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, water for injections, hydrochloric acid and sodium hydroxide for pH adjustment.

3 Pharmacotherapeutic group

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

4 Indications

Children:
Growth retardation due to growth hormone deficiency (GHD), growth retardation 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) who failed to show catch-up growth by 2 years of age.

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 IGF-I is <-2 SDS after at least four weeks off growth hormone treatment.
In all other patients an IGF-I 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.

5 Dosage and administration

Norditropin® NordiLet® is a pre-filled pen designed to be used with NovoFine® disposable 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 and must always be adjusted in accordance with individual's clinical and biochemical response to therapy. 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 deficiency:
25 to 35 µg/kg/day or
0.7 to 1.0 mg/m²/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.

In children with Turner syndrome:
45 to 67 µg/kg/day or
1.3 to 2.0 mg/m²/day

In children with Chronic renal disease:
50 µg/kg/day or 1.4 mg/m²/day

In children born small for gestational age (SGA):
33 to 67 µg/kg/day or
1.0 to 2.0 mg/m²/day

Adults:
Replacement therapy:
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-I concentration determination.
In patients with adult onset GHD, 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. Women may require higher doses than men, with men showing an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement, are under-treated while men are over-treated.
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

Hypersensitivity to the active substance or to any of the excipients.
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 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 Norditropin® NordiLet®.
For 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 ensure proper dosing and avoid injection of air, check the flow (prime the pen) before the first injection from a new Norditropin® NordiLet® pen. Do not use Norditropin® NordiLet® if a drop of growth hormone solution does not appear at the needle tip.

Children treated with somatropin should be regularly assessed by a specialist in child growth. Somatropin treatment should always be instituted by a physician with special knowledge of growth hormone deficiency and its treatment. This is true also for the management of Turner syndrome, chronic renal disease and SGA.

The maximum recommended daily dose should not be exceeded.

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

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 of age and in patients with more than 10 years of treatment in adult growth hormone deficiency is still limited.

Turner syndrome
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.

Chronic renal disease
The growth retardation in children with chronic renal disease 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 medication 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).

Neoplasms
There is no evidence for increased risk of *de novo* malignancy in children or in adults, treated with somatropin.
There is no evidence for increased risk of recurrence of malignancies in children or in adults, treated with somatropin.
An overall slight increase in second neoplasms has been observed in children 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 with previous malignant disease should be monitored carefully for recurrence of malignant disease.
Somatropin treatment should be interrupted in case of any development or recurrence of malignant disease.

Benign intracranial hypertension
Very rare cases of benign intracranial hypertension have been reported. If appropriate somatropin treatment should be discontinued.
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.
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. As hypothyroidism interferes with the response of somatropin therapy, patients should have their thyroid function tested regularly, and should receive replacement therapy with thyroid hormone when indicated.
Patients with Turner syndrome have an increased risk of developing primary hypothyroidism associated with anti-thyroid antibodies.

Scoliosis
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.

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.

Carbohydrate metabolism
Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients, and consequently hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment.
Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome or a family history of diabetes mellitus. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycaemic drugs (i.e. insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

IGF-I
It is recommended to measure the IGF–I level before start of treatment and regularly thereafter.

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. Fatalities were reported in patients who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

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

8 Interactions with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth promoting effect of somatropin. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on somatropin.

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.
In insulin treated patients adjustment of insulin dose may be needed after initiation of somatropin treatment.

9 Pregnancy and lactation

There is limited clinical experience with somatropin therapy during pregnancy. Somatropin should be given to a pregnant woman only if clearly needed. 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

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. Mild arthralgia, muscle pain and paraesthesia may also occur, but are usually self-limiting. The symptoms are usually transient, dose dependent and may require transient dose reduction.

In uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) cases **children** may experience the following side effects:
- Injection site reaction
- Injection site pain
- Headache
- Arthralgia and myalgia
- Peripheral oedema
- 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 and otitis external in Turner syndrome patients treated with high doses of Norditropin® has been observed in two open-label randomised clinical trials. 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):
- 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 reaction and injection site pain
- Pruritus
- Muscle stiffness
- Type 2 diabetes mellitus.

In rare (less than 1 in 1,000) cases the following side effects may occur in **children and adults:**
- Generalised hypersensitivity reactions.

Formation of antibodies directed against somatropin has rarely been observed during Norditropin® therapy. Increase in blood alkaline phosphatase level may be seen during treatment with Norditropin®.

12 Overdose

Acute overdosage 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.
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).

16 Special precautions for storage

Norditropin® NordiLet® should be stored in a refrigerator (2°C – 8°C) in the outer carton.
Do not freeze.
Once opened, Norditropin® NordiLet® 15 mg/1.5 ml may be stored for a maximum of 28 days in a refrigerator (2°C – 8°C) ***alternatively*** stored below 25°C for a maximum of 21 days.
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

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

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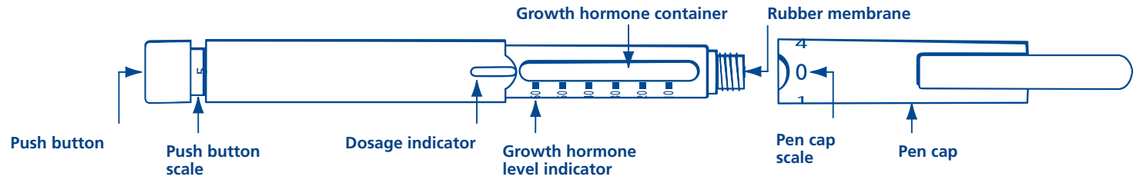
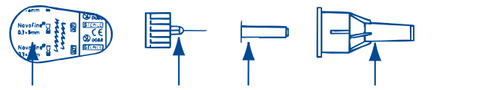
Norditropin® NordiLet® 15 mg/1.5 ml

Information on how to inject growth hormone

Introduction
Norditropin® NordiLet® 15 mg/1.5 ml is a multi-dose disposable pre-filled pen with human growth hormone solution for injection.
In each injection you can dial doses from 1 to 29 clicks.
Simply dial a dose and inject.



NovoFine® disposable needle



Norditropin® NordiLet® 15 mg/1.5 ml

Your physician/specialist will determine the correct dose for you. The dose is in mg. This must be converted to a number of clicks for Norditropin® NordiLet®.

To convert a dose from mg to clicks you should use the conversion table. Always check that the conversion table corresponds to the strength of your Norditropin® NordiLet®. For example you should use the Norditropin® NordiLet® 15 mg/1.5 ml conversion table with Norditropin® NordiLet® 15 mg/1.5 ml. First look up your dose on the mg-scale in the conversion table. Then find the equivalent number of clicks.

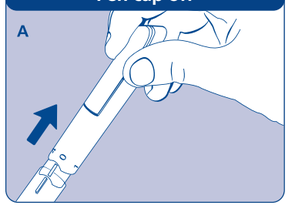
Example
If your dose is 3.60 mg the correct number of clicks is 18.

Conversion Table Norditropin® NordiLet® 15 mg/1.5 ml

Interval in mg From mg – To mg	Clicks
0.01 - 0.29	1
0.30 - 0.49	2
0.50 - 0.69	3
0.70 - 0.89	4
0.90 - 1.09	5
1.10 - 1.29	6
1.30 - 1.49	7
1.50 - 1.69	8
1.70 - 1.89	9
1.90 - 2.09	10
2.10 - 2.29	11
2.30 - 2.49	12
2.50 - 2.69	13
2.70 - 2.89	14
2.90 - 3.09	15
3.10 - 3.29	16
3.30 - 3.49	17
3.50 - 3.69	18
3.70 - 3.89	19
3.90 - 4.09	20
4.10 - 4.29	21
4.30 - 4.49	22
4.50 - 4.69	23
4.70 - 4.89	24
4.90 - 5.09	25
5.10 - 5.29	26
5.30 - 5.49	27
5.50 - 5.69	28
5.70 - 5.80	29

