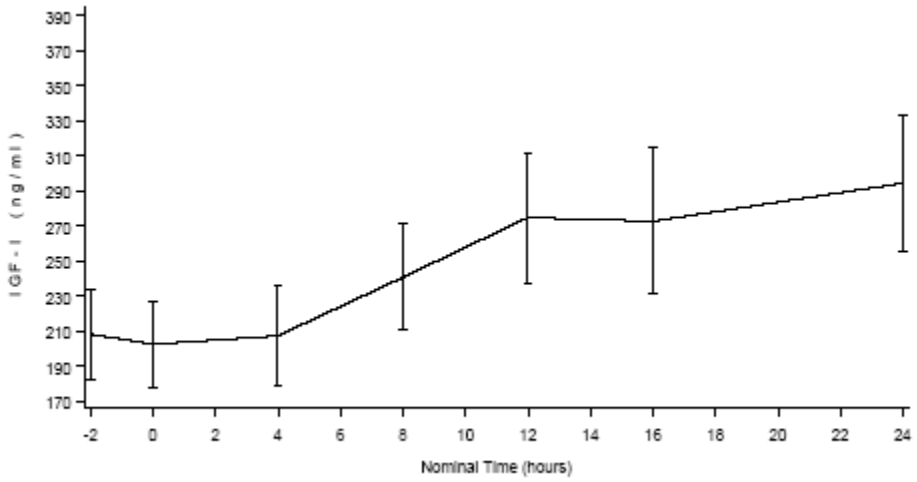
DETAILED PHARMACOLOGY

Pharmacodynamics

Somatropin exerts most of its actions through insulin-like growth factor I (IGF-I), which is produced in tissues throughout the body, but predominantly by the liver. More than 90% of IGF-I is bound to binding proteins (IGFBP's) of which IGFBP-3 is the most important. As such, the pharmacodynamics of **Norditropin®** (somatropin) was primarily evaluated on the basis of IGF-I and IGFBP-3 responses.

IGF-I levels were measured in healthy subjects following a single s.c dose (0.085 mg/kg) of **Norditropin®**. The mean IGF-I concentration-time profile is presented in Figure 2-1. Generally, IGF-I levels increased over time following administration of the compound. The IGF-I profiles were typically sigmoidal.

Figure 2–1 Mean IGF-I Profiles Following Single S.C. Dose of Norditropin® in Healthy Subjects



Profile presented for formulation '**Norditropin®** 5 mg/1.5 mL' (Dose: 0.085 mg/kg.)

IGF-I and IGFBP-3 response was also investigated. Following single dose i.v. **Norditropin®** infusion in healthy subjects (0.0009-0.009 mg/kg), serum IGF-I levels showed a small but statistically significant increase from the baseline. High maximal rate of IGF-I secretion (E_{max}: 241 ng/mL) and low GH concentration at which half-maximal IGF-I secretion occurs (EC_{50}: 1.9 ng/mL) indicated a high impact of hGH levels on IGF-I production rate. IGF-I levels and maximal IGF-I production rate were positively correlated to IGFBP-3 concentration.

Pharmacokinetics

Absorption and Plasma Concentrations

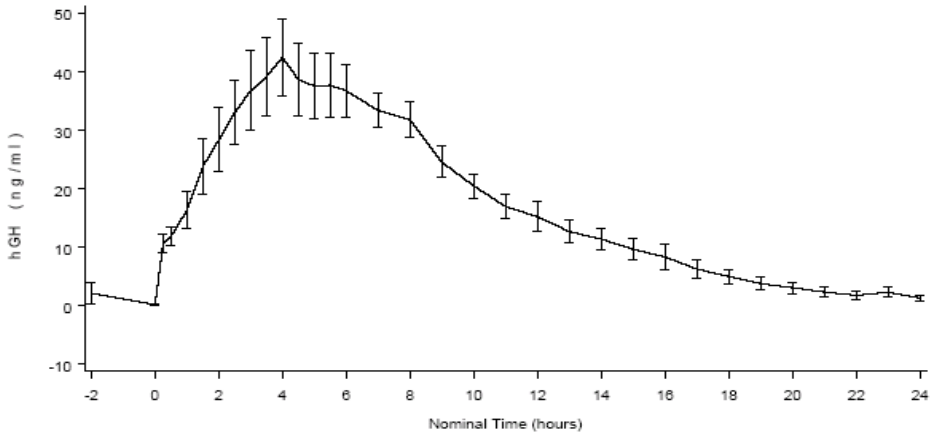
Subcutaneous (s.c.) administered **Norditropin®** exhibits "flip-flop" kinetics. That is, since the absorption process is slow relative to the elimination process, the terminal half-life after s.c. administration is related to the absorption rate.

A single s.c. injection of **Norditropin®** (2.5 mg/m^2 (0.085 mg/kg)) to healthy subjects (with endogenous somatropin suppressed by continuous infusion of somatostatin) resulted in a maximal concentration of human growth hormone of 42-46 ng/mL. The area under the drug concentration-time curve from time zero to 24 hours was 397-408 ng/mL. The mean plasma concentration-time profile following a single s.c. dose of **Norditropin®** is shown in Figure 2-2.

A single s.c. injection of 5 mg (0.054-0.082 mg/kg) to healthy subjects resulted in a maximal concentration of human growth hormone of 39-43 ng/mL. The area under the drug concentration-time curve from time zero to 24 hours was approximately 396-433 ng/mL.

Following a single s.c injection at dose levels ranging from 0.05 to 0.1 mg/kg, the time to reach maximum serum concentration (t_{max}) was 4 to 6 hours.

Figure 2–2 Mean hGH Profiles Following Single S.C. Dose of Norditropin® in Healthy Subjects



Profile presented for formulation '**Norditropin®** 5 mg/1.5 mL' (Dose: 0.085 mg/kg.)

