Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Norditropin NordiFlex 5 mg/1.5 ml solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Norditropin NordiFlex: 5 mg/1.5 ml
One ml of solution contains 3.3 mg somatropin

Somatropin (recombinant DNA origin produced in E-coli)

1 mg of somatropin corresponds to 3 IU (International Unit) of somatropin

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen

Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Children:
Growth failure due to growth hormone deficiency (GHD)
Growth failure in girls due to gonadal dysgenesis (Turner syndrome)
Growth retardation in prepubertal children due to chronic renal disease
Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later.
Growth failure due to Noonan syndrome.

Adults:
Childhood onset growth hormone deficiency:
Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after growth completion. Testing is not required for those with more than three pituitary hormone deficits, with severe GHD due to a defined genetic cause, due to structural hypothalamic pituitary abnormalities, due to central nervous system tumours or due to high-dose cranial irradiation, or with GHD secondary to a pituitary/hypothalamic disease or insult, if measurements of serum insulin-like growth factor 1 (IGF-1) is < -2 SDS after at least four weeks off growth hormone treatment.
In all other patients an IGF-1 measurement and one growth hormone stimulation test is required.

Adult onset growth hormone deficiency:
Pronounced GHD in known hypothalamic-pituitary disease, cranial irradiation and traumatic brain injury. GHD should be associated with one other deficient axis, other than prolactin. GHD should be demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis.
In adults, the insulin tolerance test is the provocative test of choice. When the insulin tolerance test is contraindicated, alternative provocative tests must be used. The combined arginine-growth hormone releasing hormone is recommended. An arginine or glucagon test may also be considered; however, these tests have less established diagnostic value than the insulin tolerance test.

4.2 Posology and method of administration

Norditropin should only be prescribed by doctors with special knowledge of the therapeutic indication of use.

Posology
The dosage is individual and must always be adjusted in accordance with the individual's clinical and biochemical response to therapy.

Generally recommended dosages:
Paediatric population:
Growth hormone insufficiency
0.025-0.035 mg/kg/day or 0.7-1.0 mg/m ^{2}/day
When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual (for guidance on dosing, see Replacement therapy in adults).

Turner syndrome
0.045-0.067 mg/kg/day or 1.3-2.0 mg/m ^{2}/day

Chronic renal disease
0.050 mg/kg/day or 1.4 mg/m^2/day (see section 4.4)

Small for Gestational Age
0.035 mg/kg/day or 1.0 mg/m^2/day

A dose of 0.035 mg/kg/day is usually recommended until final height is reached (see section 5.1).
Treatment should be discontinued after the first year of treatment, if the height velocity SDS is below +1.
Treatment should be discontinued if height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

Noonan syndrome:
0.066 mg/kg/day is the recommended dose, however in some cases 0.033 mg/kg/day may be sufficient (see section 5.1).
Treatment should be discontinued at the time of epiphyseal closure (see section 4.4).

Adult population:
Replacement therapy in adults
The dosage must be adjusted to the need of the individual patient.
In patients with childhood onset GHD, the recommended dose to restart is 0.2-0.5 mg/day with subsequent dose adjustment on the basis of IGF-1 concentration determination.
In patients with adult onset GHD, it is recommended to start treatment with a low dose: 0.1-0.3 mg/day. It is recommended to increase the dosage gradually at monthly intervals based on the clinical response and the patient's experience of adverse events. Serum IGF-1 can be used as guidance for the dose titration. Women may require higher doses than men, with men showing an increasing IGF-1 sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are undertreated while men are overtreated.
Dose requirements decline with age. Maintenance dosages vary considerably from person to person, but seldom exceed 1.0 mg/day.

Method of administration
Generally, daily subcutaneous administration in the evening is recommended. The injection site should be varied to prevent lipoatrophy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting growth hormone (GH) therapy. Treatment should be discontinued if there is evidence of tumour growth.

Somatropin should not be used for longitudinal growth promotion in children with closed epiphyses.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure, or similar conditions should not be treated with somatropin (see section 4.4).

In children with chronic renal disease, treatment with Norditropin NordiFlex should be discontinued at renal transplantation.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Children treated with somatropin should be regularly assessed by a specialist in child growth. Somatropin treatment should always be instigated by a physician with special knowledge of growth hormone insufficiency and its treatment. This is true also for the management of Turner syndrome, chronic renal disease, SGA and Noonan syndrome. Data of final adult height following the use of Norditropin are limited for children with Noonan Syndrome and are not available for children with chronic renal disease.

