

## New Zealand Datasheet

### Name of Medicine

**NORDITROPIN<sup>®</sup> SIMPLEXX<sup>®</sup>**

Somatropin 5mg, 10mg and 15mg

Biosynthetic human growth hormone for subcutaneous injection

### Presentation

Norditropin SimpleXx is a colourless liquid contained in a colourless glass cartridge. Each cartridge contains 1.5ml of liquid.

Each cartridge of Norditropin SimpleXx 5mg contains 5mg of somatropin. Each cartridge of Norditropin SimpleXx 10mg contains 10mg of somatropin. Each cartridge of Norditropin SimpleXx 15 mg contains 15 mg of somatropin.

### Uses

#### Actions

Norditropin SimpleXx contains somatropin, which is human growth hormone produced by recombinant DNA-technology. It is an anabolic peptide of 191 amino acids stabilised by two disulphide bridges with a molecular weight of approximately 22.000 Daltons.

The major effects of Norditropin SimpleXx 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 factors (IGF), which are produced in tissues throughout the body, but predominantly by the liver. More than 90% of IGF is bound to binding proteins (IGFBP's) 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.

#### Pharmacokinetics

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  $21.1 \pm 1.7$  min., metabolic clearance rate of  $2.33 \pm 0.58$  ml/kg/min. and a distribution space of  $67.6 \pm 14.6$  ml/kg.

#### Indications

Children:

Growth failure due to growth hormone deficiency.

Turner's syndrome.

Growth retardation due to chronic renal disease.

Adults:

Growth hormone insufficiency in adults.

Severe growth hormone deficiency in adults should be established by provocative testing of growth hormone secretion. At present, the insulin tolerance test is the diagnostic test of choice. Where insulin tolerance test is contraindicated alternative provocative tests must be

used. A combined arginine-growth hormone releasing hormone test is at present recommended. An arginine or a glucagon test may also be considered, however, these tests have less established diagnostic value compared to the insulin.

## **Dosage and Administration**

The dosage and the schedule for administration must be individualised for each patient. Subcutaneous administration in the evening is recommended. The injection site should be varied to prevent lipoatrophy. Dosage can be calculated according to body weight or body surface area.

The generally recommended dosages are:

### **Children:**

#### Growth hormone deficiency

25-35 µg/kg/day (0.07-0.10 IU/kg/day)

Equal to: 0.7-1.0 mg/m<sup>2</sup>/day (2-3 IU/m<sup>2</sup>/day)

#### Turner's syndrome

50 µg/kg/day (0.14 IU/kg/day)

Equal to: 1.4 mg/m<sup>2</sup>/day (4.3 IU/m<sup>2</sup>/day)

#### Chronic Renal Disease

50 µg/kg/day (0.14 IU/kg/day)

Equal to: 1.4 mg/m<sup>2</sup>/day (4.3 IU/m<sup>2</sup>/day)

### **Adults:**

#### Replacement therapy in adults

The dosage must be adjusted to the need of the individual patient. It is recommended to start treatment with a low dose 0.15-0.3 mg/day (equal to 0.45-0.9 IU/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 insulin-like growth factor I can be used as guidance for the dose titration.

Dose requirements decline with age. Maintenance dosage vary considerably from person to person, but seldom exceeds 1.0 mg/day (equal to 3 IU/day).

## **Contraindications**

Any evidence of active malignant tumours.

Intracranial neoplasm must be inactive and anti-tumour therapy should be completed prior to institution of therapy.

Norditropin SimpleXx should be withdrawn if there is any sign of recurrent tumour growth and the patient should be thoroughly re-examined.

Treatment with somatropin should be discontinued when the epiphysial discs are closed.

In the children with chronic renal disease treatment with Norditropin SimpleXx should be discontinued at renal transplantation.

Treatment during pregnancy and lactation is not recommended. Currently there is insufficient evidence of safety of somatropin therapy during pregnancy. Norditropin is therefore contraindicated during pregnancy. In the event of pregnancy occurring during treatment, Norditropin therapy should be discontinued. The possibility that somatropin is secreted in breast milk cannot be discounted.

Hypersensitivity to any of the ingredients in the preparations.

## **Warnings and Precautions**

Children treated with Norditropin SimpleXx should be regularly assessed by a specialist in child growth. Norditropin SimpleXx 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's syndrome and chronic renal disease. Data of final adult height following the use of Norditropin for conditions with Turner's syndrome and children with chronic renal disease are not available.

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

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 SimpleXx 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 SimpleXx therapy.

Patients with chronic renal disease normally experience a decline in renal function as part of the natural course of their illness. However, as a precautionary measure during Norditropin SimpleXx treatment renal function should be monitored for an excessive decline, or increase in the glomerular filtration rate (which could imply hyperfiltration).

Treatment in patients with growth retardation due to chronic renal disease should start as soon as possible after growth retardation has been diagnosed and should be discontinued at renal transplantation.

Somatropin has been found to influence carbohydrate metabolism, therefore, patients should be observed for evidence of glucose intolerance.

Because of its diabetogenic actions (insulin resistance) Norditropin should be used with caution in patients with diabetes mellitus or with a family history of diabetes mellitus. Regular urine testing for evidence of glycosuria should be carried out in all patients.

