Version 4.1 5/29/2007

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use Norditropin Cartridges safely and effectively. See full prescribing information for Norditropin Cartridges.

Norditropin® Cartridges [somatropin (rDNA origin) injection], for subcutaneous use.

Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Indications and Usage, Short Stature in Noonan Syndrome (1.1)	5/2007
Dosage and Administration, Short Stature in Noonan Syndrome (2.1)	5/2007

INDICATIONS AND USAGE

Norditropin is a recombinant human growth hormone indicated for:

- ***Pediatric***: Treatment of children with growth failure due to growth hormone deficiency (GHD) and short stature associated with Noonan syndrome (1.1)
- ***Adult***: Treatment of adults with either adult onset or childhood onset GHD (1.2)

DOSAGE AND ADMINISTRATION

Norditropin should be administered subcutaneously (2).

- ***Pediatric GHD:*** 0.024 – 0.034 mg/kg/day, 6-7 times a week (2.1)
- ***Noonan Syndrome:*** Up to 0.066 mg/kg/day (2.1)
- ***Adult GHD:*** 0.004 mg/kg/day to be increased as tolerated to not more than 0.016 mg/kg/day after approximately 6 weeks, or a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day (2.2)
- Norditropin cartridges must be used with their corresponding color-coded NordiPen® delivery systems (2.3)
- Injection sites should always be rotated to avoid lipoatrophy (2.3)

DOSAGE FORMS AND STRENGTHS

Cartridges are available for use with the corresponding NordiPens or preloaded in the Norditropin NordiFlex pens (3):

- 5 mg/1.5 mL (orange): cartridge and Norditropin NordiFlex pen
- 10 mg/1.5 mL (blue): Norditropin NordiFlex pen only
- 15 mg/1.5 mL (green): cartridge and Norditropin NordiFlex pen

CONTRAINDICATIONS

- Acute Critical Illness (4.1, 5.1)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment – reports of sudden death (4.2, 5.2)
- Active Malignancy (4.3)
- Active Proliferative or Severe Non-Proliferative Diabetic Retinopathy (4.4)
- Children with closed epiphyses (4.5)
- Known hypersensitivity to somatropin or excipients (4.6)

WARNINGS AND PRECAUTIONS

- Acute Critical Illness: Potential benefit of treatment continuation should be weighed against the potential risk (5.1)
- Prader-Willi Syndrome in Children: Evaluate for signs of upper airway obstruction and sleep apnea before initiation of treatment for GHD. Discontinue treatment if these signs occur (5.2).
- Neoplasm: Monitor patients with preexisting tumors for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin - in particular meningiomas in patients treated with radiation to the head for their first neoplasm (5.3).
- Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome – especially in adults): May occur frequently. Reduce dose as necessary (5.6).
- Hypothyroidism: May first become evident or worsen (5.7)
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain (5.8).
- Progression of Preexisting Scoliosis: May develop (5.9)

ADVERSE REACTIONS

Other common somatropin-related adverse reactions include injection site reactions/rashes and lipoatrophy (6.1) and headaches (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-NOVO-444 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1: May require the initiation of glucocorticoid replacement therapy. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance doses (7.1).
- Glucocorticoid Replacement: Should be carefully adjusted (7.2)
- Cytochrome P450-Metabolized Drugs: Monitor carefully if used with somatropin (7.3)
- Oral Estrogen: Larger doses of somatropin may be required in women (7.4)
- Insulin and/or Oral Hypoglycemic Agents: May require adjustment (7.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: m/2007

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH).

Norditropin [somatropin (rDNA origin) injection] is indicated for the treatment of children with short stature associated with Noonan syndrome.

1.2 Adult Patients

Norditropin [somatropin (rDNA origin) injection] is indicated for the replacement of endogenous GH in adults with growth hormone deficiency (GHD) who meet either of the following two criteria:

- Adult Onset (AO): Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
- Childhood Onset (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

In general, confirmation of the diagnosis of adult GHD in both groups usually requires an appropriate GH stimulation test. However, confirmatory GH stimulation testing may not be required in patients with congenital/genetic GHD or multiple pituitary hormone deficiencies due to organic disease.

2 DOSAGE AND ADMINISTRATION

For subcutaneous injection.

Therapy with Norditropin should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with short stature associated with GHD or Noonan syndrome, and adult patients with either childhood onset or adult onset GHD.

2.1 Dosing of Pediatric Patients

General Pediatric Dosing Information

The Norditropin dosage and administration schedule should be individualized based on the growth response of each patient. Serum insulin-like growth factor I (IGF-I) levels may be useful during dose titration.

Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age and antibodies to recombinant human GH (rhGH). Treatment with Norditropin for short stature should be discontinued when the epiphyses are fused.

Pediatric Growth Hormone Deficiency (GHD)

A dosage of 0.024 – 0.034 mg/kg/day, 6-7 times a week, is recommended.

Pediatric Patients with Short Stature Associated with Noonan Syndrome

Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, prior to initiating Norditropin for a patient with Noonan syndrome, establish that the patient does have short stature.

