AUSTRALIAN PRODUCT INFORMATION

Norditropin® FlexPro® (somatropin) injection solution

1. NAME OF THE MEDICINE

Somatropin (rbe). Biosynthetic human growth hormone.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somatropin is a polypeptide hormone of recombinant DNA origin. The hormone is synthesised by a special strain of E coli bacteria that has been modified by the addition of a plasmid which carries the gene for human growth hormone. Somatropin contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone with a molecular weight of about 22,000 Daltons.

Norditropin FlexPro contains somatropin (rbe) 5 mg, 10 mg or 15 mg in 1.5 mL.

1 mg of somatropin corresponds to 3 IU (International Units) of somatropin.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Children

Treatment of growth failure in children due to pituitary growth hormone deficiency.

Treatment of growth failure in girls due to gonadal dysgenesis (Turner Syndrome).

Treatment of growth failure in children due to chronic renal insufficiency whose height is on or less than the twenty-fifth percentile and whose growth velocity is on or less than the twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as a glomerular filtration rate of < 30 mL/min/1.73 m^2.

Treatment of severe growth failure due to intrauterine growth retardation (i.e., children born small for gestational age (birth weight and/or length < -2 SD) without spontaneous catch up growth by 2 years of age).

Adults

Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL.

In order to establish Childhood Onset [CO] growth hormone insufficiency, reconfirmation by one provocative test is recommended.

In order to establish isolated growth hormone deficiency two provocative tests are recommended. 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 or the glucagon test may also be considered; however these tests have less established diagnostic value than the insulin tolerance test.

4.2 Dose and Method of Administration

Dosage

Treatment of Norditropin should be directed by specialists experienced in the diagnosis and management of growth hormone deficiency. This is also true for the management of Turner syndrome, chronic renal disease and SGA. The dosage must be individualised for each patient in accordance with the individual's response to therapy. Dosages can be calculated according to body weight or body surface area.

Generally, daily subcutaneous administration in the evening, 6-7 days per week, is recommended. Rotation of the injection site is recommended to minimise the risk of lipoatrophy. Specific activity for somatropin: 1 mg = 3 International Units (IU).

Paediatric
Recommended dosages for children with growth hormone deficiency:
25-35 µg/kg/day
Equal to: 0.7 – 1.0 mg/m^2/day

Recommended dosages for Turner Syndrome and Chronic Renal Disease:
50 µg/kg/day
Equal to: 1.4 mg/m^2/day

Recommended dosages for Small for Gestational Age (SGA):
33-67 µg/kg/day
Equal to: 1-2 mg/m^2/day

The dosage must be adjusted to the need of the individual patient. It is recommended to start treatment with 33µg/kg/day. If catch-up growth has not commenced after 6 months of observation (and verification of compliance by increase in IGF1 and/or IGFBP3) then the physician may increase the dose up to 67µg/kg/day according to the patient's needs.

It is recommended that the treating physician advise the parents/guardians that their children are not being treated for growth hormone deficiency, and that treatment with Norditropin induces catch-up growth during childhood and increases adult height. It is also recommended that parents/guardians be advised that long term treatment with somatropin has been associated with impaired glucose tolerance and malignancies. However, causality has not been established and there is no evidence that somatropin treatment is associated with an increased incidence of persistent impaired glucose tolerance or malignancies.

Adults

Recommended dosages for adults with growth hormone deficiency:

The dosage must be adjusted to the need of the individual patient. It is recommended to start treatment with a low dose of 0.15-0.3 mg/day and to increase the dosage gradually at monthly intervals based on clinical response. Serum insulin-like growth factor 1 (IGF-1) can be used to guide dose titration.

Dose requirements decline with age. Maintenance dosages vary from patient to patient, but seldom exceeds 1.0 mg.

Method of administration

Instructions for use and handling

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

Do not use Norditropin FlexPro if it does not appear water-clear and colourless. Check this by turning the pen upside down once or twice.

Norditropin should not be shaken vigorously at any time.

- Norditropin FlexPro is a pre-filled pen designed to be used with NovoFine needles (8 mm 30 G or smaller).
- Detailed instructions for use are included in the package insert (Consumer Medicine Information). Patients should be advised to read these instructions very carefully.
- The product is for multiple use in one patient only.

