1. Name of the medicinal product

Norditropin NordiFlex® 10 mg/1.5 ml
Solution for injection in pre-filled pen

2. Qualitative and quantitative composition

Norditropin NordiFlex®: 10 mg/1.5 ml
One ml of solution contains 6.7 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 insufficiency, growth failure in girls due to gonadal dysgenesis (Turner syndrome), growth retardation in prepubertal children due to chronic renal disease. Growth disturbance (current height standard deviation score (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 standard deviation (SD), who failed to show catch-up growth (height velocity standard deviation score (HV SDS) <0 during the last year) by 4 years of age or later.

Adults:
Pronounced growth hormone deficiency in known hypothalamic-pituitary 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.

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

Generally recommended dosages:

Paediatric population:
Growth hormone insufficiency
0.025–0.035 mg/kg/day or 0.7–1.0 mg/m²/day

Turner syndrome
0.045–0.067 mg/kg/day or 1.3–2.0 mg/m²/day

Chronic renal disease
0.050 mg/kg/day or 1.4 mg/m²/day (see section 4.4)

Small for Gestational age
0.033 to 0.067 mg/kg/day or 1.0 to 2.0 mg/m²/day

In all children, clinicians should carefully monitor the growth response, and adjust the hGH dose as necessary. Treatment is usually recommended until final height is reached.
Treatment should be discontinued after the first year if height velocity SDS is below +1.
Treatment should be discontinued when final height is reached (defined as height velocity <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.

Adult population:
Replacement therapy in adults
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, and SGA. Data of final adult height following the use of Norditropin® for children with chronic renal disease are not available.

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. 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 (GHD) 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.

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

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. Somatropin treatment should be interrupted in case of any development or recurrence of malignant disease.

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.

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 patients 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.

Breastfeeding
There have been no clinical studies conducted with somatropin containing products in breastfeeding women. It is not known whether somatropin is excreted in human milk. Therefore caution should be exercised when somatropin containing products are administered to breastfeeding 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 paraesthesia may also occur but are usually self-limiting.

Adverse reactions in children are uncommon or rare.

Clinical trial experience:

Children may experience the following:
Uncommon effects (≥1/1,000 to <1/100):
- Injection site reaction
- Injection site pain
- Headache.

Rare effects (⩾1/10,000 to <1/1,000):
- Arthralgia and myalgia
- Peripheral oedema
- Rash.

Adults may experience the following:

Very common effects (⩾1/10):

- Peripheral oedema.

Common effects (⩾1/100 to <1/10):

- Headache and paraesthesia
- Arthralgia, joint stiffness and myalgia.

Uncommon effects (≥1/1,000 to <1/100):

- Carpal tunnel syndrome
- Injection site pain
- Pruritus
- Muscle stiffness
- Type 2 diabetes mellitus.

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. 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.
- Investigations: Increase in blood alkaline phosphatase level.

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 hypoglycaemia. 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.

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 and 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
Expiry date is stated on the pen label and carton after 'Expiry'.
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® 10 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 blue. 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® 10 mg/1.5 ml delivers a maximum of 3.0 mg somatropin per dose, in increments of 0.050 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 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.

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.

