Abbreviated prescribing information

Norditropin NordiFlex® (somatropin)
5 mg/1.5 ml, pre-filled pen, solution for injection
Norditropin NordiFlex® (somatropin)
10 mg/1.5 ml, pre-filled pen, solution for injection
Norditropin NordiFlex® (somatropin)
15 mg/1.5 ml, pre-filled pen, solution for injection

Consult Summary of Product Characteristics before prescribing.

Indications

Children: Growth failure due to growth hormone deficiency (GHD); Growth failure in girls due to gonadal dysgenesis (Turner syndrome); Growth retardation in prepubertal children due to chronic renal disease (CRD); Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later. Growth failure due to Noonan syndrome.
Adults: Childhood onset growth hormone deficiency:
Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after growth completion. Testing is not required for those with more than three pituitary hormone deficits, with severe GHD due to a defined genetic cause, due to structural hypothalamic pituitary abnormalities, due to central nervous system tumours or due to high-dose cranial irradiation, or with GHD secondary to a pituitary/hypothalamic disease or insult, if measurement of serum insulin-like growth factor 1(IGF-1) is <-2 SDS after at least four weeks off growth hormone treatment. In all other patients an IGF-1 measurement and one growth hormone stimulation test is required.
Adult onset growth hormone deficiency:
Pronounced GHD in known hypothalamic-pituitary disease, cranial irradiation, and traumatic brain injury. GHD should be associated with one other deficient axis, other than prolactin. GHD should be demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis.

Posology and method of administration

The dosage is individual and must always be adjusted in accordance with the individual's clinical and biochemical response to therapy.
Generally recommended dosages:
Paediatric population

Growth hormone insufficiency: 0.025-0.035 mg/kg/day or 0.7-1.0 mg/m^2/day. When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual.
Turner syndrome: 0.045-0.067 mg/kg/day or 1.3-2.0 mg/m^2/day
Chronic renal disease: 0.050 mg/kg/day or 1.4 mg/m^2/day
Small for Gestational Age: 0.035 mg/kg/day or 1.0 mg/m^2/day. A dose of 0.035 mg/kg/day is usually recommended until final height is reached. Treatment should be discontinued after the first year of treatment, if the height velocity SDS is below +1. Treatment should be discontinued if height velocity is <2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.
Noonan syndrome: 0.066 mg/kg/day is the recommended dose, however in some cases 0.033 mg/kg/day may be sufficient. Treatment should be discontinued at the time of epiphyseal closure
Adult population
Replacement therapy in adults: The dosage must be adjusted to the need of the individual patient. In patients with childhood onset GHD, the recommended dose to restart is 0.2-0.5 mg/day with subsequent dose adjustment on the basis of IGF-1 concentration determination. In patients with adult onset GHD, it is recommended to start treatment with a low dose 0.1-0.3 mg/day. It is recommended to increase the dosage gradually at monthly intervals based on the clinical response and the patient's experience of adverse events. Serum IGF-1 can be used as guidance for the dose titration. Women may require higher doses than men, with men showing an increasing IGF-1 sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement, are under-treated while men are over-treated. Dose requirements decline with age. Maintenance dosages vary considerably from person to person, but seldom exceed 1.0 mg/day.
Method of administration: Generally, once-daily sc administration in the evening is recommended. The injection site should be varied to prevent lipoatrophy.