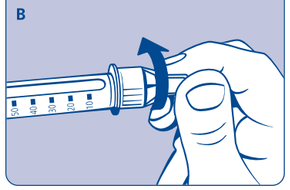
1. Preparing Norditropin® NordiLet® for injection

Pen cap off



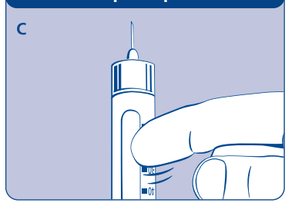
A
Pull off the pen cap.

Screw on the needle



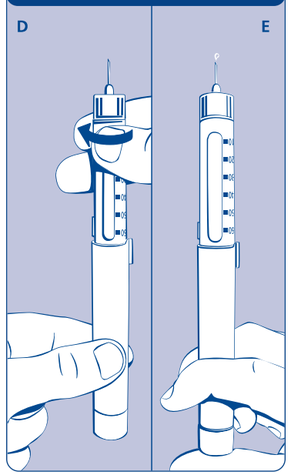
B
Remove the protective paper tab from a NovoFine® needle and screw the needle onto Norditropin® NordiLet®. Pull off the outer and inner needle caps. Put the outer needle cap aside to be used after injection.

Tap the pen



C
Check the flow:
Before you use a new pen for the first time, you need to check the flow (prime the pen) to make sure you get the proper dose and do not inject any air: Hold the Norditropin® NordiLet® pen with the needle pointing upwards and tap the cartridge gently with your finger a few times to make sure that any air bubbles will collect in the top of the growth hormone container.

Dial one click Push button in



D
Holding the Norditropin® NordiLet® pen with the needle pointing upwards, turn the growth hormone container in the direction of the arrow shown above until you dial one click.

E
Holding the pen with the needle still pointing upwards, press the push-button at the bottom of the pen as far as it can go. Repeat steps C to E until a drop of hormone solution appears at the needle tip.

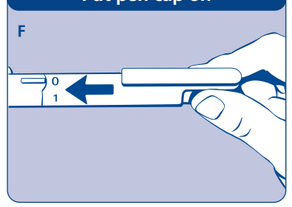
Do not use a Norditropin® NordiLet® pen if a drop of solution does not appear.

Always check the flow (prime the pen) before the first injection from a new Norditropin® NordiLet® pen. Check the flow again if the pen has been dropped or knocked against a hard surface, or if you are not sure that it is working properly.

If considered faulty, take it back to your supplier for a new one.

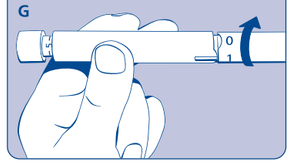
2. Setting the dose

Put pen cap on



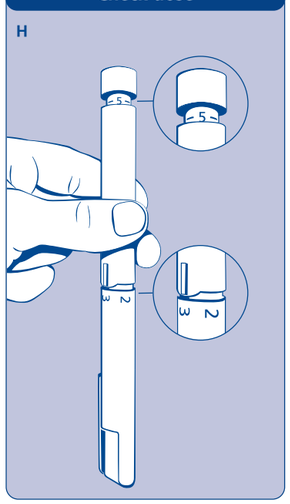
F
Put the pen cap back on the pen, with '0' next to the dosage indicator.

Dial correct number of clicks



G
Hold Norditropin® NordiLet® horizontally and turn the pen cap in the direction of the arrow shown above to set the dose you want.
Be careful not to put your hand over the push-button when you dial the dose. If the push-button cannot rise freely, growth hormone will be pushed out of the needle.
The scale on the pen cap shows the number of clicks (0, 1, 2, 3, 4 clicks). As the pen cap is turned, the push-button rises.
The push-button scale shows the number of clicks (5, 10, 15, 20 and 25 clicks).
Every time you make a full turn of the pen cap, 5 clicks will be set.
Always check both the pen cap scale and the push-button scale to ensure you have dialed the correct dose.