Distribution
The distribution following single i.v. doses (0.0009-0.009 mg/kg) of **Norditropin®** was investigated in healthy subjects. The volume of distribution (V) was 0.063 L/kg, which is approximately equal to the amount of blood in the human body, indicating that **Norditropin®** was mainly distributed in the blood.

Elimination
The terminal half-life ($t_{½}$) and clearance (CL) following single i.v. doses (0.0009-0.009 mg/kg) of **Norditropin®** in healthy subjects was investigated. Clearance at a low dose (CL_0) and maximal dose (CL_{max}) of **Norditropin®** were 3.9 and 1.2 mL/min/kg, respectively, showing that CL decreased with increasing **Norditropin®** doses. The $t_{½}$ was 13 and 21 minutes, respectively, estimated by two different models.

The $t_{½}$ following a single i.v. dose (0.05 mg/kg) in healthy subjects was estimated to 39 minutes.

The $t_{½}$ following a single s.c. dose of **Norditropin®** in healthy subjects was calculated. The $t_{½}$ following a single s.c. dose was 2.5 to 4.2 h. The substantially longer half-life with s.c. compared to i.v. administration reflects the so-called "flip-flop" kinetics of s.c. administered **Norditropin®**. That is, since the absorption process is slow relative to the elimination process, the terminal half-life after s.c. administration is related to the absorption rate.

TOXICOLOGY

Single-Dose Toxicity
Intravenous (i.v.) and subcutaneous (s.c.) toxicity after a single dose of either Norditropin® (somatropin) or Norditropin® SimpleXx® (somatropin) was assessed in four studies in mice, three studies in rats and one study in cynomolgus monkeys (see Table 2-5). The highest dose applied in both rats and mice was 56 mg/kg (185 IU/kg). The doses were well tolerated and resulted only in exaggerated pharmacological effects. A dose of 33 mg/kg (100 IU/kg) administered s.c. to cynomolgus monkeys was tolerated without any signs of toxicity.

Repeat-Dose Toxicity
Repeat s.c. dose toxicity studies were performed for 14 days up to 90 days in rats, and for a 28 day period in cynomolgus monkeys (see Table 2-6). Doses were given up to 9 mg/kg (26.9 IU/kg) in rats and approximately 5 mg/kg (15 IU/kg) in monkeys. Two rat studies specifically compared the effects of

degraded versus intact biosynthetic hGH in Norditropin® SimpleXx® for 28 and 90 days to mimic the end of shelf-life conditions.

In rats, the most prominent effects were increased body weight gain, increased organ weights and mammary gland hyperplasia. In the longer-duration studies, effects on hematology (slight decreases in RBC and hemoglobin) and slight effects on clinical chemistry (liver enzymes) were observed. However, all hematological and clinical chemistry values were not considered toxicologically significant and there were no accompanying histopathological changes.

There was no difference in the effects observed after treatment with degraded biosynthetic hGH versus intact biosynthetic hGH.

In the 4-week monkey study, the only treatment-related finding was increased secretory activity of the mammary gland in females, which was observed both clinically and histopathologically.
The observed effects in rats and monkeys were considered consistent with the pharmacological action of hGH. All repeat dose toxicity studies documented a low toxic potential for Norditropin®.

Genotoxicity
A series of genotoxicity studies comprising Ames' test, mammalian gene mutation test and mouse micronucleus test all showed the drug to be devoid of mutagenic activity (see Table 2-7).

Carcinogenicity
Due to the endogenous nature of the drug and the use for replacement therapy, carcinogenicity studies were not performed.

Reproductive and Developmental Toxicity
Reproduction studies were performed in rats and comprise a two-generation study (fertility/embryo-fetal toxicity/developmental), an embryo-fetal toxicity study, and a pre-post-natal study (see Table 2-8). The reproduction studies confirmed the pharmacological effects on body weight and the increased activity of the reproductive organs. Findings included an increased number of implantations, increased number of corpora lutea and increased pup weight. None of the studies revealed any adverse effects of the drug on reproduction.

Local Tolerance

A study in rabbits addressed the potential local irritation after i.m. injection (see Table 2-9). A slightly more marked irritation than that caused by physiological saline was observed. No difference between the effects seen after degraded biosynthetic hGH versus intact biosynthetic hGH was observed. The local effects observed in the repeat dose studies in rats were considered within the expected range for proteins injected subcutaneously.

Table 2-5: Single-Dose Toxicity Studies

Study Type	Species / Strain	Method of Admin.	Period of Dosing	Doses (mg/kg)	Gender and No. per Group	Observed Max Non-Lethal Dose (mg/kg)	Noteworthy Findings
Single-Dose Toxicity							
Acute toxicity in mice given forcedly degraded biosynthetic human growth hormone by subcutaneous injection	Mice, NMRI	s.c.	Once	0, 56 mg/kg	Control group: 5M + 5F Treatment group: 10M + 10F	56 mg/kg	No clinical signs were observed, apart from one female lying flat on the abdomen for half an hour after the injection and hyperplasia of the uterine mucosa.
Acute toxicity in mice given biosynthetic human growth hormone by subcutaneous administration. Batch no. P6	Mice, NMRI	s.c.	Once	0, 92 and 185 IU/kg (0, 28 and 56 mg/kg)	Control group: 5M + 5F Treatment groups: 10M + 10F	56 mg/kg (185 IU/kg)	No clinical signs were observed. Hyperplasia of the uterine mucosa was observed at both dose levels.
Liquid Norditropin 10 mg, Forcedly Degraded - Subcutaneous single dose toxicity in mice.	Mice, NMRI	s.c.	Once	0, 67 and 133 mg/kg	5M + 5F	133 mg/kg	No treatment-related findings.
Acute toxicity in mice given biosynthetic human growth hormone by intravenous administration. Batch no. P6	Mice, NMRI	i.v.	Once	0, 92 and 185 IU/kg (0, 28 and 56 mg/kg)	Control group: 5M + 5F. Treatment groups: 10M + 10F	56 mg/kg	No clinical signs were observed. Hyperplasia of the uterine mucosa was observed at both dose levels.
Acute toxicity in rats of biosynthetic human growth hormone, I. Batch no. P4.	Rats, Wistar (Wist/Mol)	s.c.	Once	0,50 and 100 IU/kg (0, 16.5 and 33 mg/kg)	Control group: 4M + 4F Treatment groups: 8M + 8F	100 IU/kg (33 mg/kg)	Increased body weight gain and food intake were observed at both dose levels, in males only.
Acute toxicity in rats of biosynthetic human growth hormone, II. Batch no. P 7-8-9	Rats, Wistar (Wist/Mol)	s.c.	Once	0, 90 and 180 IU/kg (0, 30 and 60 mg/kg)	Control group: 5M + 5F Treatment groups: 10M + 10F	180 IU/kg (60 mg/kg)	Hyperplasia of the uterine mucosa was observed at 180 IU/kg.
Acute toxicity in rats given intravenous injection of biosynthetic human growth hormone, III. Batch no. P6.	Rats, Wistar (Wist/Mol)	i.v.	Once	0, 92 and 185 IU/kg (0, 28 and 56 mg/kg)	Control group: 5M + 5F. Treatment groups: 10M + 10F	56 mg/kg	Superficial fast respiration was observed in the highest dosage group immediately after the injection. Enlarged uterine lumen was observed in one female rat dosed with 28