Produced by
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

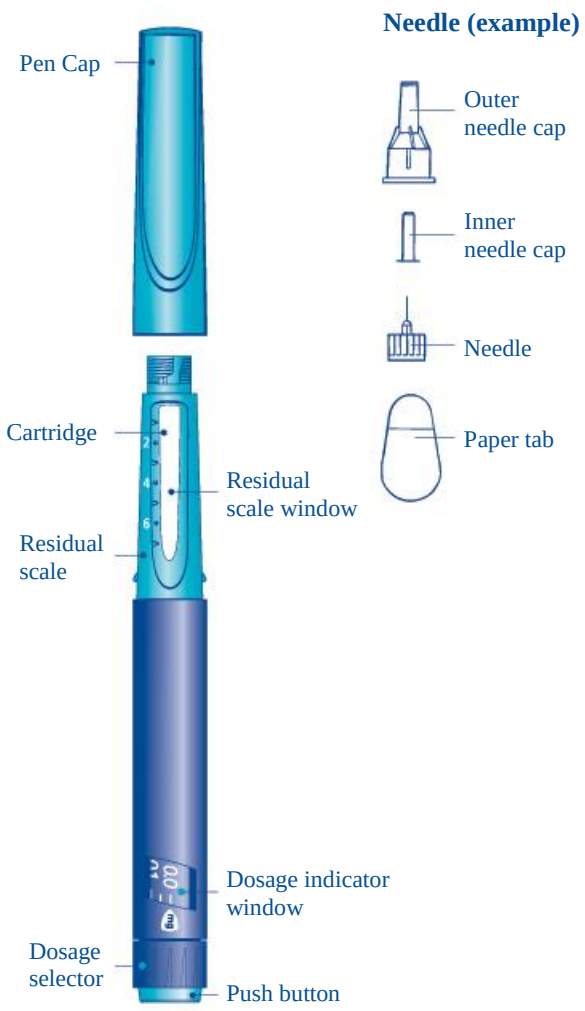
Norditropin NordiFlex®
10 mg/1.5 ml
Instructions on how to use the Norditropin NordiFlex® pen

Read these instructions carefully before using Norditropin NordiFlex®.

- Norditropin NordiFlex® 10 mg/1.5 ml is a multidose injection pen pre-filled with human growth hormone solution.
- You can use the dosage selector to select any dose from 0.050 to 3.00 mg, in increments of 0.050 mg.

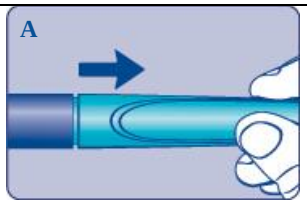
Your doctor will decide the correct dose for you.

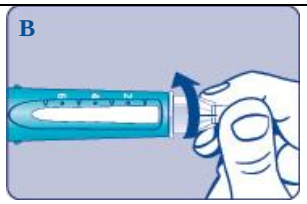
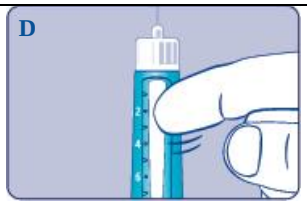
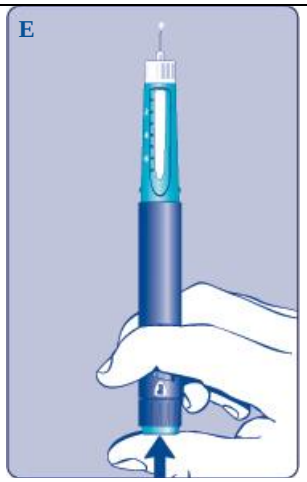
- Norditropin NordiFlex® is designed to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm.
- Start by checking the name, strength and coloured label of your Norditropin NordiFlex® pen to make sure that it contains the growth hormone strength you need.
- Only use the pen if the growth hormone solution inside the cartridge is clear and colourless.
- Always use a new needle for each injection.
- Always check the flow before the first injection with each new pen – see step 3. Check the flow.
- Never share your pen or your needles with anyone else. It might lead to cross-infection.
- Always keep your pen and needles out of sight and reach of children.
- Caregivers must be very careful when handling used needles – to reduce the risk of needle sticks and cross-infection.



1. Check the pen

- **Check the name, strength and coloured label of your Norditropin NordiFlex® pen to make sure that it contains the growth hormone strength you need.**
- Pull off the pen cap **[A].**
- Check that the solution inside the cartridge is clear and colourless by tipping the pen upside down once or twice.
- Do not use the pen if the solution inside the cartridge is unclear or cloudy.