Check dose

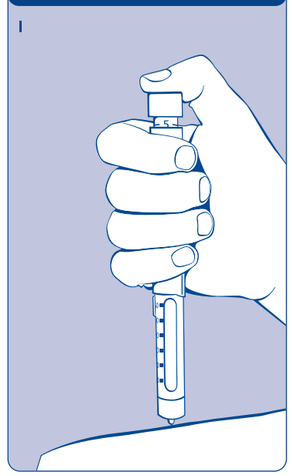


Dosage examples (see picture H)
- How to select four clicks:
  Turn the cap until '4' is next to the dosage indicator.
- How to select eight clicks:
  Turn the pen cap one full turn so '0' is next to the dosage indicator again. You have now selected five clicks and '5' will be shown on the push-button scale. Continue turning the pen cap scale until '3' is next to the dosage indicator.
  Add the '3' from the pen cap scale indicator to the '5' on the push-button scale and you have selected eight clicks altogether.

H
To check the dose set, add the figure on the pen cap scale to the highest figure shown on the push-button scale.
If you have set a wrong dose, simply turn the pen cap forwards or backwards until the right number of clicks has been set. 29 clicks is the maximum dose.
If you try to set a higher dose, growth hormone will leak out of the needle and the dose will be wrong.
If you do this by mistake, turn the pen cap back as far as you can until the push-button is fully down and you can feel resistance.
If '0' is not next to the dosage indicator remove the pen cap and put it back on as shown in picture F.
Now start again, remembering that 29 clicks is the maximum dose.
After the dose is set, remove the pen cap to make the injection.

3. How to inject the growth hormone

Press the push button to inject



I
The injection consists of two steps:
First step is inserting the needle into the skin. Second step is to press the push-button to inject the dose.
- Use the injection technique recommended by your physician/specialist.
- After the injection of growth hormone the needle should remain under the skin for at least 6 seconds. Keep the push-button fully pressed down until the needle has been withdrawn from the skin. This will ensure that the full dose has been injected.
- After the injection replace the outer needle cap, unscrew the needle and carefully dispose of it for safety reasons. Put the pen cap back on the pen, with '0' next to the dosage indicator.
- Healthcare professionals, relatives and other carers should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.

4. Subsequent injections

Always check that the push-button is fully down. If not, turn the pen cap until the push-button is completely down.
Then proceed as described in sections 1 to 3.
Do not use the clicking sound as a means of determining or confirming your dose. Always check both scales to ensure you have dialed the correct dose.
Please remember:
- Always keep the pen cap fully closed on Norditropin® NordiLet® when you are not using it.
- Always use a new needle for each injection.
- Do not keep the needle screwed onto Norditropin® NordiLet® when you are not using it.
- You can use the growth hormone level indicator to estimate how many clicks of growth hormone are left. You must not use the growth hormone level indicator to set your dose.
- You cannot set a dose greater than the number of clicks left.
- When emptied dispose of the used Norditropin® NordiLet® carefully without the needle attached.

5. Maintenance

Your Norditropin® NordiLet® pen is designed to work accurately and safely. Norditropin® NordiLet® should not be shaken vigorously. It should be handled with care. Avoid situations where Norditropin® NordiLet® might get damaged. Protect Norditropin® NordiLet® from dust, dirt and direct sunlight.
Do not use Norditropin® NordiLet® if the growth hormone solution in the pre-filled pen does not appear water-clear and colourless.
You can clean the exterior of your Norditropin® NordiLet® pen by wiping it with cotton wool moistened with alcohol.
Do not soak it in alcohol, wash or lubricate it as this may damage the mechanism.