Study Type	Species / Strain	Method of Admin.	Period of Dosing	Doses (mg/kg)	Gender and No. per Group	Observed Max Non-Lethal Dose (mg/kg)	Noteworthy Findings
							mg/kg.
Biosynthetic Human growth hormone, (Norditropin) Single dose subcutaneous toxicity study in Cynomolgus monkeys (Batch 5002)	Cynomol. monkeys	s.c.	Once	0, 100 IU/kg (0, 33 mg/kg)	2 M + 2F	100 IU/kg (33 mg/kg)	No treatment-related findings.

Table 2-6: Repeat-Dose Toxicity Studies

Study Type	Species / Strain	Method of Admin.	Period of Dosing	Doses (mg/kg)	Gender and No. per Group	NOEL (mg/kg)
Repeat-Dose Toxicity						
Assessment of the toxicity of biosynthetic human growth hormone (B-hGH) Nordisk in rats after subcutaneous administration for 14 days.	Rats, Wistar (Wist/Mol)	s.c.	Daily for 14 days	0, 0.4, 2.6 and 19.2 IU/kg (0, 0.1, 0.9 and 6 mg/kg)	6 males and 6 females	19.2 IU/kg (6 mg/kg)
	Brief conclusion: Findings included an increase in body weight gain, food intake and food efficiency, 2.6 and 19.2 IU/kg, females only; and mammary gland hyperplasia, females only, 2.6 and 19.2 IU/kg bw/day.					
Assessment of the toxicity of biosynthetic human growth hormone (B-hGH) Nordisk in rats after subcutaneous administration for 28 days	Rats, Wistar (Wist/Mol)	s.c.	Daily for 28 days	0.5, 3.6 and 26.9 IU/kg (0.17, 0.72 and 9 mg/kg)	Control group: 10M + 10F Treatment groups: 10M + 10F	15 IU/kg (5 mg/kg)
	Brief conclusion: Findings included an increase in body weight gain and food consumption, 2 (females only) and 15 IU/kg; increased organ weights at all dose levels without corresponding histopathological changes; and glandular hyperplasia of the mammary gland in females and decidual reaction of the uterus at 2 and 15 IU/kg.					
Norditropin® SimpleXx® Degraded versus nondegraded. 28 Day subcutaneous toxicity study in the rat	Rats, Wistar (Wist/Mol)	s.c.	Daily for 28 days	0, 2.4 and 24 IU/kg (0, 0.8 and 8 mg/kg) degraded and non-degraded	Control group: 10M + 10F Treatment groups: 10M + 10F	24 IU/kg (8mg/kg)
	Brief conclusion: Findings included increased body weight gain and food consumption, both sexes, all dose levels, increased organ weights at all dose levels without corresponding histopathological changes, increased extramedullary hemopoiesis in the spleen, both sexes, 24 IU/kg, lobular hyperplasia and secretory activity of the mammary glands, all dose levels, both sexes, and a disturbance/arrest in the reproductive cycling and excessive mucification of the vaginal/cervical epithelium seen in females at 8 mg/kg/day. No difference between the effects of degraded and non-degraded Norditropin® SimpleXx® was found.					

90-day subcutaneous toxicity in the rat	Rats, Wistar (Wist/Mol)	s.c.	Daily for 90 days	0, 0.5, 3.3 and 25 IU/kg (0, 0.2, 1.2 and 8 mg/kg)	Control group: 10M + 10F Treatment groups: 10M + 10F (a further 10M + 10F were included in the control and the high dose group as recovery animals).	25 IU/kg (8 mg/kg)
	Brief conclusion: Findings included increased body weight gain and increased food consumption, 3.3 and 25 IU/kg, both sexes, increased urinary excretion at week 10 of Ca and P for males at 3.3 and 25.0 IU/kg, and increased Ca excretion for females at 25.0 IU/kg, increased relative weight of adrenals, without corresponding histopathological changes (end of treatment only); extramedullary hematopoiesis, both sexes, 25 IU/kg, at the end of treatment only, mammary gland hyperplasia, both sexes, 3.3 and 25 IU/kg, which was still observed at the end of the recovery period in the 25 IU/kg group, both sexes (3.3 IU/kg group was not examined); and mucification of the vaginal epithelium at 25 IU/kg, end of the treatment period only. As expected when dosing a human peptide to rats, most animals developed anti-drug antibodies during treatment.					
Liquid Norditropin 10 mg, degraded. Three month subcutaneous toxicity study in the rat	Rats, Wistar (Wist/Mol)	s.c.	Daily for 90 days	0, 0.08, 0.8 and 8 mg/kg degraded and 8 mg/kg nondegraded	Control group: 10M + 10F Treatment groups: 10M + 10F	25 IU/kg (8 mg/kg/day)
	Brief conclusion: Effects of the degraded test article were comparable to those of the non-degraded test article. Findings included an increase in body weight gain and food intake, 8.0 mg/kg, both sexes, an increase in various organ weights, 8.0 mg/kg, without corresponding histopathological changes; mammary gland hyperplasia at 8.0 mg/kg, both sexes; in addition, all females in the 8.0 mg/kg group were noted to be in the same stage of the estrous cycle (diestrous) - (only high dose group animals were examined).					
Biosynthetic human growth hormone (B-hGH) 4-week subcutaneous toxicity study in cynomolgus monkey	Cynomolgus monkeys	s.c.	Daily for 28 days	0, 0.3 and 15 IU/kg (0, 0.1 and 5 mg/kg)	Control group: 4M + 4F Treatment groups: 4M + 4F	15 IU/kg (5 mg/kg)
	Brief conclusion: Lactation/secretory activity in the mammary glands was observed in high-dose females. Anti-hGH antibodies were detected in 3/8 high-dose animals.					

