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# NORDITROPIN® NORDILET® 15 MG/1.5 ML

*NOVO NORDISK A/S*

## 1. Name of the medicinal product

Norditropin® NordiLet® 15 mg/1.5 ml

Pre-filled pen, solution for injection

## 2. Composition

Norditropin® NordiLet® is a solution for injection into the skin in a multi-dose disposable pre-filled pen.

Norditropin® NordiLet® contains biosynthetic human growth hormone (somatropin), which is the active substance. Other ingredients are: Mannitol, histidine, poloxamer 188, phenol and water for injections.

## 3. Pharmacotherapeutic group

Somatropin is an endocrine hormone with metabolic and growth promoting effects.

## 4. Indications

***Children:***

Growth failure due to growth hormone insufficiency, growth failure in girls due to gonadal dysgenesis (Turner syndrome), growth retardation in prepubertal children due to chronic renal disease and short children born small for gestational age (SGA).

***Adults:***

Pronounced growth hormone deficiency in known hypothalamicpituitary disease (one other deficient axis, other than prolactin), demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis.

Childhood onset growth hormone insufficiency, reconfirmed by two provocative tests.

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.

## 5. Dosage and administration

Norditropin® NordiLet® is a pre-filled pen, which is designed to be used with NovoFine® needles. The dose is delivered in clicks. Norditropin® NordiLet® delivers 1–29 clicks in increments of 1 click for each injection.

The dose per click is 0.2000 mg (15 mg/1.5 ml). In the package leaflet for each strength a range of doses in mg per number of clicks is given in a conversion table.

The dosage is individual. Generally, daily subcutaneous injection in the evening is recommended. The injection site should be varied to prevent lipoatrophy. Prescription only.

For the injection procedure, please see the instruction manual for Norditropin® NordiLet® 15 mg/1.5 ml.

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

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

General recommendations for dosages are shown below.

**Children:**

***Growth hormone insufficiency:***

25 to 35 microgram/kg/day or 0.7 to 1.0 mg/m²/day

***In children with Turner syndrome:***

45 to 67 microgram/kg/day or 1.3 to 2.0 mg/m²/day

***In children with Chronic renal disease:***

50 microgram/kg/day or 1.4 mg/m²/day

***In children born small for gestational age (SGA):***

33 to 67 microgram/kg/day or 1.0 to 2.0 mg/m²/day

**Adults:**

***Replacement therapy:***

It is recommended to start treatment with a low dose 0.1–0.3 mg/day and to increase the dosage gradually at monthly intervals in order to meet the need of the individual patient. Serum IGF–I can be used as guidance for the dose titration. Dose requirements decline with age. Maintenance dosages vary from

person to person, but seldom exceed 1.0 mg/day (equal to 3 IU/day).

**6. Contraindications**

Any evidence of active malignant tumours. Intracranial neoplasm must be inactive and anti-tumour therapy should be completed prior to institution of therapy. Pregnancy and lactation. 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 Norditropin® NordiLet®.

Hypersensitivity to any of the ingredients in the preparation. In children with chronic renal disease treatment with Norditropin® NordiLet® should be discontinued at renal transplantation.

**7. Special warnings and precautions for use**

**Do not use Norditropin® NordiLet® if the growth hormone solution in the pre-filled pen does not appear water–clear and colourless. Check this by turning the pen upside down once or twice. To make sure you get the proper dose and do not inject air, check the flow (called 'priming' the pen) before the first injection from a new Norditropin® NordiLet® pen. Do not use the pen if a drop of growth hormone solution does not appear at the needle tip.**

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

Norditropin® NordiLet® treatment should always be initiated 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 and SGA.

The growth disturbance in children with chronic renal disease should be clearly established before Norditropin® NordiLet® treatment by following growth on optimal treatment for renal disease over one year. Conservative management of uraemia with customary medication and if needed dialysis should be maintained during Norditropin® NordiLet® 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 Norditropin® NordiLet® treatment, renal function should be monitored for an excessive decline, or increased in the glomerular filtration rate (which could imply hyperfiltration).

Somatropin decreases insulin sensitivity, and consequently hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. Therefore, patients should be observed for evidence of glucose intolerance. In patients with diabetes mellitus, requirement for adjustment of antidiabetic therapy should be assessed and glycaemia should be monitored.