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

Special warnings and precautions for use

Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Children treated with somatropin should be regularly assessed by a specialist in child growth. Somatropin treatment should always be instigated by a physician with special knowledge of growth hormone insufficiency and its treatment. This is true also for the management of Turner syndrome, chronic renal disease, SGA and Noonan syndrome. Data of final adult height following the use of Norditropin® are limited for children with Noonan Syndrome and are not available for children with chronic renal disease. The maximum recommended daily dose should not be exceeded. The stimulation of longitudinal growth in children can only be expected until epiphyseal closure.
Children: 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.
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.
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.
The dosage in children with chronic renal disease is individual and must be adjusted according to the individual response to therapy. 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 is known to be more frequent in some of the patient groups treated with somatropin for example Turner syndrome and Noonan syndrome. In addition, rapid growth in any child can cause progression of scoliosis. Somatropin treatment has not been shown to increase the incidence or severity of scoliosis. Signs of scoliosis should be monitored during treatment.
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.
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 is a lifelong disease and needs to be treated accordingly, however, experience in patients older than 60 years and in patients with more than five years of treatment in adult growth hormone deficiency is still limited.
Adults and Children: Although rare, pancreatitis should be considered in somatropin-treated patients who develop abdominal pain, especially in children.
General
Neoplasms. There is no evidence for increased risk of new primary cancers in children or in adults treated with somatropin. In patients in complete remission from tumours or malignant disease, somatropin therapy has not been associated with an increased relapse rate. An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for second neoplasms seems to be prior exposure to radiation. Patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of somatropin therapy.
Leukaemia 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.
In the event of severe or recurrent headache, visual problems, nausea, and/or vomiting, a fundoscopy 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.
Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. 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.
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 reduce 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.
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.
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.

Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effect of Norditropin® . Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective. 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.
Interaction studies have only been performed in adults.

Fertility, pregnancy and lactation

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

Undesirable effects

In adults: *very common:* peripheral oedema; *common:* headache and paraesthesia, arthralgia, joint stiffness and myalgia; *uncommon:* diabetes mellitus type 2, carpal tunnel syndrome, pruritus, muscle stiffness,gynecomastia, injection site pain. The symptoms are usually transient, dose dependent and may require transient dose reduction.

In children: Adverse events in children are uncommon (headache, gynecomastia, injection site pain) or rare (rash, arthralgia and myalgia, peripheral oedema). In children with Turner syndrome increased growth of hands and feet has been reported during somatropin therapy. A tendency for increased incidence of otitis media in Turner syndrome patients treated with high doses of Norditropin® has been observed in one open-label randomised clinical trial. However, the increase in ear infections did not result in more ear operations/tube insertions compared to the lower dose group in the trial.

Post marketing experience (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.

Immune system disorders: Hypersensitivity. 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 somatotropin administration

Endocrine disorders: Hypothyroidism. Decrease in serum thyroxin levels

Metabolism and nutrition disorders: Hyperglycaemia

Nervous system disorders: Benign intracranial hypertension

Musculoskeletal and connective tissue disorders: Legg-Calvé-Perthes disease may occur more frequently in patients with short stature.

Investigations: Increase in blood alkaline phosphatase level

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

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 somatropin excess.

Presentations

Norditropin NordiFlex® is a colour-coded, multi-dose, disposable, pre-filled pen containing Norditropin® 5 mg/1.5 ml (Orange push-button), 10 mg/1.5 ml (Blue push-button) and 15 mg/1.5 ml (Green push-button).

Constituents

Norditropin NordiFlex® contains somatropin, mannitol, histidine, poloxamer 188, phenol, water for injections, hydrochloric acid for pH adjustment and sodium hydroxide for pH adjustment.

Storage and handling

Prior to use, the shelf life is 2 years stored in a refrigerator (2°C – 8°C). 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. Do not freeze. Do not store close to any cooling elements.

Norditropin NordiFlex® is a pre-filled pen designed to be used with NovoFine® or NovoTwist® disposable needles. The device delivers a maximum of 1.5 mg (5 mg/1.5 ml), 3.0 mg (10 mg/1.5 ml) and 4.5 mg (15 mg/1.5 ml) somatropin per dose, in increments of 0.025 mg, 0.050 mg and 0.075 mg somatropin, respectively. For instructions for use/handling please refer to package insert for full details.

Supply details

The available range of products may vary from country to country.

 Please refer to local prescribing information for full details. **Legal category:** Prescription-only

medicine (POM). **Marketing authorisation holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd Denmark.
Summary of Product Characteristics can be obtained from Novo Nordisk A/S.