Table 2-7: Genotoxicity Studies

Study Type	Species / Strain/no. and gender		Method of Admin.	Period of Dosing /sampling time	Doses (mg/kg)
Genotoxicity					
Ames Salmonella/microsome assay for bacterial mutagenicity	*Salmonella typhimurium* TA 98, 100, 1535 and 1537		-	-	8, 40, 200, 1000 and 5000 µg/plate
	Brief conclusion: No evidence of mutagenic potential of b-hGH was observed in the Ames test with or without metabolic activation.				
Assessment of the activity of biosynthetic growth hormone (b-hGH) Nordisk in the Escherichia coli reverse mutation assay for bacterial mutagenicity	*Escherichia coli*, WP-2, WP-2 urvA and WP-2 uvrA pKM 101		-	-	8, 40, 200 1000 and 5000 µg/plate
	Brief conclusion: No evidence of mutagenic potential of b-hGH was observed in the E. coli Reverse Mutation Assay.				
In vitro mammalian gene mutation test	Human lymphoblast TK-6		-	-	0.05, 0.1, 0.2 and 0.4 mg/ml
	Brief conclusion: No evidence of mutagenic potential of b-hGH was observed in the mammalian gene mutation test.				
Assessment of the activity of biosynthetic growth hormone (b-hGH) Nordisk the micronucleus test	Mice, NMRI	5M+5F	s.c.	Once /sampling 24, 48 or 72 hours post-dose	33 IU/kg (100 mg/kg)
	Brief conclusion: No evidence of genotoxic potential was observed in the mouse micronucleus test.				

Table 2-8: Reproductive and Developmental Toxicity Studies

Study Type	Species / Strain	Method of Admin.	Period of Dosing	Doses (mg/kg)	NOAEL (mg/kg)
Reproductive and Developmental Toxicity					
Two-generation reproduction toxicity study in the rat	Rats, Wistar (Wist/Mol)	s.c.	Only F0 females: Two weeks prior to mating and through to Day 7 of gestation. F0 males were untreated	0, 0.3, 1 and 3.3 IU/kg (0, 0.1, 0.33 and 1.1 mg/kg)	F0 Males: N.A. F0 Females: 0.3 IU/kg (0.1 mg/kg) F1 Litters: 3.3 IU/kg (1.1 mg/kg)
	Brief conclusion: The test article was not found to cause adverse effects on pregnancy or on postnatal development in the rat. Findings included increased body weight gains in the treated F0 females throughout pregnancy and lactation and increased food consumption at 1.0 and 3.3 IU/kg. In mid- and high-dose F0 females, mating took place at a reduced rate, and therefore, pregnancy rate was lower at these dose levels. The total number of implantations increased at 1 and 3.3 IU/kg as did the number of corpora lutea. Number of fetuses/litter and litter size increased at 1 IU/kg whereas increased number of early resorptions were seen in the 3.3 IU/kg group. F1 pup body weights were increased in the 3.3 IU/kg group. The number of mating days and the pregnancy rate (F1) were comparable between the control group and treated groups. Postnatal physical and functional development (F1) was not influenced by the treatment.				
Embryofetal study in the rat	Rats, Wistar (Wist/Mol)	s.c.	Day 6-17 of gestation F0 animals only	0, 0.3, 1 and 3.3 IU/kg (0, 0.1, 0.33 and 1.1 mg/kg)	F0 Females: 3.3 IU/kg (1.1 mg/kg) F1 Litters: 3.3 IU/kg (1.1 mg/kg)
	Brief conclusion: The test article was not found to cause adverse effects on pregnancy, embryofetal development or postnatal development in the rat. Body weight gain was increased in the 1 and 3.3 IU/kg groups. There were no obvious adverse effects in treated groups on litter parameters (litter size, pre- and post-implantation loss, sex ratio, litter and mean fetal weight) or on embryonic and fetal development (incidences of malformation and visceral and skeletal anomalies). Placenta weight (F0-generation) of top-dose animals was higher than control level. There was an increased incidence of wavy ribs noted at all dose levels, however, this is a reversible finding and is not considered adverse. A fraction of the pregnant rats were allowed to give birth and post-natal clinical signs, physical and functional development were evaluated in the F1 generation with no evidence of treatment-related effects. Fertility of F1 animals was not affected by the maternal treatment and no treatment-related changes found at necropsy of the F1 animals used for mating				
Pre- and post-natal study in the rat	Rats, Wistar (Wist/Mol)	s.c.	Day 17 of gestation Through weaning F0 animals only	0, 0.3, 1 and 3.3 IU/kg (0, 0.1, 0.33 and 1.1 mg/kg)	F0 Females: 3.3 IU/kg (1.1 mg/kg) F1 Males: 3.3 IU/kg (1.1 mg/kg) F1 Females: 3.3 IU/kg (1.1 mg/kg)
	Brief conclusion: The test article was not found to cause adverse effects on pregnancy, pre- and post-natal performance or offspring development in the rat. Body weight gain was increased in the 1 and 3.3 IU/kg groups. No adverse effects of treatment were observed in litter parameters (gestation period, litter size, litter growth) or on progeny development. Increased bodyweight gains were seen				

	during lactation in the F1 offspring from treated dams in the 1 and 3.3 IU/kg groups. Post-natal physical and functional development was not influenced by the treatment and no abnormal clinical signs were observed from weaning and until day 20 of pregnancy. The number of pregnancy days and the pregnancy rate (F1) were comparable between the control group and groups maternally exposed. There were no treatment-related changes found at necropsy of the F1-generation males and females used for mating.

