PROFESSIONAL INFORMATION FOR NORDITROPIN®

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Norditropin® 5 mg solution for injection

Norditropin® 10 mg solution for injection

Norditropin® 15 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Norditropin® 5 mg: contains somatropin 5 mg per 1,5 mL (equivalent to 3,33 mg per mL).

Norditropin® 10 mg: contains somatropin 10 mg per 1,5 mL (equivalent to 6,7 mg per mL).

Norditropin® 15 mg: contains somatropin 15 mg per 1,5 mL (equivalent to 10,0 mg per mL).

Excipients with known effects:

Preservative:

Phenol 0,3 % *m/v.*

Contains sweetener:

Norditropin® 5 mg and 10 mg: Each mL contains 40 mg mannitol.

Norditropin® 15 mg: Each mL contains 39 mg mannitol.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Norditropin® is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of children who have growth failure due to somatropin deficiency. The diagnosis should be verified by an investigation of pituitary function before the preparation is administered. Norditropin® is only effective as long as the epiphysial fusion has not taken place.
  Levels of growth hormone or IGF-1 are not required to commence treatment but may be required to set the diagnosis of growth hormone deficiency.
- Turner syndrome.
  In Turner syndrome 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.

4.2 Posology and method of administration

Posology

1 mg of somatropin corresponds to 3 IU (international unit) of somatropin.

The dosage is individual, based on body weight or body surface and must always be adjusted in accordance with the individual's response to therapy.

Generally, daily subcutaneous administration in the evening is recommended.

The injection site should be varied to prevent lipo-atrophy.

Pre-treatment glucose tolerance should be assessed by means of fasting blood glucose and HbA1c. These parameters should be monitored during treatment.

Growth hormone deficiency

0,025 - 0,035 mg/kg/day

The Norditropin® dosage and administration schedule should be individualised based on the growth response of each patient. Serum insulin-like growth factor I (IGF-1) levels may be useful during dose titration.

Turner syndrome

0,045 – 0,067 mg/kg/day

The Norditropin ® dosage and administration schedule should be individualised based on the growth response of each patient.

Method of administration

Patients should wash their hands thoroughly with soap and water and/or disinfectant prior to contact with Norditropin®.

The solution should be protected from light and not be shaken vigorously at any time.

Norditropin® is a pre-filled pen designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm.

Norditropin ® 5 mg/1,5 mL delivers a maximum of 1,5 mg somatropin per dose in increments of 0,025 mg somatropin.

Norditropin ® 10 mg/1,5 mL delivers a maximum of 3,0 mg somatropin per dose in increments of 0,050 mg somatropin.

Norditropin ® 15 mg/1,5 mL delivers a maximum of 4,5 mg somatropin per dose in increments of 0,075 mg somatropin.

To ensure proper dosing and avoid injection of air, the flow must be checked before the first injection. A dose is selected by turning the dosage 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.

Always use a new needle for each injection.

Always replace the pen cap on the Norditropin ® pre-filled pen after each injection.

The needle must not be screwed onto the pre-filled pen when it is not in use.

4.3 Contraindications

Hypersensitivity to somatropin or to any of the other ingredients in Norditropin ® (see section 6.1).

Norditropin ® should not be used when there is any evidence of activity of any tumour. Intracranial neoplasm must be inactive and anti-tumour therapy should be complete prior to the institution of therapy.

Norditropin ® should be discontinued if there is any evidence of recurrent tumour growth and the patient should be thoroughly re-examined.

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

Patients with acute critical illness suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Norditropin ®.

Growth hormone is contraindicated in patients with proliferative or pre-proliferative diabetic retinopathy.

Uncontrolled or poorly controlled diabetes mellitus (Type I and II).

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Children treated with Norditropin® should be regularly assessed by a specialist in child growth.

Norditropin ® treatment should always be investigated by a medical practitioner with special knowledge of growth hormone insufficiency and its treatment.