Novo Nordisk Health Care AG
The Circle 32/38
8058 Zürich
Switzerland
www.novonordisk.com

Abbreviated prescribing information

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Indications

Children: Growth failure due to growth hormone deficiency (GHD); Growth failure in girls due to gonadal dysgenesis (Turner syndrome); Growth retardation in prepubertal children due to chronic renal disease (CRD); Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later. Growth failure due to Noonan syndrome.
Adults: Childhood onset growth hormone deficiency:
Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after growth completion. Testing is not required for those with more than three pituitary hormone deficits, with severe GHD due to a defined genetic cause, due to structural hypothalamic pituitary abnormalities, due to central nervous system tumours or due to high-dose cranial irradiation, or with GHD secondary to a pituitary/hypothalamic disease or insult, if measurement of serum insulin-like growth factor 1 (IGF-1) is <-2 SDS after at least four weeks off growth hormone treatment. In all other patients an IGF-1 measurement and one growth hormone stimulation test is required.
Adult onset growth hormone deficiency:
Pronounced GHD in known hypothalamic-pituitary disease, cranial irradiation, and traumatic brain injury. GHD should be associated with one other deficient axis, other than prolactin. GHD should be demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis.

Posology and method of administration

The dosage is individual and must always be adjusted in accordance with the individual's clinical and biochemical response to therapy.
Generally recommended dosages:
Paediatric population

Growth hormone insufficiency: 0.025-0.035 mg/kg/day or 0.7-1.0 mg/m^2/day. When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual.
Turner syndrome: 0.045-0.067 mg/kg/day or 1.3-2.0 mg/m^2/day.
Chronic renal disease: 0.050 mg/kg/day or 1.4 mg/m^2/day
Small for Gestational Age: 0.035 mg/kg/day or 1.0 mg/m^2/day. A dose of 0.035 mg/kg/day is usually recommended until final height is reached. Treatment should be discontinued after the first year of treatment, if the height velocity SDS is below +1. Treatment should be discontinued if height velocity is <2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.
Noonan syndrome: 0.066 mg/kg/day is the recommended dose, however in some cases 0.033 mg/kg/day may be sufficient. Treatment should be discontinued at the time of epiphyseal closure
Adult population
Replacement therapy in adults: The dosage must be adjusted to the need of the individual patient. In patients with childhood onset GHD, the recommended dose to restart is 0.2-0.5 mg/day with subsequent dose adjustment on the basis of IGF-1 concentration determination. In patients with adult onset GHD, it is recommended to start treatment with a low dose 0.1-0.3 mg/day. It is recommended to increase the dosage gradually at monthly intervals based on the clinical response and the patient's experience of adverse events. Serum IGF-1 can be used as guidance for the dose titration. Women may require higher doses than men, with men showing an increasing IGF-1 sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement, are under-treated while men are over-treated. Dose requirements decline with age. Maintenance dosages vary considerably from person to person, but seldom exceed 1.0 mg/day.
Method of administration: Generally, once-daily sc administration in the evening is recommended. The injection site should be varied to prevent lipoatrophy.

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 (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. In children with chronic renal disease, treatment with Norditropin® FlexPro® should be discontinued at renal transplantation.