Table 2-9: Local Tolerance Studies

Study Type	Species / Strain	Method of Admin.	Period of Dosing	Doses (mg/kg)	Gender and No. per Group
Local Tolerance					
Single dose local tolerance in rabbits	Rabbits NZW	i.m.	Once	1 ml/animal	Group 1: 10 males given 0.9% NaCl Group 2: 10 males given 10 mg Norditropin® SimpleXx® Group 3: 6 males given 10 mg Norditropin® SimpleXx® and 0.9% NaCl contralaterally.
	Brief conclusion: Injection with Norditropin® SimpleXx® 10 mg (1 ml) caused slight to moderate hemorrhage. Similarly, slight hemorrhage was seen after injection with 0.9% NaCl. Microscopically there was no difference between tissue injected with Norditropin® SimpleXx® 10 mg and 0.9% NaCl. No significant difference between group 1 and 2 in relation to Creatine Kinase depletion was observed.				

REFERENCES

1. Albanese A, Stanhope R. GH treatment induces sustained catch-up growth in children with intrauterine growth retardation: 7-year results. Horm Res. 1997; 48(4):173-7.

2. Boonstra V, Van Pareren Y, Mulder P, Hokken-Koelega A. Puberty in growth hormone-treated children born small for gestational age (SGA). J Clin Endocrinol Metab. 2003 Dec; 88(12):5753-8.

3. Chatelain P, Job JC, Blanchard J, Ducret JP, Oliver M, Sagnard L, Vanderschueren-Lodeweyckx M. Dose-dependent catch-up growth after 2 years of growth hormone treatment in intrauterine growth-retarded children. Belgian and French Pediatric Clinics and Sanofi-Choay (France). J Clin Endocrinol Metab. 1994 Jun; 78(6):1454-60.

4. Cohen P, Rogol A, Howard C, Bright G, Kappelgaard A, Rosenfeld R. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. J Clin Endocrinol Metab. 2007 Jul; 92(7):2480-2486.

5. Cohen P, Bright G, Rogol A, Kappelgaard A, Rosenfeld R. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: Implications for efficacy and safety. J Clin Endocrinol Metab. 2002; 87(1):90-98.

6. Coutant R, Carel JC, Letrait M, Bouvattier C, Chatelain P, Coste J, Chaussain JL. Short stature associated with intrauterine growth retardation: final height of untreated and growth hormone-treated children. J Clin Endocrinol Metab. 1998 Apr; 83(4):1070-4.

7. de Waal WJ, Hokken-Koelega A, Th Stijnen, SMPF de Muinck Keizer-Schrama, SLS Drop, and the Dutch Working Group on Growth Hormone. Endogenous and stimulated GH secretion, urinary GH secretion, and plasma IGF-I and IGF-II levels in prepubertal children with short stature after intrauterine growth retardation (IUGR). Clin Endocrinol 1994; 41:621-630.

8. de Zegher F, Albertsson-Wikland K, Wollmann HA, Chatelain P, Chaussain JL, Lofstrom A, Jonsson B, Rosenfeld RG. Growth hormone treatment of short children born small for gestational age: growth responses with continuous and discontinuous regimens over 6 years. J Clin Endocrinol Metab. 2000 Aug; 85(8):2816-21.

9. de Zegher F, Du Caju MV, Heinrichs C, Maes M, De Schepper J, Craen M, Vanweser K, Malvaux P, Rosenfeld RG. Early, discontinuous, high dose growth hormone treatment to normalize height and weight of short children born small for gestational age: results over 6 years. J Clin Endocrinol Metab. 1999 May; 84(5):1558-61.

10. de Zegher F, Maes M, Gargosky SE, Heinrichs C, Du Caju MV, Thiry G, De Schepper J, Craen M, Breysem L, Lofstrom A, Jonsson P, Bourguignon JP, Malvaux P, Rosenfeld RG. High-dose growth hormone treatment of short children born small for gestational age. J Clin Endocrinol Metab. 1996 May; 81(5):1887-92.

11. Hokken-Koelega A, Van Pareren Y, Sas T, Arends N. Final height data, body composition and glucose metabolism in growth hormonetreated short children small for gestational age. Horm Res. 2003; 60 Suppl 3:113-4.

12. Hokken-Koelega et al. Small for gestational age: Endocrine and metabolic consequences and effects of growth hormone treatment. J Pediatr Endocrinol Metab. 2004 Mar; 17 Suppl 3:463-9.

13. Job JC, Chaussain JL, Job B, Ducret JP, Maes M, Olivier M, Ponte C, Rochiccioli P, Vanderschueren-Lodeweyckx M, Chatelain P. Follow-up of three years of treatment with growth hormone and of one post-treatment year, in children with severe growth retardation of intrauterine onset. Pediatr Res. 1996 Feb; 39 (2):354-9.

14. Sas T, De Waal W, Mulder P, Houdijk M, Jansen M, Reeser M and Hokken-Koelega ACS. Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, doubleblind, dose- response trial. J Clin Endocrinol Metab 1999; 84(9): 3064-3070.