A dosage of up to 0.066 mg/kg/day is recommended.

2.2 Dosing of Adult Patients

Adult Growth Hormone Deficiency (GHD)

Based on the weight-based dosing utilized in the clinical studies, the recommended dosage at the start of therapy is not more than 0.004 mg/kg/day. The dose may be increased to not more than 0.016 mg/kg/day after approximately 6 weeks according to individual patient requirements. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used without consideration of body weight. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women.

2.3 Preparation and Administration

Norditropin Cartridges must be administered using the NordiPen delivery systems. Each cartridge size has a corresponding, color-coded pen which is graduated to deliver the appropriate dose based on the concentration of Norditropin in the cartridge.

Norditropin® Cartridges 5 mg/1.5 mL and 15 mg/1.5 mL:
Each cartridge of Norditropin must be inserted into its corresponding NordiPen delivery system. Instructions for delivering the dosage are provided in the NordiPen INSTRUCTION booklet.

Norditropin NordiFlex® 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:
Instructions for delivering the dosage are provided in the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflets enclosed with the Norditropin NordiFlex prefilled pen.

Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Norditropin MUST NOT BE INJECTED if the solution is cloudy or contains particulate matter. Use it only if it is clear and colorless.

Injection sites should always be rotated to avoid lipoatrophy.

3 DOSAGE FORMS AND STRENGTHS

Cartridges are available for use with the corresponding NordiPens or preloaded in the Norditropin NordiFlex pens:

- 5 mg/1.5 mL (orange): cartridge and Norditropin NordiFlex prefilled pen
- 10 mg/1.5 mL (blue): Norditropin NordiFlex prefilled pen only
- 15 mg/1.5 mL (green): cartridge and Norditropin NordiFlex prefilled pen

4 CONTRAINDICATIONS

4.1 Acute Critical Illness

Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units 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 and Precautions (5.1)]*.

4.2 Prader-Willi Syndrome in Children

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment *[see Warnings and Precautions (5.2)]*. Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Norditropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

4.3 Active Malignancy

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since GHD may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such

tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

4.4 Diabetic Retinopathy

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

4.5 Closed Epiphyses

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

4.6 Hypersensitivity

Norditropin is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Localized reactions are the most common hypersensitivity reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin *[see Contraindications (4.1)]*. The safety of continuing somatropin 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 somatropin in patients experiencing acute critical illnesses should be weighed against the potential risk.

5.2 Prader-Willi Syndrome in Children

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, 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 apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively *[see Contraindications (4.2)]*. Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, Norditropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

5.3 Neoplasms

Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Patients should be monitored carefully for potential malignant transformation of skin lesions, i.e. increased growth of preexisting nevi.

5.4 Glucose Intolerance

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of

antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

5.5 Intracranial Hypertension (IH)

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose.

Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for the development of IH.

5.6 Fluid Retention

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

5.7 Hypothyroidism

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

5.8 Slipped Capital Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

5.9 Progression of Preexisting Scoliosis in Pediatric Patients

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated patients with Turner syndrome and Noonan syndrome. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

5.10 Confirmation of Childhood Onset Adult GHD

Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in *Indications and Usage (1.2)* before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults.

5.11 Local and Systemic Reactions

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site *[see Dosage and Administration (2.3)]*.

As with any protein, local or systemic allergic reactions may occur. Parents/Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

5.12 Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase after somatropin therapy.

6 ADVERSE REACTIONS

6.1 Most Serious and/or Most Frequently Observed Adverse Reactions

This list presents the most serious[b] and/or most frequently observed[a] adverse reactions during treatment with somatropin:

- [b]Sudden death in pediatric patients with Prader-Willi syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*
- [b]Intracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*
- [a,b]Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus *[see Warnings and Precautions (5.4)]*
- [b]Intracranial hypertension *[see Warnings and Precautions (5.5)]*
- [b]Significant diabetic retinopathy *[see Contraindications (4.4)]*
- [b]Slipped capital femoral epiphysis in Children *[see Warnings and Precautions (5.8)]*
- [b]Progression of preexisting scoliosis in Children*[see Warnings and Precautions (5.9)]*
- [a]Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias *[see Warnings and Precautions (5.6)]*
- [a]Unmasking of latent central hypothyroidism *[see Warnings and Precautions (5.7)]*
- [a]Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) *[see Warnings and Precautions (5.11)]*

6.2 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatropin formulation, and may not reflect the adverse reaction rates observed in practice.

Clinical Trials in Pediatric GHD Patients

As with all protein drugs, a small percentage of patients may develop antibodies to the protein. GH antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In a very small number of patients, when binding capacity was greater than 2 mg/L, interference with the growth response was observed. In clinical trials, patients receiving Norditropin for up to 12 months were tested for induction of antibodies, and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Amongst these patients, 165 had previously been treated with other somatropin formulations, and 193 were previously untreated naive patients.

