

NDA 19-721/S-007

AUG 11 2000

Novo Nordisk Pharmaceuticals, Inc.
Attention: Bany Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center
Suite 200
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your supplemental new drug application dated February 14, 2000, received February 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norditropin (somatropin [rDNA origin] for injection).

We acknowledge receipt of your submissions dated March 7 and April 3, 2000.

This supplemental new drug application provides for the following additions to the Norditropin package insert:

To the **CONTRAINDICATIONS** section, the following statement has been added:

“Norditropin should not be used or should be discontinued when there is any evidence of active malignancy. Anti-malignancy treatment must be complete with evidence of remission prior to the institution of growth hormone therapy.”

To the **PRECAUTIONS** section of the package insert, the following statement has been added:

“Progression of scoliosis can occur in children who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis.”

To the **ADVERSE REACTIONS** section of the package insert, the following sentence has been added:

“Fluid retention and peripheral edema may occur.”

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

The minor editorial revision is as follows:

The word “subcutaneous” should be deleted from the established name in the logo of the package insert as requested and approved in your Supplement-006 submission dated October 18, 1999.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted April 3, 2000). These revisions are terms of the approval of this application.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format NDAs* (January 1999). For administrative purposes, this submission should be designated “FPL for approved supplement NDA 19-721/S-007.” Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Norditropin®

4 mg or 8 mg (approximately 12 or 24IU) vials

Somatropin (rDNA origin) for subcutaneous injection

DESCRIPTION

Norditropin® is the Novo Nordisk Pharmaceuticals, Inc. registered trademark for somatropin, a polypeptide hormone of recombinant DNA origin. The hormone is synthesized 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. Norditropin® 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® is a sterile, almost white, lyophilized powder. It is a highly purified preparation intended for subcutaneous injection in the thighs after reconstitution with 2 mL diluent.

Each vial of lyophilized drug contains the following:

4 mg (approximately 12 IU) Vial

Somatropin	4 mg
Glycine	8.8 mg
Disodium Phosphate Dihydrate (Na ₂ HPO ₄ ·2H ₂ O)	1.3 mg
Sodium Dihydrogen Phosphate Dihydrate (NaH ₂ PO ₄ ·2H ₂ O)	1.1 mg
Mannitol	44 mg

8 mg (approximately 24 IU) Vial

Somatropin	8 mg
Glycine	8.8 mg
Disodium Phosphate Dihydrate (Na ₂ HPO ₄ ·2H ₂ O)	1.3 mg
Sodium Dihydrogen Phosphate Dihydrate (NaH ₂ PO ₄ ·2H ₂ O)	1.1 mg
Mannitol	44 mg

Each vial of lyophilized drug is supplied in a combination package which also contains a vial of diluent. Each mL contains 1.5% benzyl alcohol as preservative.

The pH of the reconstituted solution is about 7.3.

CLINICAL PHARMACOLOGY

a. Tissue 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.

1. 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 sulfate 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, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissue. Somatomedin C is low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, but its presence can be demonstrated after treatment with somatropin.
2. 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.
3. Organ growth - somatropin influences the size of internal organs, and it also increases red cell mass.

b. 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.

c. Carbohydrate Metabolism

Hypopituitary children sometimes experience fasting hypoglycemia that may be improved by treatment with somatropin. In healthy subjects, 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.

d. Fat Metabolism

Somatropin 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.

e. Mineral Metabolism

Administration of somatropin results in the retention of total body potassium and phosphorus and to a lesser extent sodium. This retention is thought to be the result of cell growth. 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.

f. *Connective Tissue Metabolism*

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

g. *Pharmacokinetics*

A 180-min IV infusion of Norditropin® (33 ng/kg/min) was given to 9 GHD patients. A mean (\pm SD) hGH steady-state serum level of approximately 23.1 (\pm 15.0) ng/mL was reached at 150 min and a mean clearance rate of approximately 2.3 (\pm 1.8) mL/min/kg or 139 (\pm 105) mL/min for hGH was obtained. Following infusion, serum hGH levels had a biexponential decay with a terminal elimination half-life ($T_{1/2}$) of approximately 21.1 (\pm 5.1) min.

In a study conducted in 18 GHD adult patients, where a SC dose of 0.024 mg/kg or 3 IU/m² was given in the thigh, the mean (\pm SD) C_{max} values of 13.8 (\pm 5.8) and 17.1 (\pm 10.0) ng/mL were obtained for the 4 and 8 mg Norditropin® vials, respectively, at approximately 4 to 5 hr. post dose. The mean apparent terminal $T_{1/2}$ values were estimated to be approximately 7 to 10 hr. However, the absolute bioavailability for Norditropin® after the SC route of administration is currently not known.

INDICATIONS AND USAGE

Norditropin® is indicated for the long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

CONTRAINDICATIONS

Norditropin® should not be used in subjects with closed epiphyses.