The maximum recommended daily dose should not be exceeded (see section 4.2).

The stimulation of longitudinal growth in children can only be expected until epiphyseal closure.

Children
Treatment of growth hormone deficiency in patients with Prader-Willi syndrome
There have been reports of sudden death after initiating somatropin therapy in patients with Prader-Willi syndrome, who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

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

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 patients with Silver-Russell syndrome is limited.

Turner syndrome
Monitoring of growth of hands and feet in Turner syndrome patients treated with somatropin is recommended, and a dose reduction to the lower part of the dose range should be considered if increased growth is observed.

Girls with Turner syndrome generally have an increased risk of otitis media, which is why otological evaluation is recommended on at least an annual basis.

Chronic renal disease
The dosage in children with chronic renal disease is individual and must be adjusted according to the individual response to therapy (see section 4.2). The growth disturbance should be clearly established before somatropin treatment by following growth on optimal treatment for renal disease over one year. Conservative management of uraemia with customary medicinal product and if needed dialysis should be maintained during somatropin therapy.

Patients with chronic renal disease normally experience a decline in renal function as part of the natural course of their illness. However, as a precautionary measure during somatropin treatment, renal function should be monitored for an excessive decline or increase in the glomerular filtration rate (which could imply hyperfiltration).

Scoliosis
Scoliosis is known to be more frequent in some of the patient groups treated with somatropin for example Turner syndrome and Noonan syndrome. In addition, rapid growth in any child can cause progression of scoliosis. Somatropin has not been shown to increase the incidence or severity of scoliosis. Signs of scoliosis should be monitored during treatment.

Blood glucose and insulin
In Turner syndrome and SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk of diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans), oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, somatropin should not be administered.

Somatropin has been found to influence carbohydrate metabolism, therefore, patients should be observed for evidence of glucose intolerance.

IGF-1
In Turner syndrome and SGA children it is recommended to measure the IGF-1 level before start of treatment and twice a year thereafter. If on repeated measurements IGF-1 levels exceed +2 SD compared to references for age and pubertal status, the dose should be reduced to achieve an IGF-1 level within the normal range.
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.

Adults
Growth hormone deficiency in adults
Growth hormone deficiency in adults is a lifelong disease and needs to be treated accordingly, however, experience in patients older than 60 years and in patients with more than five years of treatment in adult growth hormone deficiency is still limited.

Adults and Children
Pancreatitis
Although rare, pancreatitis should be considered in somatropin-treated patients who develop abdominal pain, especially in children.

General
Neoplasms
There is no evidence for increased risk of new primary cancers in children or in adults treated with somatropin.

In patients in complete remission from tumours or malignant disease, somatropin therapy has not been associated with an increased relapse rate.

An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for second neoplasms seems to be prior exposure to radiation.

Patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of somatropin therapy.

Leukaemia
Leukaemia has been reported in a small number of growth hormone deficient patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in somatropin recipients without predisposition factors.

Benign intracranial hypertension
In the event of severe or recurrent headache, visual problems, nausea, and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the somatropin treatment should be discontinued.

At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If somatropin treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

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

Thyroid function
Somatropin increases the extrathyroidal conversion of T4 to T3 and may, as such, unmask incipient hypothyroidism. Monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism, standard replacement therapy must be closely monitored when somatropin therapy is administered.

In patients with a pituitary disease in progression, hypothyroidism may develop.

Patients with Turner syndrome have an increased risk of developing primary hypothyroidism associated with anti-thyroid antibodies. As hypothyroidism interferes with the response to somatropin therapy patients should have their thyroid function tested regularly and should receive replacement therapy with thyroid hormone when indicated.

Insulin sensitivity
Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance (see section 4.5). For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin containing product therapy is instituted. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy.

Antibodies
As with all somatropin containing products, a small percentage of patients may develop antibodies to somatropin. The binding capacity of these antibodies is low, and there is no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy.

Acute adrenal insufficiency
Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see section 4.5).

Use with oral oestrogen therapy
If a woman taking somatropin begins oral oestrogen therapy, the dose of somatropin may need to be increased to maintain the serum IGF-1 levels within the normal age-appropriate range. Conversely, if a woman on somatropin discontinues oral oestrogen therapy, the dose of somatropin may need to be reduced to avoid excess of growth hormone and/or side effects (see section 4.5).

Slipped capital femoral epiphysis
In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. A patient treated with somatropin who develops a limp or complains of hip or knee pain should be evaluated by a physician.