4.3 Contraindications

Norditropin should not be used in children with closed epiphyses; in patients with retarded growth due to any other cause than pituitary growth hormone deficiency unless specifically indicated (see Section 4.1 Therapeutic Indications); or in patients with a known hypersensitivity to any of the ingredients.

Norditropin should not be used in patients with any evidence of active malignant tumours. Intracranial neoplasm must be inactive and anti-tumour therapy must be completed prior to instituting Norditropin therapy. Treatment with Norditropin should be discontinued if there is any evidence of recurrent tumour growth.

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

Growth hormone is contraindicated in those patients with Prader-Willi syndrome who would otherwise qualify for Somatropin therapy (see Section 4.1 Therapeutic Indications) who are severely obese or have respiratory impairment.

In children with chronic renal disease, Norditropin treatment after renal transplantation should not be initiated if the child has a history of more than one acute rejection episode or if the time since transplantation is less than 12 months. In addition to this Norditropin treatment should be discontinued in case of a new acute rejection episode.

Norditropin should not be initiated to treat patients with acute critical illness due to complications following open heart surgery or abdominal surgery, multiple accident trauma or to patients having acute respiratory failure (see Section 4.4 Special Warnings and Precautions for Use).

4.4 Special Warnings and Precautions for Use

Treatment with Norditropin should be directed by specialists experienced in the diagnosis and management of growth hormone deficiency. This is true also for the management of Turner syndrome, chronic renal disease and SGA.

The maximum recommended daily dose should not be exceeded (see Section 4.2 Dose and Method of Administration).

Norditropin contains the excipient poloxamer 188, which acts as a surfactant. Poloxamer 188 is excreted predominantly in the urine and its exposure is inversely proportional to glomerular filtration rate. High s.c. doses of poloxamer 188, approximately 650 times the maximal expected clinical exposure based on body surface area, have been shown to induce vacuolation of the renal tubules in rats. The findings from some clinical trials of poloxamer 188 have demonstrated that similar extremely high i.v. dosages of poloxamer 188 cause a reversible acute renal dysfunction (i.e. decreased creatinine clearance observed).

Clinical trial experience

Two placebo-controlled clinical trials of patients in intensive care units treated with somatropin in high doses (5.3-8 mg/day) 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. The safety of continuing growth hormone 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 growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

Thyroid function

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

Hypothyroidism may develop in patients with pituitary disease. As hypothyroidism interferes with the response to Norditropin therapy patients should have periodic thyroid function tests and thyroid hormone should be substituted when indicated. Patients with Turner syndrome have an increased risk of developing primary hypothyroidism associated with anti-thyroid antibodies.

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, and careful otological evaluation is recommended.

Treatment in growth hormone deficient adults should be attempted only after definitive treatment of pituitary tumour (if present) is completed and all other pituitary hormone deficiencies are corrected, as clinically indicated.

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

Tumours or malignant disease

Leukaemia has been reported in a small number of growth hormone deficient patients some of whom have been treated with somatropin. Based on current evidence it is unlikely that somatropin is responsible for this. In patients in complete remission from tumours or malignant disease, growth hormone therapy has not been associated with an increased relapse rate.

Nevertheless, patients who have achieved complete remission of malignant disease should be followed closely for relapse after commencement of Norditropin therapy.

Benign intracranial hypertension

Very rare cases of benign intracranial hypertension have been reported. If appropriate, somatropin treatment should be discontinued.

In cases of severe or recurrent headache, visual symptoms, 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, 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.

Lipoatrophy

If injected subcutaneously, the injection site should be rotated to minimise the risk of lipoatrophy.

Pancreatitis

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

Acute adrenal insufficiency

Introduction of Norditropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with Norditropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of Norditropin treatment (see section 4.5 Interactions with Other Medicines and Other Forms of Interaction).

Glucose Intolerance and Diabetes Mellitus

Treatment with Norditropin 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 Norditropin, 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 Norditropin therapy (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions). The doses of antihyperglycaemic drugs (i.e. insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

Use in renal impairment

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 Norditropin treatment by following growth on optimal treatment for renal disease over one year. Conservative management of uraemia with customary medication and if needed dialysis should be maintained during Norditropin therapy.

Patients with chronic renal disease normally experience a decline in renal function as part of the natural course of their illness. However, as part of the clinical management of the patient during somatropin treatment, renal function should be monitored for excessive decline, including signs of rejection episodes in transplanted patients. Particular caution should be exercised if somatropin is used in children who have had a previous episode of rejection or in whom immunosuppression is not assured (see Section 5.1 Clinical trials).