15. Sas T, Gerver WJ, De Bruin R, Mulder PG, Cole TJ, De Waal W and Hokken-Koelega ACS. Body proportions during 6 years of GH treatment in children with short stature born small for gestational age participating in a randomised, double-blind, dose-response trial. Clin Endocrinol (Oxf) 2000; 53(6):675-681.

16. Sas T, Mulder P, Hokken-Koelega A. Body composition, blood pressure, and lipid metabolism before and during long-term growth hormone (GH) treatment in children with short stature born small for gestational age either with or without GH deficiency. J Clin Endocrinol Metab 2000; 85(10): 3786-3792.

17. Van Pareren Y, Mulder P, Houdijk M, Jansen M, Reser M. Hokken-Koelega A. Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomised, double-blind, dose-response GH trial. J Clin Endocrinol Metab. 2003 Aug; 88(8):3584-90.

18. Van Pareren Y, Mulder P, Houdijk M, Jansen M, Reser M. Hokken-Koelega A.Effect of discontinuation of growth hormone treatment on risk factors for cardiovascular disease inadolescents born small for gestational age. J Clin Endocrinol Metab. 2003 Jan; 88(1):347-53.

PART III: CONSUMER INFORMATION

[Pr]Norditropin® SimpleXx®
Somatropin injection

[Pr]Norditropin NordiFlex®
Somatropin for injection

This leaflet is Part III of a three-part "Product Monograph" published when **Norditropin®** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Norditropin®**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Children:
- **Norditropin®** is used for the long-term treatment of children with growth failure due to an inability to produce adequate amounts of growth hormone.
- **Norditropin®** is also used for the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2.

What it does:
Norditropin® provides growth hormone for children unable to produce adequate amounts of growth hormone naturally.

Norditropin® may produce bone growth in children where the ends of the long bones have not yet hardened. **Norditropin®** has many effects on growth and metabolism.

When it should not be used:
- If the child has acute critical illness due to complications following open heart surgery, abdominal surgery, multiple trauma, or acute respiratory failure.
- If the child's growth areas of the bones have closed (closed epiphyses) and cannot grow any longer.
- If the child has active cancer or tumours. Tumours must be inactive and anti-tumour treatment must be finished before starting treatment with **Norditropin®**. Therapy with **Norditropin®** should be discontinued if evidence of cancer develops.
- **Norditropin®** is not to be used for long-term treatment of growth failure due to genetically confirmed Prader-Willi syndrome.
- There have been reports of deaths in children with Prader-Willi syndrome who were treated with growth hormone and had one or more of the following risk factors: severely obese, breathing problems, or colds and lung infections.
- If the child is hypersensitive to this drug or to any ingredient in the formulation or component of the container.

What the medicinal ingredient is:
Somatropin (recombinant human growth hormone)

What the nonmedicinal ingredients are:
histidine, mannitol, phenol, poloxamer 188 and water for injections

What dosage forms it comes in:
Norditropin® SimpleXx® is available as a cartridge in 3 strengths (5 mg/1.5 mL; 10 mg/1.5 mL and 15 mg/1.5 mL) for use with the **NordiPen®** delivery system.

Norditropin NordiFlex® is available as a pre-filled disposable pen in 3 colour coded strengths:
- 5 mg/1.5 mL pen with an orange pen cap and push button
- 10 mg/1.5 mL pen with a blue pen cap and push button
- 15 mg/1.5 mL pen with a green pen cap and push button

WARNINGS AND PRECAUTIONS

Norditropin® therapy should be carried out under the regular guidance of a doctor who is experienced in the diagnosis and management of patients with growth hormone deficiency.

BEFORE using **Norditropin®** talk to your doctor or pharmacist if:

- The child has Prader-Willi syndrome and breathing problems, sleep apnea (not breathing while sleeping), snoring or a respiratory infection.
- The child has diabetes or a family history of diabetes. If the child is on insulin, the dose may need to be adjusted because **Norditropin®** may affect the body's response to insulin.
- The child is experiencing headache, nausea, visual changes and/or vomiting. These are symptoms of a condition called intracranial hypertension.
- The child has a history of lesions or tumour of the brain.
- The child has a history of hypothyroidism (low levels of thyroid hormone), since **Norditropin®** may reduce the levels of thyroid hormone in the body.
- The child has a history of scoliosis (a condition which affects the spine). Since growth hormone increases

growth rate, patients with a history of scoliosis who are treated with **Norditropin®** should be monitored for progression of scoliosis.

If the child develops any of these symptoms during treatment with **Norditropin®** please speak with your doctor immediately**.**

*This information will help your doctor and you decide whether you should use **Norditropin®** and what extra care may need to be taken while your child is on the medication.*

INTERACTIONS WITH THIS MEDICATION

Norditropin® is generally safe to take with other medicines. You should, however, tell the doctor about all medicines that the child is taking, including those obtained without a doctor's prescription.

Corticosteroids (steroids) may decrease the effects of **Norditropin®**. If the child is currently receiving concomitant steroid therapy talk to your doctor. Doses of the steroid may need to be adjusted.

Norditropin® may also affect the body's response to insulin. Tell your doctor if your child is currently taking insulin. Your child's insulin dose may need to be adjusted.

PROPER USE OF THIS MEDICATION

*Your doctor has prescribed **Norditropin®** after carefully studying your child's case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours.*

Usual dose:
The child's doctor will calculate the dose of **Norditropin®** most appropriate for the child, based on the child's body weight.

Overdose:
Call your doctor **immediately** if your child takes more than the amount of **Norditropin®** prescribed by the doctor.

Missed Dose:
Missing doses can interfere with the effectiveness of the medication. Talk to the child's doctor if this happens. If you miss a dose, it is not recommended to double the next dose. Administer the regular dose at the next scheduled dosage time.

It is important to keep changing the injection site to minimize the risk of lipoatrophy.