Clinical trial experience
Two placebo-controlled clinical trials of patients in intensive care units have demonstrated an increased mortality among patients suffering from acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure, who were treated with somatropin in high doses (5.3-8 mg/day). The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.

One open-label, randomised clinical trial (dose range 0.045-0.090 mg/kg/day) with patients with Turner syndrome indicated a tendency for a dose-dependent risk of otitis externa and otitis media. The increase in ear infections did not result in more ear operations/tube insertions compared to the lower dose group in the trial.

Excipients
Norditropin contains less than 1 mmol sodium (23 mg) per 1.5 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effect of Norditropin. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth. Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.4).

Data from an interaction study performed in growth hormone deficient adults suggest that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds

metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

The effect of somatropin on final height can also be influenced by additional therapy with other hormones, e.g. gonadotropin, anabolic steroids, oestrogen and thyroid hormone.

In insulin treated patient's adjustment of insulin dose may be needed after initiation of somatropin treatment (see section 4.4).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies are insufficient with regard to effects on pregnancy, embryo-foetal development, parturition or postnatal development. No clinical data on exposed pregnancies are available.
Therefore, somatropin containing products are not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
There have been no clinical studies conducted with somatropin containing products in breast-feeding women. It is not known whether somatropin is excreted in human milk. Therefore caution should be exercised when somatropin containing products are administered to breast-feeding women.

Fertility
Fertility studies with Norditropin have not been performed.

4.7 Effects on ability to drive and use machines

Norditropin NordiFlex has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Growth hormone deficient patients are characterised by extracellular volume deficit. When treatment with somatropin is initiated, this deficit is corrected. Fluid retention with peripheral oedema may occur especially in adults. Carpal tunnel syndrome is uncommon, but may be seen in adults. The symptoms are usually transient, dose dependent and may require transient dose reduction.
Mild arthralgia, muscle pain and paresthesia may also occur but are usually self-limiting.

Adverse reactions in children are uncommon or rare.

Clinical trial experience:

System organ classes	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Metabolism and nutrition disorders			In adults Diabetes mellitus type 2	
Nervous system disorders		In adults headache and paraesthesia	In adults carpal tunnel syndrome. In children headache	
Skin and subcutaneous tissue disorders			In adults pruritus	In children rash
Musculoskeletal, connective		In adults arthralgia,	In adults muscle stiffness	In children arthralgia

tissue disorders		joint stiffness and myalgia		and myalgia
Reproductive system and breast disorders			In adults and children Gynaecomastia	
General disorders and administration site conditions	In adults peripheral oedema (see text above)		In adults and children injection site pain. In children injection site reaction	In children peripheral oedema

In children with Turner syndrome increased growth of hands and feet has been reported during somatropin therapy.

A tendency for increased incidence of otitis media in Turner syndrome patients treated with high doses of Norditropin has been observed in one open-label randomised clinical trial. However, the increase in ear infections did not result in more ear operations/tube insertions compared to the lower dose group in the trial.

Post-marketing experience:
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. Frequencies of these adverse events cannot be estimated from the available data:

- Neoplasms benign and malignant (including cysts and polyps):Leukaemia has been reported in a small number of growth hormone deficiency patients (see section 4.4)
- Immune system disorders:Hypersensitivity (see section 4.3). Formation of antibodies directed against somatropin. The titres and binding capacities of these antibodies have been very low and have not interfered with the growth response to Norditropin administration
- Endocrine disorders: Hypothyroidism. Decrease in serum thyroxin levels (see section 4.4)
- Metabolism and nutrition disorders: Hyperglycaemia (see section 4.4)
- Nervous system disorders: Benign intracranial hypertension (see section 4.4)
- Musculoskeletal and connective tissue disorders: Legg-Calvé-Perthes disease. Legg-Calvé-Perthes disease may occur more frequently in patients with short stature
- Investigations: Increase in blood alkaline phosphatase level.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Acute overdosage can lead to low blood glucose levels initially, followed by high blood glucose levels. These decreased glucose levels have been detected biochemically, but without clinical signs of hypoglycemia. Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatropin and somatropin agonists. ATC: H01AC01.

Mechanism of action

Norditropin NordiFlex contains somatropin, which is human growth hormone produced by recombinant DNA-technology. It is an anabolic peptide of 191 amino acids stabilised by two disulphide bridges with a molecular weight of approximately 22,000 Daltons.

The major effects of somatropin are stimulation of skeletal and somatic growth and pronounced influence on the body's metabolic processes.