Patients with chronic renal disease may develop hyperparathyroidism which should be treated appropriately before initiation of Norditropin therapy.

Use in the elderly

Experience in patients older than 60 years and in patients with more than 10 years' of treatment in adult growth hormone deficiency is still limited.

Paediatric use

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

In fast growing children and patients with endocrine disorders, slipped epiphysis of the hip may occur more frequently than in the general population.

Slipped capital femoral epiphysis, osteonecrosis of femoral head (including Legg-Calvé-Perthes disease) have been reported in children treated with somatropin. Legg-Calvé-Perthes disease may occur more frequently in patients with short stature.

Children with persistent hip/knee pain and/or limping during treatment with somatropin should be examined clinically.

The dosage in children with intrauterine growth retardation is individual and must be adjusted according to the individual response to therapy. Norditropin treatment is not indicated for idiopathic short stature or familial short stature.

In SGA children it is recommended that fasting insulin and blood glucose be measured before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, Turner syndrome, severe insulin resistance, acanthosis nigricans), oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.

In SGA children it is recommended that the IGF-1 level be measured 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 IGF-1 / IGFBP-3 ratio could be taken into account to consider dose adjustment.

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

Effects on laboratory tests

No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Acute adrenal insufficiency

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of Norditropin. Patients with adrenocorticotropic hormone (ACTH) deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4 Special Warnings and Precautions for Use).

Other hormones

The effect of growth hormone on final height can also be influenced by additional therapy with other hormones, e.g. gonadotrophin, anabolic steroids, oestrogen and thyroid hormone. Concomitant administration with gonadal steroids may not be optimal clinical practice, since there is evidence that treatment with gonadal steroids plus somatropin may reduce the final height compared to treatment with somatropin alone.

In insulin treated patients, adjustment of insulin dose may be needed after initiation of Norditropin treatment (see 4.4 Special Warnings and Precautions for more information on carbohydrate metabolism).

Cytochrome P450 isoenzymes

Data from an interaction study performed in growth hormone deficient adults, suggests that Norditropin 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.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

In a fertility study, female rats were treated s.c. with Norditropin for 2 weeks prior to mating and for the first 7 days of pregnancy. Pregnancy rate was reduced at doses ≥ 1 IU/kg/day (equivalent to 2 mg/m^2/day, approximately 1.4 times the maximum clinical dose on a body surface area basis) and resorption rate was increased at 3.3 IU/kg/day. However, litter size was increased due to an increased number of released ova. In studies with other recombinant human growth hormone preparations, increased incidences of irregular oestrous cycles and delayed mating time were observed in rats treated with somatropin at s.c. doses of 0.1 IU/kg/day (equivalent to 0.2 mg/m^2/day, about 15% of the maximum clinical dose on a body surface area basis) or greater.

Use in pregnancy

Pregnancy Category B1

Animal reproduction studies have not been conducted with Norditropin. It is not known whether Norditropin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Another form of recombinant human growth hormone was not teratogenic in rats or rabbits at respective doses of up to 15 and 28 times the maximum recommended clinical dose based on body surface area. In rats, recombinant human growth hormone administered from late gestation to weaning, at 15 times the clinical dose based on body surface area, was associated with increased body weight of pups at birth and postnatally. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in lactation

There have been no studies conducted with Norditropin in nursing mothers and it is not known whether Norditropin is excreted in breast milk. It is unlikely that the intact growth hormone would be excreted in the milk; however, following subcutaneous administration of radiolabelled recombinant human growth hormone to lactating rats, radioactivity was transferred to milk reaching four times the concentration found in maternal plasma. Absorption of any intact protein in the gastrointestinal tract of the infant is extremely unlikely.

4.7 Effects on Ability to Drive and Use Machines

Norditropin is not expected to affect the ability to drive or use machinery.

4.8 Adverse Effects (Undesirable Effects)

When treatment with somatropin is initiated, fluid retention with peripheral oedema may occur, especially in adults.

Carpal tunnel syndrome is common in adults. The symptoms are usually transient, dose dependant and may require transient dose reduction.

Adverse reactions in children are uncommon or rare.