This is also true for the management of Turner syndrome.

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

The stimulation of skeletal growth in children can only be expected until the epiphysial discs are closed.

Turner syndrome

Monitoring the growth of hands and feet in Turner syndrome patients treated with growth hormone 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 have an increased risk of otitis media, therefore regular otological evaluation is recommended.

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

Scoliosis

Scoliosis is known to be more frequent in some of the patient groups treated with somatropin for example Turner 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 children it is recommended to measure fasting blood glucose before the start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be considered. If overt diabetes occurs, growth hormone should not be administered.

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

IGF-1

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

Neoplasms

There is no evidence for increased risk of new primary cancers in children treated with Norditropin®.

In patients in complete remission from tumours or malignant disease, growth hormone 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 Norditropin® therapy.

Leukaemia

Leukaemia has been reported in a small number of growth hormone deficient patients some of whom have been treated with somatropin. Based on 10 years of global assessment there is no indication of increased risk of development of leukaemia during somatropin treatment.

Benign intracranial hypertension

Some cases of benign intracranial hypertension have been reported.
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 growth hormone treatment should be discontinued.
At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone therapy is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Thyroid function

A state of hypothyroidism may develop during Norditropin® treatment due to the increased peripheral deiodination of T4 to T3.
Monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism, standard replacement therapy must be closely monitored when Norditropin® treatment is administered.

In patients with a pituitary disease in progression, hypothyroidism may also 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 Norditropin® therapy patients should have a periodic thyroid function test and should be treated 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).

Due to the diabetogenic action of growth hormone, Norditropin® should be used with caution in patients with diabetes mellitus or with a family history of diabetes mellitus. In insulin treated patients adjustment of insulin dose may be needed after initiation of Norditropin® treatment.

Patients with diabetes or glucose intolerance should be monitored closely during Norditropin® treatment.

Antibodies

Formation of antibodies directed against somatropin has been observed during therapy. The binding capacity of these antibodies is low, and there is no effect on growth rate. Patients failing to respond to treatment should be tested for antibodies.

Acute adrenal insufficiency

Introduction of Norditropin® treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with Norditropin®, 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 Norditropin® treatment (see section 4.5).

Slipped capital femoral epiphysis

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders and Legg-Calvé-Perthes disease may occur more frequently in patients with short stature. These diseases may present as the development of a limp or complaints of hip or knee pain and medical practitioners and parents should be alerted to this possibility.

Pancreatitis

Although rare, pancreatitis should be considered in somatropin-treated patients who develop severe abdominal pain, especially in children.

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.

4.5 Interaction with other medicines and other forms of interaction

Concomitant glucocorticoid therapy may inhibit growth and thereby oppose the growth-promoting effect of Norditropin®.

Patients with adrenocorticotropic hormone (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).

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 growth hormone 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 patients, adjustment of insulin dose may be needed after initiation of Norditropin® treatment (see section 4.4).
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Norditropin® is contraindicated during pregnancy (see section 4.3). In the event of pregnancy occurring during treatment, Norditropin® therapy should be discontinued.

Lactation

The possibility that somatropin is secreted in breast milk cannot be discounted.
Mothers should not breastfeed their infants while on Norditropin® therapy.

Fertility

Fertility studies with Norditropin® have not been performed.

4.7 Effects on ability to drive and use machines

No influence on ability to drive and use machines.

4.8 Undesirable effects

Growth hormone deficient patients are characterised by extracellular volume deficit. When treatment with Norditropin® is initiated, this deficit is corrected.

Mild arthralgia, muscle pain and paraesthesia may occur.

Adverse reactions in children are uncommon or rare.