If your child is taking **Norditropin NordiFlex®** please see the section "**INFORMATION ON HOW TO INJECT NORDITROPIN NORDIFLEX®**"at the end of this leaflet.

If your child is taking **Norditropin® SimpleXx®** please refer to the separate user guide provided in the package containing **NordiPen®**.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

*Unwanted effects are possible with all medicines. Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well while you are receiving treatment with **Norditropin®**.*

The following side effects may occur while using **Norditropin®**:

- Redness and itching may appear at the injection site. If this appears to be particularly troublesome or if the injection area becomes painful, you should discuss this with your child's doctor.
- Growth hormone like **Norditropin®** may bring about insulin resistance. Insulin resistance means your body cannot make good use of the insulin it produces. This causes higher levels of glucose in your blood. It is important to check your child's blood glucose levels if your child has diabetes or a family history of diabetes.
- Nausea, vomiting, headache or visual changes. If your child experiences any of these side effects notify your doctor.
- Breathing problems in patients with Prader-Willi syndrome. If your child has Prader-Willi syndrome and develops signs of breathing problems, sleep apnea (not breathing while sleeping) or new or increased snoring, contact your child's doctor.
- If the child shows an unexplained limp, or complaints of hip/knee pain, please contact your child's doctor.

*This is not a complete list of side effects. For any unexpected effects while taking **Norditropin®**, contact your doctor.*

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE NORDITROPIN®

Storage Options

Norditropin® SimpleXx® or Norditropin NordiFlex®	Before Use	In-Use (After 1st Injection)	
	Storage Requirement	Storage Option 1 (Refrigeration)	Storage Option 2 (Room Temp)
5 mg/1.5 mL	2-8 ºC Until expiry date	2-8 ºC for 4 weeks	up to 25ºC for 3 weeks
10 mg /1.5 mL			
15 mg /1.5 mL			

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novonordisk.ca or by contacting Novo Nordisk Canada Inc., at: 1-800-465-4334

This leaflet was prepared by Novo Nordisk Canada Inc.
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INFORMATION ON HOW TO INJECT NORDITROPIN NORDIFLEX®

Introduction

Norditropin NordiFlex® is a multi-dose pre-filled pen with human growth hormone solution for injection. The dose is in milligrams (mg).

Your health care professional will provide the correct dose for you.

For **Norditropin NordiFlex®** 5 mg/1.5 mL, you can use the dose selector to dial any dose from 0.025 to 1.50 mg.

For **Norditropin NordiFlex®** 10 mg/1.5 mL, you can use the dose selector to dial any dose from 0.05 to 3.00 mg.

For **Norditropin NordiFlex®** 15 mg/1.5 mL, you can use the dose selector to dial any dose from 0.075 to 4.50 mg.

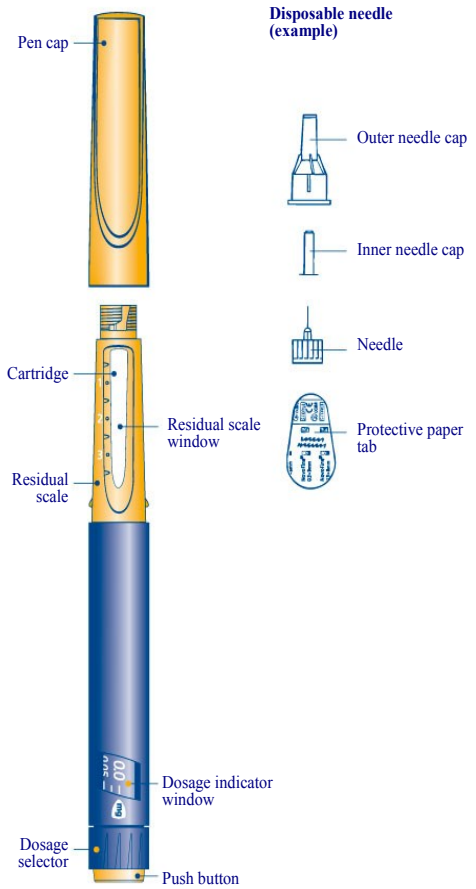
Norditropin NordiFlex® is designed to be used with **NovoFine®, NovoFine® Plus** or **NovoTwist®** disposable needles up to a length of 8 mm.

The **Norditropin NordiFlex®** pen should not be shared with anyone else.

Prior to any contact with **Norditropin NordiFlex®** wash hands thoroughly with soap and water.

Norditropin NordiFlex® should not be shaken vigorously at any time.

Please read the following instructions carefully before using **Norditropin NordiFlex®**.

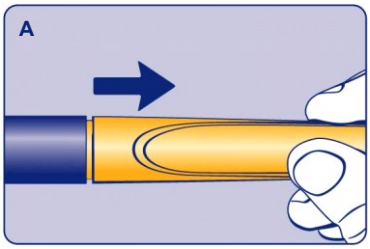


1. Check the solution

Pull off the pen cap **[A]**.

Check the solution inside the pen by turning it upside down once or twice.

Only use the **Norditropin NordiFlex®** pen if the solution inside is clear and colourless.



2. Attach the needle

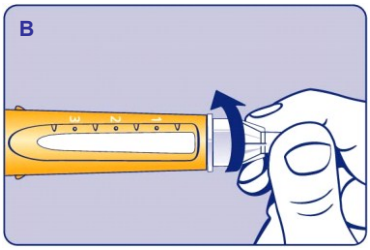
Always use a new disposable needle for each injection in order to receive the correct dose and prevent contamination.