Clinical trial experience

Table 1: Adverse drug reactions from clinical trials

System organ class	Very common > 1/10	Common > 1/100; < 1/10	Uncommon > 1/1000; < 1/100	Rare > 1/10000; <1/1000
Metabolism and nutrition disorder			In adults: Diabetes mellitus type 2 (Please see Post marketing experience)	
Nervous system disorder		In adults: headache and paraesthesia/ abnormal sensation	In children: benign intracranial hypertension, headache, seizure, motor problems	

System organ class	Very common > 1/10	Common > 1/100; < 1/10	Uncommon > 1/1000; < 1/100	Rare > 1/10000; <1/1000
Skin and subcutaneous tissue disorder			In adults: pruritus In children: skin rash, transient local skin reactions at the injection site; lipoatrophy	In children: allergy, alopecia
Musculoskeletal, connective tissue and bone disorder		In adults: arthralgia, joint stiffness and myalgia/skeletal pain/stiffness, carpal tunnel syndrome	In adults: muscle stiffness In children: arthralgia, slipped epiphysis, scoliosis/ kyphoscoliosis	In children: myalgia
Reproductive system and breast disorders			In adults and children: Gynaecomastia	
General disorders and administration site conditions	In adults: peripheral oedema (Please see text above)	In adults: injection site reaction	In adults and children: injection site pain. In children: injection site reaction, oedema	
Gastrointestinal disorders			In children: nausea	

In children with Turner syndrome increased growth of hands and feet has been reported during growth hormone therapy.

Post marketing experience

Rare (less than 1 in 1000) cases of generalised hypersensitivity reactions (e.g. anaphylactic reactions) have been reported. See Section 4.3 Contraindications.

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.

Slipped capital femoral epiphysis, osteonecrosis of femoral head, and Legg-Calvé-Perthes disease have been reported in children treated with somatropin.

There have been reports of fatalities after initiating therapy with growth hormone in paediatric patients with Prader-Willi syndrome, for which Norditropin is not approved, who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnoea before initiation of treatment with growth hormone. If pathological findings are observed during the assessment of upper airway obstruction, the patient should be referred to an ear, nose, throat specialist for treatment and resolution of the respiratory disorder before initiating somatropin treatment. The patient should

be monitored if sleep apnoea is suspected. If during treatment with growth hormone, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnoea, treatment should be discontinued and a new ear, nose, throat assessment should be performed. All patients with Prader-Willi syndrome treated with growth hormone should also have effective weight control and be monitored for signs of respiratory infection.

The following table lists further conditions reported in post-marketing experience.

Table 2: Further conditions reported in post-marketing experience

Observation	CIOMS Frequency	Notes
Formation of antibodies directed against somatropin	Rare: > 1/10,000; <1/1000	The titres and binding capacities of these antibodies have been very low and have not interfered with the growth response to Norditropin administration. Antibodies have potential for inhibition of further linear growth response to continued somatropin treatment. Patients failing to respond to treatment should therefore be tested for antibodies.
Decrease in serum thyroxin levels during Norditropin therapy (see Section 4.4 Special Warnings and Precautions for Use).	Very Rare: <1/10,000	
Increase in blood alkaline phosphatase level may be seen during the treatment with Norditropin.	Very rare: <1/10,000	
Benign intracranial hypertension	Very Rare: <1/10,000	
Diabetes mellitus type 2 cases have been reported	Very Rare: <1/10,000	Most of the available literature does not demonstrate an increased incidence of diabetes associated with somatropin treatment.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

The maximum generally recommended dosage should not be exceeded due to the potential risk of side effects.

Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Changes in 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC: H 01 AC 01.

Mechanism of action

Norditropin increases the growth rate in humans by stimulation of protein synthesis and other metabolic processes.

Growth

The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in patients with somatropin deficiency.

Skeletal growth - the measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulphate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGF). The somatomedins, among them somatomedin-C (otherwise known as IGF-1), are polypeptide hormones which are synthesised in the liver, kidney and various other tissues. Somatomedin-C (IGF-1) is low in the serum of hypopituitary dwarfs and hypophysectomised humans or animals, but its presence can be demonstrated after treatment with somatropin.

Cell growth - it has been shown that the total number of skeletal muscle cells is markedly decreased in short stature children lacking endogenous somatropin compared with normal children, and that treatment with somatropin results in an increase in both the number and size of muscle cells.