Clinical trial experience:

System organ class	**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**
Nervous system disorders			Headache	
Skin and subcutaneous tissue disorders				Rash
Musculoskeletal and connective tissue disorders				Arthralgia, myalgia
Reproductive system and breast disorders			Gynaecomastia	
General disorders and administration site conditions			Injection site pain, injection site reaction	Peripheral oedema

In children with Turner syndrome increased growth of hands and feet has been reported during Norditropin® 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 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: Generalised hypersensitivity reactions (e.g. anaphylactic reactions) have been reported. 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X

SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and to Novo Nordisk (Pty) Ltd at infoZa@novonordisk.com or telephone 010 500 8699 (toll free).

4.9 Overdose

Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. These decreased glucose levels have been detected biochemically, but without clinical signs of hypoglycaemia.

Long-term overdosage could result in signs and symptoms consistent with the effects of excess human growth hormone (acromegaly).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.10 Trophic hormones

Pharmacotherapeutic group: Somatropin and somatropin agonists

ATC code: H01AC01

Somatropin is an anabolic peptide of 191 amino acids stabilised by two disulphide bridges with a molecular weight of 22 125 Daltons.

Somatropin increases the growth rate by stimulation of the protein synthesis and other metabolic processes.

Somatropin exerts most of its actions through insulin-like growth factor I (IGF-1), which are produced in tissues throughout the body, but predominantly by the liver.

More than 90 % of IGF-1 is bound to binding proteins (IGFBP's) of which IGFBP-3 is the most important.

Somatropin also increases bone turnover indicated by an increase in plasma levels of biochemical bone makers.

5.2 Pharmacokinetic properties

Intravenous 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.

Subcutaneous injection of Norditropin® (2,5 mg/m^2) to 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.

5.3 Preclinical safety data

The general pharmacological effects on the central nervous system (CNS), cardiovascular and respiratory systems following administration of somatropin with and without forced degradation were investigated in mice and rats; renal function was also evaluated. The preparation showed the expected dose dependent decrease in urine volume and retention of sodium and chloride ions.

Single and repeated dose toxicity and local tolerance studies of somatropin 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Hydrochloric acid (E507)/Sodium hydroxide (E425) (for pH adjustment)

Mannitol (E421)

Poloxamer 188

Phenol

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, Norditropin® must not be mixed with other medicines.

6.3 Shelf life

2 years.

Store at 2 ˚C – 8 ˚C (in a refrigerator) in the outer carton.

6.4 Special precautions for storage

Do not freeze.

Do not store close to any cooling elements.

After first use, Norditropin® may be kept up to a maximum of 28 days at 2 ˚C – 8 ˚C (in a refrigerator).

Alternatively, Norditropin® 5 mg and 10 mg may be stored at room temperature not exceeding 25 ˚C for a maximum of 21 days. Always keep Norditropin® 15 mg up to a maximum of 28 days at 2 ˚C – 8 ˚C (in a refrigerator) after first use.

Norditropin® which has been frozen or exposed to excessive temperatures should not be used.

Never use Norditropin® after the expiry date printed on the package.

6.5 Nature and contents of container

Norditropin® comes in a disposable pen.

Disposable pen

This is a multi-dose disposable pre-filled pen, which consists of a 1,5 mL cartridge (Type I colourless glass) permanently sealed in a plastic pen-injector. The cartridge is closed at the bottom with a rubber stopper shaped as a plunger and at the top with a laminate
rubber stopper shaped as a disc and sealed with an aluminium cap.

The push button on the pen-injector is colour coded according to strength.

5 mg/1,5 mL – orange.

10 mg/1,5 mL – blue.

15 mg/1,5 mL – green.

The pre-filled pen is packed in a carton.

6.6 Special precautions for disposal and other handling

For instructions on handling of Norditropin®, see section 4.2.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

90 Grayston Drive

Sandown

Sandton

Gauteng

2031

8. REGISTRATION NUMBERS

Norditropin® 5 mg: 33/21.10/0420

Norditropin® 10 mg: 33/21.10/0421

Norditropin® 15 mg: 33/21.10/0422

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 May 2001

10. DATE OF REVISION OF THE TEXT

23 December 2025