Pharmacodynamic effects
When growth hormone deficiency is treated a normalisation of body composition takes place resulting in an increase in lean body mass and a decrease in fat mass.
Somatropin exerts most of its actions through insulin-like growth factor 1 (IGF-1), which is produced in tissues throughout the body but predominantly by the liver.
More than 90% of IGF-1 is bound to binding proteins (IGFBPs) of which IGFBP-3 is the most important.

A lipolytic and protein sparing effect of the hormone becomes of particular importance during stress.

Somatropin also increases bone turnover indicated by an increase in plasma levels of biochemical bone markers. In adults bone mass is slightly decreased during the initial months of treatment due to more pronounced bone resorption, however, bone mass increases with prolonged treatment.

Clinical efficacy and safety
In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg/day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg/day) and +2.19 SDS (0.067 mg/kg/day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. Long-term safety data are still limited.

A growth promoting effect was observed following 104 weeks (primary endpoint) and 208 weeks treatment with once-daily dosing of Norditropin 0.033 mg/kg/day and 0.066 mg/kg/day in 51 children aged 3 to <11 years with short stature due to Noonan syndrome.

A statistically significant increase from baseline in mean height SDS at 104 weeks (primary endpoint) was observed with 0.033 mg/kg/day (0.84 SDS) and 0.066 mg/kg/day (1.47 SDS). A mean difference of 0.63 SDS [95 % CI: 0.38; 0.88] was observed between the groups at 104 weeks; the difference was greater after 208 weeks with an mean difference of 0.99 SDS [95 % CI: 0.62; 1.36] (figure 1).