Organ growth - somatropin influences the size of internal organs, and it also increases red cell mass.

Protein metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. This synthesis and growth are reflected by nitrogen retention which can be quantitated by observing the decline in urinary nitrogen excretion and blood urea nitrogen following the initiation of somatropin therapy.

Carbohydrate metabolism

Somatropin has a diabetogenic effect. Hypopituitary children sometimes experience hypoglycaemia, and acromegalic adults often suffer from diabetes mellitus. In healthy subjects, very large doses of somatropin may impair glucose tolerance. Although the precise mechanism of the diabetogenic effect of somatropin is not known, it is attributed to blocking the action of insulin rather than blocking insulin secretion. Insulin levels in serum actually increase as somatropin levels increase.

Fat metabolism

Growth hormone stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids, cholesterol and triglycerides. Untreated growth hormone

deficiency is associated with increased body fat stores including increased subcutaneous adipose tissue. On somatropin replacement a general reduction of fat stores and of subcutaneous tissue in particular, takes place.

Mineral metabolism

The retention of sodium is less than that of potassium. Serum levels of phosphate increase in patients with growth hormone deficiency after somatropin therapy due to metabolic activity associated with bone growth. Serum calcium levels are not altered. Although calcium excretion in the urine is increased, there is a simultaneous increase in calcium absorption from the intestine. Negative calcium balance, however, may occasionally occur during somatropin treatment.

Connective tissue metabolism

Somatropin stimulates the synthesis of chondroitin sulphate and collagen as well as the urinary excretion of hydroxyproline.

Clinical trials

Turner Syndrome

There were two prospective, open label studies conducted to establish the efficacy of Norditropin in girls with Turner Syndrome.

GHTUR/BPD/6&12/NL was a prospective, randomised open label study in girls ≥11 years (mean 13.6 years at study entry). All subjects received somatropin 6 IU/m^2/day as either a single daily dose or two divided doses until final height. All subjects received oestrogen to induce puberty and later progesterone to induce withdrawal bleeds (although this may not be optimal clinical practice, since there is evidence that treatment with gonadal steroids plus somatropin may reduce the final height compared to treatment with somatropin alone). Nineteen subjects were randomised with the mean duration of treatment of 43.1 months. Seventeen reached final height, and two withdrew at close to final height. Final height was defined by a height velocity <2 cm/year.

The baseline mean height (n=19) was 137.71 cm with a mean Karlberg standard deviation score (SDS) of +0.663 and Roede SDS of -3.4. There was no difference in the effect on growth of administering somatropin once or twice per day and the treatment groups were pooled. The mean final height of the 17 subjects who reached final height was 155.08 cm with a mean Karlberg SDS of +1.28 and Roede SDS of –2.13. If all subjects are included, the mean final height is 155.2 cm. Height velocity increased compared to baseline.

Somatropin treated subjects remained shorter than girls without Turner syndrome but gained on average 7.9 cm as a result of somatropin treatment (calculated according to Roede standards).

GHTUR/BPD/5-13/NL is an ongoing prospective, open label multi-centre study comparing three doses of somatropin (4, 6 and 8 IU/m^2/day) in girls aged 2-11 years, combined with one of two different dosing regimens of 17β-estradiol to induce puberty. 68 subjects are enrolled with 13 at final height in January 1998, 14 withdrawn and 41 remaining in the study. By April 1999, an additional 12 subjects had attained final height.

In January 1998, of the 14 withdrawn subjects, three had withdrawn due to adverse effects, and the other 11 due to reaching near final height. Analysis of the 13 subjects who had reached a

mean final height of 159 ± 7.2 cm by January 1998 showed an average height gain of 9.8 cm as a result of treatment with somatropin after a mean duration of treatment of 7.2 ± 0.69 years. The change from baseline score in the Karlberg and Roede SDS were +2.05 and +1.58 respectively in these 13 subjects.

The two prospective Turner Syndrome studies included 85 patients in total. Seven patients experienced peripheral oedema during the trials; however, a dose relationship was not shown. One out of 17 patients in GHTUR/BPD/6&12/NL showed impaired glucose tolerance at more than one assessment after three years of growth hormone treatment. In the dose-response study, GHTUR/BPD/5-13/NL, no changes in glucose metabolism was detected; however, all but one patient showed an increase in insulin AUC during the trial.