Norditropin® should not be used in hypopituitary children who have evidence of actively growing intracranial tumors. Therapy with somatropin should be discontinued if there is evidence of recurrent tumor growth.

Norditropin® should not be used in any subjects with known hypersensitivity to any of the constituents of the preparation.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin treated patients (doses 5.3-8 mg/day) compared to those receiving placebo (see WARNINGS).

WARNINGS

Benzyl alcohol as a preservative has been associated with toxicity in newborns. Norditropin® may be reconstituted in sterile water for injection. If Norditropin® is reconstituted in this manner, use only one dose per vial and discard the unused portion.

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

Norditropin® should be used only by physicians with experience in the diagnosis and management of patients with growth hormone deficiency.

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

Because growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.

Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Norditropin®. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

A state of hypothyroidism may develop during Norditropin® treatment. Since untreated hypothyroidism may interfere with the response to Norditropin®, patients should have a periodic thyroid function test and should be treated with thyroid hormone when indicated.

Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any child with the onset of a limp or complaints of hip or knee pain during growth hormone therapy should be evaluated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies for carcinogenicity and impairment of fertility with Norditropin® have not been performed. There has been no evidence to date of Norditropin-induced mutagenicity.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rats at doses up to 7 mg/m² or about 7 times the maximum recommended human dose

on a body surface area basis (mg/m^2) and have revealed no evidence of impaired fertility or harm to the fetus due to Norditropin®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: There have been no studies conducted with Norditropin® in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin® is administered to a nursing woman.

ADVERSE REACTIONS

As with all protein drugs, a small percentage of patients may develop antibodies to the protein. Growth hormone antibody with binding capacity lower than 2 mg/L has not been associated with growth attenuation. In some cases, when binding capacity is greater than 2 mg/L, interference with growth response has been observed.

In clinical trials, patients receiving Norditropin® for up to 12 months have been tested for induction of antibodies and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Among these patients, 165 had previously been treated with other preparations of growth hormone and 193 were previously untreated naive patients.

Since antibodies to somatotropin have the potential to inhibit further linear growth, only patients failing to respond to treatment should be tested for antibodies.

The following adverse events have been reported from clinical studies: headache, localized muscle pain, weakness, mild hyperglycemia and glucosuria.

Leukemia has been reported in a small number of children who have been treated with growth hormone, including growth hormone of pituitary origin and recombinant somatrem and somatotropin. On the basis of current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences. If there is any risk to an individual patient, it is minimal.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The Norditropin® dosage and schedule for administration must be individualized for each patient. Generally, subcutaneous administration in the evening, 6-7 times a week, is recommended. It is furthermore recommended to give the injections in the thighs and to vary the injection site on the thigh on a rotating basis. Dosage can be calculated according to body weight.

Generally recommended dosage:

Subcutaneous injection:

0.024-0.034 mg/kg body weight, 6-7 times a week.

Dissolution Procedure:

The Norditropin® solution for subcutaneous injection is prepared by adding the 2 mL diluent to the drug powder in the vial

1. Use a syringe and needle for injection. Before injection the rubber closures should be wiped with an antiseptic solution to prevent contamination of the contents after repeated needle insertions. Push the needle through the rubber closure on the top of the vial with the diluent. Draw up the diluent. It is easier to draw up the diluent if you have first injected air into the vial.
2. Pull out the needle. Take the vial with dry powder, push the needle through the rubber closure and inject the diluent into the vial aiming the stream of liquid against the glass wall.
3. Dissolve the dry powder completely by gently turning the vial upside down several times. **DO NOT SHAKE** the vial. The contents **MUST NOT BE INJECTED** if the solution is cloudy or contains particulate matter.

Measuring the Prescribed Dose:

4 mg (approximately 12 IU) Vial

After the dry powder has been dissolved, the solution contains 2 mg Norditropin® per mL. If the prescribed dose is e.g. 1 mg Norditropin®, draw up 0.5 mL of the solution into a syringe suitable for small volumes.

8 mg (approximately 24 IU) Vial

After the dry powder has been dissolved, the solution contains 4 mg Norditropin® per mL. If the prescribed dose is e.g. 1 mg Norditropin®, draw up 0.25 mL of the solution into a syringe suitable for small volumes.

Storage:

Before and after reconstitution with diluent Norditropin® must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

Norditropin® retains its biological potency until the date of expiry indicated on the label. Reconstituted vials should be used within 14 days after dissolution.

HOW SUPPLIED

Norditropin® is supplied as 4 mg or 8 mg (approximately 12 or 24 IU) of lyophilized, sterile somatotropin per vial.

Each 4 mg carton contains one vial of Norditropin® (4 mg per vial) and one vial of diluent (2 mL of Water for Injection USP with benzyl alcohol 1.5%).

NDC 0169-7774-11

Each 8 mg carton contains one vial of Norditropin® (8 mg per vial) and one vial of diluent (2 mL of Water for Injection USP with benzyl alcohol 1.5%).

NDC 0169-7778-12

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Rx only

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