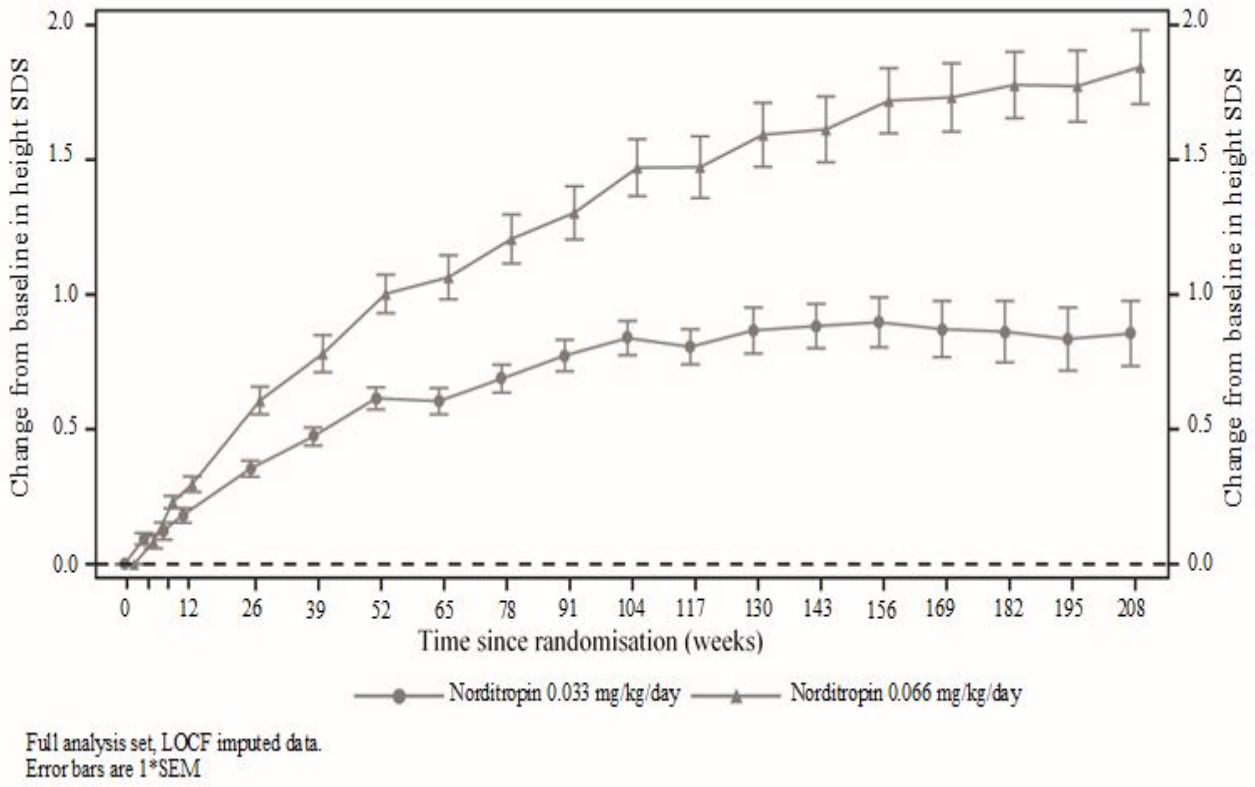
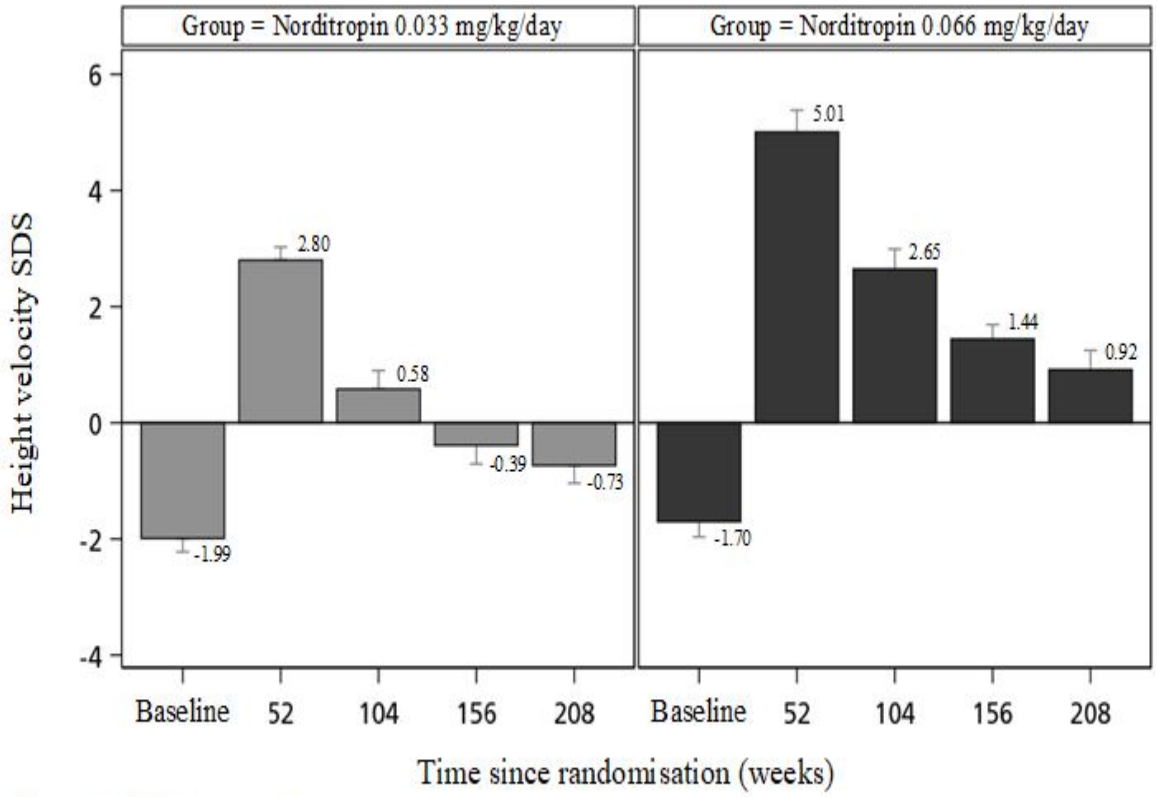


Figure 1 Height SDS (national) change from baseline to week 208

The mean height velocity and height velocity SDS increased markedly from baseline during the first year of treatment with a greater increase with 0.066 mg/kg/day than with 0.033 mg/kg/day. The mean height velocity SDS was maintained above 0 in both groups after a two-year treatment and also after four years of treatment in the 0.066 mg/kg/day group. The height velocity SDS was greater with 0.066 mg/kg/day than with 0.033 mg/kg/day throughout the trial period (figure 2).



Full analysis set, LOCF imputed data.
Baseline: Height velocity from 1 year prior to screening to week 0.
Error bars are 1*SEM

Figure 2 Height velocity SDS (national) from baseline to week 208

Final height data were collected in 24 paediatric patients (18 included in a two-year prospective, open label, randomised, parallel group study and six who had followed the protocol without randomisation). After the initial two-years prospective study, Norditropin continued until final height. At the end of the treatment the majority of the subjects (16/24) achieved a final height within the normal national reference range (> 2 SDS).