Chronic Renal Failure

Five studies (including some with sub-studies) were conducted to establish the efficacy of Norditropin on growth in children with chronic renal failure (CRF) pre-transplant. One multi-part study was conducted in children with CRF post-transplant. Two of the sub-studies were prospective, double blind, placebo-controlled studies of the effect on growth of six months of treatment with Norditropin 28 IU/m^2/week in children with CRF pre-transplant (GHCRF/BPD/1/NL Study 1) and post-transplant (the first year of GHCRF/BPD/2-5/NL in pre-pubertal patients). The other studies were either dose-comparison studies (14 vs 28 or 32 and 28 vs 56 IU/m^2/week for up to 30 months) or follow-up studies in patients continuing to receive somatropin after previous participation in one of the placebo-controlled or dose comparison studies. There are no final height data on children who began treatment prior to puberty and quality of life data are not available.

GHCRF/BPD/1/NL (Study 1) and GHCRF/BPD/2-5/NL (first 12 months) were randomised, double-blind, placebo-controlled studies on pre-pubertal children, involving 22 and 11 patients, respectively. In both studies, children were randomised to receive placebo or Norditropin 28 IU/m^2/week for 6 months, followed by the alternate treatment for 6 months. Although final height data were not attained, both studies showed that there was a significantly greater height velocity (equivalent of 9.8 vs 3 and 9.2 vs 3.75 cm/year, respectively) and height velocity standard deviation score (5.9 vs 1.75 and 6.7 vs -0.6, respectively) with Norditropin than placebo, indicating that six months treatment increased height velocity. No longer-term placebo-controlled studies have been conducted.

The results of Norditropin treatment in children with CRF indicate that it resulted in short-term increases in growth velocity, which diminished after the first 6-12 months. The safety profile of Norditropin in post-transplant children is similar to that in the pre-transplant setting; however, there is uncertainty about whether there is an increase in the frequency of renal allograft rejection episodes in children with renal transplants who are treated with somatropin. An increase in the incidence of rejection was seen in some trials but not in others. The risk appeared greatest in children who had had a previous episode of rejection, in whom immunosuppression was not maintained, or who received higher than the recommended dose of somatropin.

Peripheral oedema was not reported during the five CRF studies. In three subjects (out of 124 patients randomised to the trials) OGTT were categorised as diabetic during the trial, of which one diabetic response was assumed to be prednisone induced.

Small for Gestational Age (SGA)

There were three studies conducted to establish the efficacy of Norditropin in short children born SGA mainly due to intrauterine growth retardation. The efficacy parameters did not include quality of life measures as endpoints and were based on auxological criteria alone.

GHRETARD/BPD/14-20-21/NL (Study 1) is an ongoing multi-centre, double-blind, randomised, two-arm study comparing two doses of somatropin (3 or 6 IU/m^2/day (0.033 or 0.067 mg/kg/day)) for up to nine years. In the original study (14/NL), 79 short children born with IUGR without catch-up growth were included; 78 children completed two years and continued in the extension trial (20/NL) for a further two years. A total of 75 children completed four years and entered the second extension of the trial (21/NL), and somatropin treatment was continued at the same dose until final height. By August 2001, 18 children completed the study, 37 were still ongoing, and 24 were withdrawn (18 withdrawn due to attaining satisfactory height) during the nine-year trial period.

During the first year of therapy, height velocity (HV) increased from a mean of 5.6 cm/year to 10.0 cm/year in the low-dose group and from 5.4 cm/year to 11.7 cm/year in the high-dose group. HV subsequently decreased with time, but remained higher than pre-treatment HV up to seven years. The difference in HV between the two dose groups was statistically significant at Years 1 and 2. Results of other efficacy variables indicated a substantial effect on linear growth resulting in a mean change in Roede SDS from -3.1 to -0.6 and from -3.1 to -0.1 in the two dose-groups, respectively, after eight years of somatropin treatment. Long-term treatment (up to 9 years) was safe and well tolerated, and there were no withdrawals due to serious adverse events.

GHRETARD/BPD/16-20/NL (Study 2) was a single centre, open label study, in which 11 (8 females and 3 males) children (who failed to meet the inclusion criteria for inclusion in 14/NL due to age and/or puberty) were included. Trial conduct in 16/NL was the same as that for 14/NL with the exception that all children received somatropin at a dose of 6 IU/m^2/day. After two years of treatment, these children were allowed to continue in 20/NL for a further two years. After a total of four years, children, who had not reached final height, continued treatment in 21/NL at the same dose of somatropin until final height was reached. Of the 11 children, nine completed the study (four reaching final height, and five reaching near final height).