Special warnings and precautions for use

Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Children treated with somatropin should be regularly assessed by a specialist in child growth. Somatropin treatment should always be instigated by a physician with special knowledge of growth hormone insufficiency and its treatment. This is true also for the management of Turner syndrome, chronic renal disease, SGA and Noonan syndrome. Data of final adult height following the use of Norditropin® are limited for children with Noonan Syndrome and are not available for children with chronic renal disease. The maximum recommended daily dose should not be exceeded. The stimulation of longitudinal growth in children can only be expected until epiphyseal closure.
Children: 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.
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.
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.
The dosage in children with chronic renal disease is individual and must be adjusted according to the individual response to therapy. 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 is known to be more frequent in some of the patient groups treated with somatropin for example Turner syndrome and Noonan syndrome. In addition, rapid growth in any child can cause progression of scoliosis. Somatropin treatment has not been shown to increase the incidence or severity of scoliosis. Signs of scoliosis should be monitored during treatment.
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.
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 is a lifelong disease and needs to be treated accordingly, however, experience in patients older than 60 years and in patients with more than five years of treatment in adult growth hormone deficiency is still limited.
Adults and Children: Although rare, pancreatitis should be considered in somatropin-treated patients who develop abdominal pain, especially in children.
General
Neoplasms. There is no evidence for increased risk of new primary cancers in children or in adults treated with somatropin. In patients in complete remission from tumours or malignant disease, somatropin therapy has not been associated with an increased relapse rate. An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for second neoplasms seems to be prior exposure to radiation. Patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of somatropin therapy.
Leukaemia 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.
In the event of severe or recurrent headache, visual problems, nausea, and/or vomiting, a fundoscopy 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.
Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. 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.
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 reduce 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.
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-I 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.
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.

Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effect of Norditropin®. Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective. 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.
Interaction studies have only been performed in adults.

Fertility, pregnancy and lactation

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

Undesirable effects

In adults: *very common:* peripheral oedema; *common:* headache and paraesthesia, arthralgia, joint stiffness and myalgia; *uncommon:* diabetes mellitus type 2, carpal tunnel syndrome, pruritus, muscle stiffness,gynecomastia injection site pain. The symptoms are usually transient, dose dependent and may require transient dose reduction.
In children: Adverse events in children are uncommon (headache,gynecomastia, injection site pain) or rare (rash, arthralgia and myalgia, peripheral oedema). In children with Turner syndrome increased growth of hands and feet has been reported during somatropin therapy. A tendency for increased incidence of otitis media in Turner syndrome patients treated with high doses of Norditropin® has been observed in one open-label randomised clinical trial. However, the increase in ear infections did not result in more ear operations/tube insertions compared to the lower dose group in the trial.
Post marketing experience (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.
Immune system disorders: Hypersensitivity. 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 somatotropin administration.
Endocrine disorders: Hypothyroidism. Decrease in serum thyroxin levels
Metabolism and nutrition disorders: Hyperglycaemia
Nervous system disorders: Benign intracranial hypertension
Musculoskeletal and connective tissue disorders: Legg-Calvé-Perthes disease may occur more frequently in patients with short stature.
Investigations: Increase in blood alkaline phosphatase level.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via their national reporting system.

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 somatropin excess.

Presentations

Norditropin® FlexPro® is a colour-coded, multi-dose, disposable, pre-filled pen containing Norditropin® 5 mg/1.5 ml (Orange push-button), 10 mg/1.5 ml (Blue push-button) and 15 mg/1.5 ml (Green push-button).

Constituents

Norditropin® FlexPro® contains somatropin, mannitol, histidine, poloxamer 188, phenol, water for injections, hydrochloric acid for pH adjustment and sodium hydroxide for pH adjustment.

Storage and handling

Prior to use, the shelf life is 2 years stored in a refrigerator (2°C – 8°C). 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. Do not freeze. Do not store close to any cooling elements.
Norditropin® FlexPro® is a pre-filled pen designed to be used with NovoFine® or NovoTwist® disposable needles. The device delivers a maximum of 2.0 mg (5 mg/1.5 ml), 4.0 mg (10 mg/1.5 ml) and 8.0 mg (15 mg/1.5 ml) somatropin per dose, in increments of 0.025 mg, 0.050 mg and 0.1 mg somatropin, respectively. For instructions for use/handling please refer to package insert for full details.

Supply details

The available range of products may vary from country to country.
Norditropin® and FlexPro® are registered trademarks of Novo Nordisk Health Care AG, Switzerland. NovoFine® and NovoTwist® are registered trademarks of Novo Nordisk A/S, Denmark. Please refer to local prescribing information for full details. **Legal category:**

Prescription-only medicine (POM). **Marketing authorisation holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd Denmark.
Summary of Product Characteristics can be obtained from Novo Nordisk A/S.

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