Insulin sensitivity may improve on continued Norditropin® therapy as changes in body composition occur resulting in reduced requirements for antidiabetic therapy.

In Turner syndrome and SGA children it is recommended to measure fasting blood glucose before 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.

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

In insulin treated patients adjustment of insulin dose may be needed after initiation of Norditropin® NordiLet® treatment.

Serum thyroxine levels may fall during treatment with Norditropin® NordiLet® due to the increased peripheral deiodination of T4 to T3.

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 antithyroid antibodies.

As hypothyroidism interferes with the response to

Norditropin® NordiLet® therapy patients should have their thyroid function tested regularly, and should receive replacement therapy with thyroid hormone when indicated.

Monitoring of 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 generally have an increased risk of otitis media, which is why careful 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.

There have been reports of fatalities after initiating therapy with growth hormone in paediatric patients with Prader-Willi syndrome, for which Norditropin® is not approved, who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnoea before initiation of treatment with growth hormone. If during treatment with growth hormone, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnoea, treatment should be discontinued. All patients with Prader- Willi syndrome treated with growth hormone should also have effective weight control and be monitored for signs of respiratory infection. Growth hormone treatment has been efficacious in increasing lean body mass, decreasing fat mass as well as increasing height in patients with Prader-Willi syndrome.

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment.

However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis.

Leukaemia has been reported in a small number of growth hormone deficient patients some of whom have been treated with somatropin. Based on current evidence it is unlikely that somatropin is responsible for this. In patients in complete remission from tumours or malignant disease, growth hormone therapy has not been associated with an increased relapse rate. Nevertheless, patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of Norditropin® NordiLet® therapy.

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 physicians and parents should be alerted to this possibility.

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 treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Norditropin® NordiLet® replacement in adult GHD patients should preferably be monitored by an endocrinologist with special experience in pituitary disease.

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

**8. Interactions with other medicinal products and other forms of interaction**

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

hormone on final height can also be influenced by additional therapy with other hormones, e.g. gonadotrophin, anabolic steroids, estrogens and thyroid hormone.

**9. Pregnancy and lactation**

Currently there is insufficient evidence of safety of somatropin therapy during pregnancy. The possibility that somatropin is secreted in breast milk cannot be discounted.

**10. Effects on ability to drive and use machinery**

No influence on the ability to drive and use machinery.

**11. Undesirable effects**

In uncommon (≥1/1000 to <1/100) and rare (≥1/10,000 to <1/1000) cases children may experience the following side effects:

- Redness, itching and pain in the area you inject
- Headache
- Muscle and joint pain
- Swollen hands and feet due to fluid retention
- Rash

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.

**Adults** may experience the following:

Very common effects (≥1/10):

- Swollen hands and feet due to fluid retention

Common effects (≥1/100 to <1/10):

- Headache
- Joint stiffness
- Joint and muscle pain

Uncommon effects (≥1/1000 to <1/100):

- Tingling, numbness or perhaps pain primarily in the fingers due to pressure on the nerves
- Itching and pain in the area you inject
- Muscle stiffness
- Type 2 diabetes mellitus or hyperglycaemia

In very rare (<1/10,000) cases the following side effects may occur in **children and adults**:

- Raised pressure within the brain
- Hypersensitivity reactions

The formation of antibodies directed against somatropin has rarely been observed during Norditropin® therapy.

**12. Overdose**

Acute over dosage can initially lead to hypoglycaemia and subsequently to hyperglycaemia. The hypoglycaemia was only detected biochemically (i.e. without clinical signs). Long–term overdose could result in signs and symptoms consistent with known effects of human growth hormone excess.

**13. Pharmacodynamic properties**

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

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 I (IGF–I), which are produced in tissues throughout the body, but predominantly by the liver.

More than 90% of IGF–I 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.

**14. 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-time 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.

**15. Presentations**

Norditropin® NordiLet® is delivered ready for use.

Norditropin® NordiLet® 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 laminated rubber stopper shaped as a disc and sealed with an aluminium cap.

**16. Special precautions for storage**

Norditropin® NordiLet® should be stored at +2°C – +8°C (in a refrigerator) in the outer carton.

Avoid freezing.

Once opened, Norditropin® NordiLet® 15 mg/ 1.5 ml may be stored for a maximum of 28 days at +2°C – +8°C.

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

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

**17. Produced by**

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*Please go to www.novonordisk.com for more information.*