Data on the first four years of treatment were analysed; final height data on children in this study were pooled with 21/NL and reported separately (see Table 3). Overall, there was an increase in HV from pre-treatment to Year 1. HV then declined yearly primarily due to the fact that subjects were nearing final height. Height standard deviation score (HSDS) increased from a mean of -2.62 at baseline to -1.85 at Year 4.

Data on final height (defined by a height velocity <1 cm/year) are available on 40 subjects in Studies 1 and 2. Of the subjects (26 males and 14 females) analysed, 10 subjects were GHD and 30 (20 males and 10 females) were non-GHD, including 11 subjects (7 males and 4 females) with a baseline height < -3 SD. Mean final height data are shown in the following table.

Table 3: Mean final height data from Studies GHRETARD/BPD/14-20-21/NL and GHRETARD/BPD/16-20/NL

Baseline Height	Male		Female	
	3 IU/m^2/day (0.033mg/kg/day)	6 IU/m^2/day (0.067mg/kg/day)	3 IU/m^2/day (0.033mg/kg/day)	6 IU/m^2/day (0.067mg/kg/day)
< -2 SD (GHD + non-GHD)	168.3 ± 6.5 (n = 13)	172.1 ± 6.5 (n = 13)	160.8 ± 3.7 (n = 5)	158.7 ± 4.8 (n = 9)
< -2 SD (non-GHD)	168.5 ± 5.9 (n = 10)	171.5 ± 6.1 (n = 10)	160.9 ± 5.5 (n = 2)	158.5 ± 5.1 (n = 8)
< -3 SD (non-GHD)	164.6 ± 4.9 (n = 5)	172.9 ± 4.0 (n = 2)	- (n = 0)	155.4 ± 4.6 (n = 4)

GHRETARD/F/1/F (Study 3) was a prospective, randomised, open label, parallel group, multi-centre study comparing three regimens of somatropin for two years. Patients were randomised to one of three treatment groups: 0.2 IU/kg/day (six days/week) continuous treatment; 0.2 IU/kg/day (six days/week) non-continuous treatment (alternating periods of six months treatment and non-treatment); and 0.4 IU/kg/day (six days/week) non-continuous treatment (alternating periods of six months treatment and non-treatment). Of the 139 children randomised and allocated to the three treatment groups (46, 47, and 46, respectively), 133 completed the study.

A dramatic change in HV from approximately 4.8 cm/year to 10 cm/year was found in all treatment groups during the first six months of the study. Continuous treatment with 1.2 IU/kg/week resulted in the most beneficial growth in comparison to the alternating treatment regimens. Except for during off-treatment periods, all regimens resulted in increased HV and height gain during childhood. The alternating 2.4 IU/kg/week regimen did not appear to be more efficient than the alternating 1.2 IU/kg/week regimen. There was a statistically significant difference ($p<0.001$) in HSDS between the treatment groups, showing an increase of 1.42 from -3.19, of 0.86 from -3.06, and of 1.02 from -3.11 in the three groups, respectively.

Deficiency in Adults

Clinical data are available on seven placebo-controlled studies and uncontrolled extensions from four of these studies. The placebo-controlled studies range in duration from 4 to 12 months involving a total of 420 subjects (222 and 198 subjects in the somatropin and placebo arms, respectively, equivalent to 94 patient years (somatropin treatment) and 84 patient years (placebo treatment)). Two thirds of the subjects had Adult Onset [AO] growth hormone insufficiency. Results, available on 203 subjects from 3 of the 4 studies which used the insulin tolerance test to diagnose GH deficiency, showed 71% of subjects had a peak growth hormone concentration of less than 2.5ng/mL. Primary outcomes commonly measured across the studies included the efficacy and safety of Norditropin on body composition, muscle strength, exercise capacity, and bone metabolism. Secondary outcomes included the effects of Norditropin on lipid metabolism, thyroid metabolism, pituitary, adrenal and gonadal function, cellular and humoral immune function and quality of life. Overall, the studies demonstrated progressive improvement and partial normalisation of some surrogate outcome parameters measured in those patients administered somatropin. Outcomes statistically significantly improved by the end of twelve months as compared to placebo included: body composition [total body fat, skinfold thickness, total body fat, total body lean mass, waist/hip ratio]; bone metabolism

[increased osteocalcin]; mineral metabolism [increased alkaline phosphatase]; and thyroid metabolism [increased serum free T_3]. Trial analyses were undertaken in accordance with approved study protocols and subsequent amendments. Due to unknown correlations between the assessments and dependencies between hypotheses on primary efficacy and safety outcomes, adjustment for multiple comparisons was not carried out.