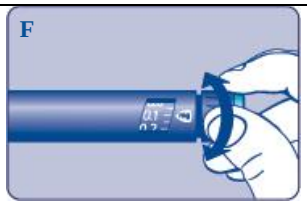


2. Attach the needle • **Always use a new needle for each injection.** This reduces the risk of contamination, infection, leakage of solution, blocked needles and inaccurate dosing. Never bend or damage the needle. • Remove the protective paper tab from the needle. • Screw the needle straight onto the pen **[B]**. Make sure the needle is on tight. The needle has two needle caps. You need to remove them both: • Pull off the outer needle cap and keep it to correctly remove the needle from the pen after the injection. • Remove the inner needle cap by pulling on the central tip and throw it away.	B 
3. Check the flow • **Before your first injection with each new pen, you need to check the flow** to make sure you get the correct dose and do not inject any air: Select 0.05 mg **[C]**. This is one 'click' after 0.0 on the dosage selector at the end of the pen.	C 
• Hold the pen with the needle pointing up and tap the top of the pen a few times to let any air bubbles rise to the top **[D]**.	D 
• Holding the pen with the needle up, press the push button at the bottom of the pen all the way in [E]. A drop of solution will appear at the needle tip. • If no drop appears, repeat steps C to E up to 6 times until a drop appears. If there is still no drop, change the needle and repeat step C to E once more. • **Do not use the pen if a drop does not appear.** Use a new pen. • Always check the flow before the first injection with each new pen. Check the flow again if your pen has been dropped or knocked against a hard surface, or if you suspect something is wrong with it.	E 

4. Select the dose

- Check that the dosage selector is set at 0.0. Select the number of mg your doctor has prescribed for you **[F]**.
- The dose can be increased or decreased by turning the dosage selector in either direction. When turning the dosage selector backwards, be careful not to press the push button as solution will come out. You cannot set a dose larger than the number of mg left in the pen.

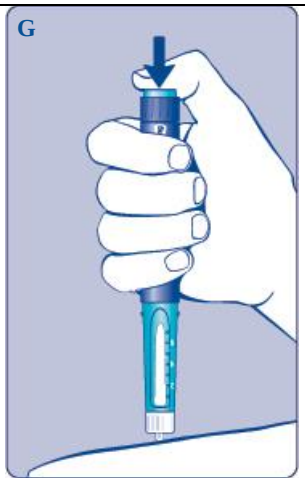
F



5. Inject the dose

- Use the injection method shown to you by your doctor or nurse.
- Vary the area you inject so you do not harm your skin.
- 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]**.
- **Keep the push button fully depressed and let the needle remain under the skin for at least 6 seconds.**
  This will ensure that the full dose has been delivered.

G

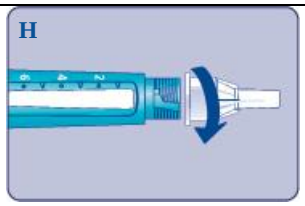


6. Remove the needle

- Carefully put the outer needle cap back on the needle without touching the needle. Unscrew the needle and throw it away carefully as instructed by your doctor or nurse **[H].**

  Never put the inner needle cap back on once you have removed it from the needle. You may accidentally stick yourself with the needle.
- Put the pen cap back on after every use.
- **Always remove and dispose of the needle after each injection and store the pen without the needle attached.** This reduces the risk of contamination, infection, leakage of solution, blocked needles and inaccurate dosing.
- When the pen is empty, throw it away without a needle on as advised by your doctor or nurse and local authorities.
- **Caregivers must be very careful when handling used needles - to reduce the risk of needle sticks and cross-infection.**

H



7. Maintenance

- Your Norditropin NordiFlex® pen must be handled with care.
- Do not drop your pen or knock it against hard surfaces. If you drop it or suspect that

something is wrong with it, always screw on a new needle and check the flow before you inject.

- Do not try to refill your pen – it is pre-filled.
- Do not try to repair your pen or pull it apart.
- Protect your pen from dust, dirt, frost and direct sunlight.
- Do not try to wash, soak or lubricate your pen. If necessary clean it with a mild detergent on a moistened cloth.
- Do not freeze your pen or store it close to any cooling element, e.g. in a refrigerator.
- See section 6.4 ‘Special precautions for storage’ on the reverse page for information about how to store your pen.