5.2 Pharmacokinetic properties

I.v. infusion of Norditropin (33 ng/kg/min for 3 hours) to nine growth hormone deficient patients, gave the following results: serum half-life of 21.1±1.7 min., metabolic clearance rate of 2.33±0.58 ml/kg/min. and a distribution space of 67.6±14.6 ml/kg.

S.c. injection of Norditropin SimpleXx (Norditropin SimpleXx is the cartridge containing the solution for injection in Norditropin NordiFlex) 2.5 mg/m^2 in 31 healthy subjects (with endogenous somatropin suppressed by continuous infusion of somatostatin) gave the following results:
Maximal concentration of human growth hormone (42-46 ng/ml) after approximately 4 hours. Thereafter human growth hormone declined with a half-life of approximately 2.6 hours.
In addition the different strengths of Norditropin SimpleXx were demonstrated to be bioequivalent to each other and to Norditropin for reconstitution after subcutaneous injection to healthy subjects.

5.3 Preclinical safety data

The general pharmacological effects on the CNS, cardiovascular and respiratory systems following administration of Norditropin SimpleXx with and without forced degradation were investigated in mice and rats; renal function was also evaluated. The degraded product showed no difference in effect when compared with Norditropin SimpleXx and Norditropin. All three preparations showed the expected dose dependent decrease in urine volume and retention of sodium and chloride ions.

In rats, similar pharmacokinetics has been demonstrated between Norditropin SimpleXx and Norditropin. Degraded Norditropin SimpleXx has also been demonstrated to be bioequivalent with Norditropin SimpleXx.

Single and repeated dose toxicity and local tolerance studies of Norditropin SimpleXx or the degraded product did not reveal any toxic effect or damage to the muscle tissue.

The toxicity of poloxamer 188 has been tested in mice, rats, rabbits and dogs and no findings of toxicological relevance were revealed.
Poloxamer 188 was rapidly absorbed from the injection site with no significant retention of the dose at the site of injection.
Poloxamer 188 was excreted primarily via the urine.

Norditropin SimpleXx is the cartridge containing the solution for injection in Norditropin NordiFlex.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Histidine
Poloxamer 188
Phenol
Water for injection
Hydrochloric acid for pH adjustment
Sodium hydroxide for pH adjustment.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening: Store for a maximum of 4 weeks in a refrigerator (2°C – 8°C).
Alternatively, the medicinal product may be stored for a maximum of 3 weeks below 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) in the outer carton, in order to protect it from light. Do not freeze. Do not store close to any cooling elements. For storage conditions after first opening of the medicinal product, see section 6.3. Do not freeze.

When in use, always replace the pen cap on the Norditropin NordiFlex pre-filled pen after each injection. Always use a new needle for each injection.
The needle must not be screwed onto the pre-filled pen when it is not in use.

6.5 Nature and contents of container

Norditropin NordiFlex 5 mg/1.5 ml is a multidose disposable pre-filled pen, which consists of a cartridge (Type I colourless glass) permanently sealed in a plastic pen-injector. The cartridge is closed at the bottom with a rubber stopper (Type I rubber closures) shaped as a plunger and at the top with a laminated rubber stopper (Type I rubber closures) shaped as a disc and sealed with an aluminium cap. The push button on the pen-injector is coloured orange. Pack sizes of 1 pre-filled pen and multipacks with 5 and 10 x 1 pre-filled pens. Not all pack sizes may be marketed.

The pre-filled pen is packed in a carton.

6.6 Special precautions for disposal and other handling

Norditropin NordiFlex is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm.
Norditropin NordiFlex 5 mg/1.5 ml delivers a maximum of 1.5 mg somatropin per dose, in increments of 0.025 mg somatropin.

To ensure proper dosing and avoid injection of air, check the growth hormone flow before the first injection. Do not use Norditropin NordiFlex if a drop of growth hormone does not appear at the needle tip. A dose is selected by turning the dose selector, until the desired dose appears at the window of the housing. If the wrong dose is selected, the dose can be corrected by turning the dosage selector the opposite way. The push button is pressed to inject the dose.

Norditropin NordiFlex should not be shaken vigorously at any time.

Do not use Norditropin NordiFlex if the growth hormone solution for injection is cloudy or discoloured. Check this by turning the pen upside down once or twice.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0218/040/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 September 2004
Date of lastest renewal: 31 December 2008

10 DATE OF REVISION OF THE TEXT

December 2022