Uncontrolled extension data are available from four of the seven studies. Involving over 182 subjects and ranging in duration from 16 months to five years [83 subjects ≥ 2 years, 40 subjects ≥ 4 years], these demonstrated overall that some of the modifications seen in the shorter term, placebo-controlled studies continued to show progressive change (relative to baseline) and approach values close to normal individuals at three years. The long-term clinical significance of these changes is not clear. By three years, adults on somatropin replacement show normalisation/progressive improvement in the following outcomes: body composition [lean body mass to fat ratio]; bone metabolism [lumbal spine BMC, osteocalcin, whole body BMC]; thyroid metabolism [increased serum free T_3]; lipid metabolism [LDL, HDL, cholesterol] and cardiac status [resting systolic/diastolic BP levels]. Following four years of somatropin replacement, sustained change was shown with the following outcomes: body composition [muscle volume and mass, body weight, total body fat, waist/hip ratio]; bone metabolism [lumbal spine BMD, osteocalcin, hydroxyproline]; thyroid metabolism [increased serum free T_3]; and cardiac status [systolic/diastolic BP levels]. There was no statistically significant improvement in quality of life measurements; however, the changes were consistent and in a direction denoting improvement.

The somatropin-related adverse effects observed in the studies were mild to moderate and reversible with the most frequent side effects arising from the salt and water retaining effects of the hormone manifesting mainly as fluid retention. These symptoms occurred in the early weeks of treatment and improved or disappeared with dosage reduction.

Overall, the studies demonstrated that somatropin replacement leads to a correction of the abnormalities in body composition caused by untreated growth hormone deficiency. The long-term studies not only showed that the early changes are maintained, but also that some endpoints continue to improve beyond twelve months of somatropin replacement. This observation demonstrates that several of the actions of somatropin on body structure and function occur slowly and may take several years to normalise.

5.2 Pharmacokinetic Properties

IV infusion of Norditropin SimpleXx®[1] solution for injection (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.

5.3 Preclinical Safety Data

Genotoxicity

There was no evidence of Norditropin-induced genotoxicity in assays for gene mutation in bacteria or chromosomal damage in mouse bone marrow cells *in vivo*.

[1] *Norditropin SimpleXx is no longer registered in Australia*

Carcinogenicity

Somatropin raises the serum levels of IGF-1. Associations between elevated serum IGF-1 concentrations and risk of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mannitol, histidine, poloxamer, phenol and water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, the medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Before use: Store in a refrigerator (2°C-8°C) in the outer carton, in order to protect from light. Do not store close to any cooling elements. Do not freeze.

When in use, the product may be stored for a maximum of 28 days in a refrigerator (2°C-8°C), *alternatively* stored for a maximum of 21 days below 25°C. Do not store close to any cooling elements. Do not freeze.

Norditropin retains its biological potency until the date of expiry indicated on the label.

6.5 Nature and Contents of Container

Carton containing 1 x 1.5 mL pre-filled pen

- Multi-dose, disposable, pre-filled pen, consisting of somatropin 5 mg, 10 mg or 15 mg solution for s.c. injection in a colourless glass cartridge, permanently sealed in a pen-injector.
- The push button, pen cap and cartridge holder on the pen-injector is colour coded according to strength: 5 mg/1.5 mL (yellow), 10 mg/1.5 mL (blue) and 15 mg/1.5 mL (green)
- The cartridge contains a rubber plunger and is closed with a rubber closure.

*Not all presentations and pack sizes may be available.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure

Not applicable.

CAS number

Not applicable.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

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9. DATE OF FIRST APPROVAL

9 May 2011

10. DATE OF REVISION

26 September 2025

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of osteonecrosis of the femoral head in Paediatric Use section. Minor editorial changes to add subheadings.
4.8	Addition of osteonecrosis of femoral head in post-marketing experience section.