Serum thyroxine levels may fall during treatment with Norditropin SimpleXx due to the increased peripheral deiodination of T<sub>4</sub> to T<sub>3</sub>. In patients with a pituitary disease in progression, hypothyroidism may develop. Patients with Turner's syndrome have an increased risk of developing primary hypothyroidism associated with anti-thyroid antibodies. As hypothyroidism interferes with the response to Norditropin SimpleXx therapy patients should have a periodic thyroid function test and should be substituted with thyroid hormone when indicated.

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

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

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 SimpleXx therapy.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders and Legg-Calvé-Perthes disease may occur more frequently in patients with short stature. These diseases may present as the development of a limp or complaints of hip or knee pain and physicians and parents should be alerted to this possibility.

In the event of severe or recurrent headache, visual problems, nausea, and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the growth hormone treatment should be discontinued. At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

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

### **Use in Pregnancy and Lactation**

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

### **Effect on Ability to Drive and Use Machines**

Norditropin SimpleXx is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

### **Adverse Effects**

Fluid retention with peripheral oedema may occur and especially in adults carpal tunnel syndrome may be seen. The symptoms are usually transient and dose dependent, but may require dose reduction. Mild arthralgia may also occur in adults, but is usually self-limiting.

Formation of antibodies directed against somatropin has rarely been observed during Norditropin therapy. The titres and binding capacities of these antibodies have been very low and have not interfered with the growth response to Norditropin administration. During treatment with Norditropin SimpleXx local injection site reactions may occur.

Some rare cases of benign intracranial hypertension have been reported.

### **Interactions**

Concomitant glucocorticoid therapy may inhibit growth and thereby oppose the growth promoting effect of Norditropin SimpleXx. The effect of growth hormone on final height can also be influenced by additional therapy with other hormones, e.g. gonadotrophin, anabolic steroids, estrogen and thyroid hormone.

### **Overdosage**

Information on overdose and poisoning is lacking.

Acute overdosage can lead to low blood glucose levels initially, followed by high blood glucose levels. These decreased glucose levels have been detected biochemically, but without clinical signs of hypoglycaemia. Long-term overdosage could result in signs and symptoms consistent with the known effects of human growth hormone excess.

## **Pharmaceutical Precautions**

### **Incompatibilities**

It is not recommended to add Norditropin SimpleXx to other compounds.

### **Shelf life**

Norditropin Simplexx 5 mg and 10 mg: 2 years stored at 2°C – 8°C

After first use Norditropin Simplexx may be kept at 2°C – 8°C for a maximum of 28 days or alternatively under 25°C for a maximum of 21 days.

Norditropin Simplexx 15 mg:

2 years stored at 2°C – 8°C

After first use Norditropin Simplexx may be kept at 2°C – 8°C for a maximum of 28 days.

### **Special precautions for storage**

Store at 2°C - 8°C

Do not freeze

Protect from light

### **Container**

Norditropin SimpleXx is contained in a colourless cartridge made of glass. The cartridge is closed at the bottom with a rubber stopper shaped as a plunger and at the top with a laminated rubber plunger shaped as a disc and sealed with an aluminium cap. The cartridge is contained in a blister packed in a carton.

### **Instructions for use/handling**

Patients should be reminded to wash their hands thoroughly with soap and water and/or disinfectant prior to any contact with Norditropin. Norditropin should not be shaken vigorously at any time.

Norditropin SimpleXx 5 mg, 10 mg and 15 mg should only be prescribed for use with NordiPen<sup>®</sup> 5 mg, 10 mg, 15 mg, respectively. Instructions for use of Norditropin SimpleXx in NordiPen are provided within the respective packs. Patients should be advised to read these instructions.

## **Medicine Classification**

Prescription Medicine

## **Package Quantities**

Norditropin SimpleXx 5mg: 1.5ml cartridge

Norditropin SimpleXx 10mg: 1.5ml cartridge

Norditropin SimpleXx 15mg: 1.5ml cartridge

## **Further Information**

### **Pre-clinical Safety Data**

The general pharmacological effects on the CNS, cardiovascular and respiratory systems following administration of Norditropin SimpleXx with and without forced degradation were investigated in mice and rats; renal function was also evaluated. The degraded product showed no difference in effect when compared with Norditropin SimpleXx and Norditropin. All three preparations showed the expected dose dependent decrease in urine volume and retention of sodium and chloride ions.

In rats, bioequivalence has been demonstrated between Norditropin SimpleXx and Norditropin. Degraded Norditropin SimpleXx has also been demonstrated to be

bioequivalent with Norditropin SimpleXx.

Single and repeated dose toxicity and local tolerance studies of Norditropin SimpleXx or the degraded product did not reveal any toxic effect or damage to the muscle tissue.

The toxicity of poloxamer 188 has been tested in mice, rats, rabbits and dogs and no findings of toxicological relevance were revealed.

Poloxamer 188 was rapidly absorbed from the injection site with no significant retention of the dose at the site of injection. Poloxamer 188 was excreted primarily via the urine.

### **List of Excipients**

Mannitol, Histidine, Poloxamer 188, Phenol, Water for injections.

### **Name and Address**

Novo Nordisk Pharmaceuticals Ltd  
PO Box 51-268  
Pakuranga  
Auckland

Tel: (09) 579 0653

Fax: (09) 579 0654

### **Date of Preparation**

12 July 2004

Norditropin<sup>®</sup>, SimpleXx<sup>®</sup> and NordiPen<sup>®</sup> are registered trademarks owned by Novo Nordisk A/S