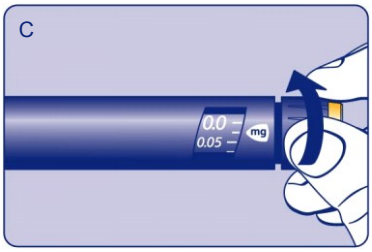
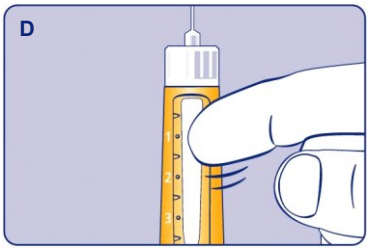
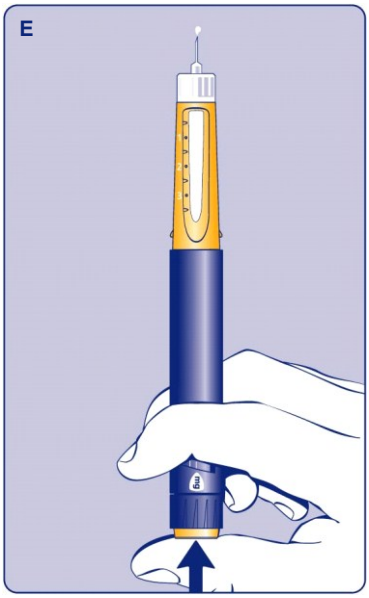
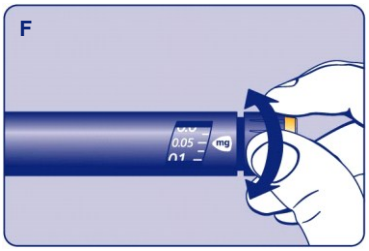
Take a new needle and **remove the protective paper tab.**

Screw the needle tightly onto the injection pen **[B]**.

The needle has two needle caps. You need to remove them both.

Pull off the outer needle cap and keep it to dispose of the used needle later.



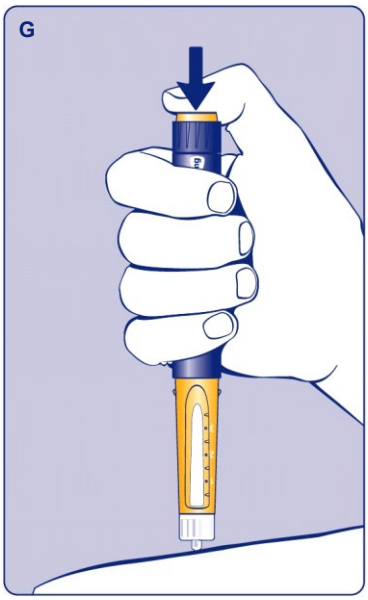
Remove the inner needle cap by pulling on the central tip and throw it away.	
3. Check the flow Before you use a new pen for the first time, you need to check the flow (called 'priming' the pen) to make sure you get the correct dose and do not inject any air **[C].** • For **Norditropin NordiFlex®** 5 mg/1.5 mL **dial** 0.025 mg. This is one 'click' after 0.0 on the dose selector at the end of the pen. • For **Norditropin NordiFlex®** 10 mg/1.5 mL **dial** 0.05 mg. This is one 'click' after 0.0 on the dose selector at the end of the pen. • For **Norditropin NordiFlex®** 15 mg/1.5 mL **dial** 0.075 mg. This is one 'click' after 0.0 on the dose selector at the end of the pen.	
Hold **Norditropin NordiFlex®** with the needle pointing upwards and tap the cartridge gently with your finger a few times **[D]**.	
Holding the **Norditropin NordiFlex®** pen with the needle upwards, press the push button at the bottom of the pen all the way in **[E]**. Repeat steps C to E until a drop of growth hormone solution appears at the needle tip. **Do not use the Norditropin NordiFlex® pen if a drop of growth hormone solution does not appear.** Always check the flow (prime the pen) before the first injection from a new **Norditropin NordiFlex®** pen. Check the flow again if your pen has been dropped or knocked against a hard surface or if you are not sure that **Norditropin NordiFlex®** works properly.	
4. Dial the dose Check that the dosage selector is set at 0.0. Dial the number of mg your doctor has recommended for you **[F]**. The dose can be increased or decreased by turning the dosage selector in either direction. When dialing back, be careful not to press the push button as growth hormone will come out. You cannot set a dose larger than the amount of solution left in the pen.	
5. Inject the solution	

Use the injection technique recommended to you. Your doctor or nurse will teach you how to locate appropriate injection sites. It is very important that you rotate the site of an injection each time you give the medication.

Prepare the injection site by wiping with an alcohol swab.

Insert the needle into your skin. Deliver the dose by pressing the push button all the way in. Be careful only to press the push button when injecting **[G]**.

After the injection, keep the needle under the skin for at least 6 seconds and then withdraw it. Keep the push button fully depressed until the needle is withdrawn from the skin. This ensures that you get the full dose.



6. Remove the needle

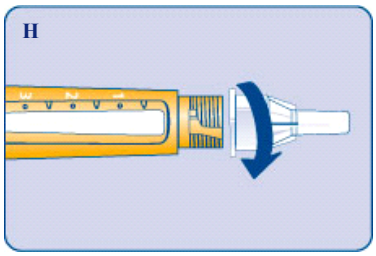
Replace the outer needle cap and unscrew the needle **[H]**. Dispose of it carefully.

Always use a new needle for each injection and always remove a used needle immediately after the injection. If you do not remove the needle immediately, air may enter into the cartridge, which may mean you get the wrong dose next time.

Caregivers should be most careful when handling used needles to avoid needle sticks.

When the **Norditropin NordiFlex®** pen is empty, dispose of it carefully without the needle attached.

Ask your health care professional how to dispose of used needles and empty **Norditropin NordiFlex®** pens.



7. Maintenance

Look after your **Norditropin NordiFlex®** pen so that it continues to work accurately and safely.

Norditropin NordiFlex® should be handled with care. Avoid situations where **Norditropin NordiFlex®** might be damaged.

Protect **Norditropin NordiFlex®** from dust, dirt and direct sunlight.

You can clean the exterior of your **Norditropin NordiFlex®** by wiping it with cotton wool moistened with alcohol.

Do not soak **Norditropin NordiFlex®** in alcohol, wash, or lubricate it as this may damage it.