Clinical Trials in Children with Noonan Syndrome

Norditropin was studied in a two-year prospective, randomized, parallel dose group trial in 21 children, 3-14 years old, with Noonan syndrome. Doses were 0.033 and 0.066 mg/kg/day. After the initial two-year randomized trial, children continued Norditropin treatment until final height was achieved; randomized dose groups were not maintained. Final height and adverse event data were later collected retrospectively from 18 children; total follow-up was 11 years. An additional 6 children were not randomized, but followed the protocol and are included in this assessment of adverse events.

Based on the mean dose per treatment group, no significant difference in the incidence of adverse events was seen between the two groups. The most frequent adverse events were the common infections of childhood, including upper respiratory infection, gastroenteritis, ear infection, and influenza. Cardiac disorders was the system organ class with the second most adverse events reported. However, congenital heart disease is an inherent component of Noonan syndrome, and there was no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography) during this study. Children who had baseline cardiac disease judged to be significant enough to potentially affect growth were excluded from the study; therefore the safety of Norditropin in children with Noonan syndrome and significant cardiac disease is

not known. Among children who received 0.033 mg/kg/day, there was one adverse event of scoliosis; among children who received 0.066 mg/kg/day, there were four adverse events of scoliosis. Mean serum IGF-I standard deviation score (SDS) levels did not exceed +1 in response to somatropin treatment. The mean serum IGF-I level was low at baseline and normalized during treatment.

Clinical Trials in Adult GHD Patients

Adverse events with an incidence of ≥5% occurring in patients with AO GHD during the 6 month placebo-controlled portion of the largest of the six adult GHD Norditropin trials are presented in Table 1. Peripheral edema, other types of edema, arthralgia, myalgia, and paraesthesia were common in the Norditropin-treated patients, and reported much more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. In general, these adverse events were mild and transient in nature. During the placebo-controlled portion of this study, approximately 5% of patients without preexisting diabetes mellitus treated with Norditropin were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group, consistent with the known hyperglycemic effects of somatropin. Anti-GH antibodies were not detected.

Of note, the doses of Norditropin employed during this study (completed in the mid 1990s) were substantially larger than those currently recommended by the Growth Hormone Research Society, and, more than likely, resulted in a greater than expected incidence of fluid retention- and glucose intolerance-related adverse events. A similar incidence and pattern of adverse events were observed during the other three placebo-controlled AO GHD trials and during the two placebo-controlled CO GHD trials.

Table 1 – Adverse Reactions with ≥5% Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin During a Six Month Placebo-Controlled Clinical Trial

	Norditropin (N=53)		Placebo (N=52)	
Adverse Reactions	n	%	n	%
Peripheral Edema	22	42	4	8
Edema	13	25	0	0
Arthralgia	10	19	8	15
Leg Edema	8	15	2	4
Myalgia	8	15	4	8
Infection (non-viral)	7	13	4	8
Paraesthesia	6	11	3	6
Skeletal Pain	6	11	1	2
Headache	5	9	3	6
Bronchitis	5	9	0	0
Flu-like symptoms	4	8	2	4
Hypertension	4	8	1	2
Gastroenteritis	4	8	4	8
Other Non-Classifiable Disorders (excludes accidental injury)	4	8	3	6
Increased sweating	4	8	1	2
Glucose tolerance abnormal	3	6	1	2
Laryngitis	3	6	3	6

The adverse event pattern observed during the open label phase of the study was similar to the one presented above.

6.3 Post-Marketing Surveillance

Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in Sections 6.1 and 6.2 in children and adults.

Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of

leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy *per se* was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established *[see Contraindications (4.3) and Warnings and Precautions (5.3)]*.
The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children).

7 DRUG INTERACTIONS

7.1 Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1 (11ßHSD-1)

Somatropin inhibits 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11βHSD-1 enzyme.

7.2 Glucocorticoid Replacement

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.

7.3 Cytochrome P450-Metabolized Drugs

Limited published data indicate that somatropin treatment increases cytochrome P450 (CYP450)-mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes. However, formal drug interaction studies have not been conducted.

7.4 Oral Estrogen

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal *[see Dosage and Administration (2.2)]*.

7.5 Insulin and/or Oral Hypoglycemic Agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated *[see Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. 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. Norditropin should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Norditropin 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.

8.5 Geriatric Use

The safety and effectiveness of Norditropin in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients *[see Dosage and Administration (2.2)]*.

10 OVERDOSAGE

Short-Term
Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention.

Long-Term
Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone.

See Dosage and Administration (2).

11 DESCRIPTION

Norditropin is a registered trademark of Novo Nordisk Health Care AG 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 cartridges are supplied as sterile solutions for subcutaneous injection in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL.

Each **Norditropin Cartridge** contains the following (see Table 2):

Table 2

Component	**5 mg/1.5 mL**	**10 mg/1.5 mL**	**15 mg/1.5 mL**
Somatropin	5 mg	10 mg	15 mg
Histidine	1 mg	1 mg	1.7 mg
Poloxamer 188	4.5 mg	4.5 mg	4.5 mg
Phenol	4.5 mg	4.5 mg	4.5 mg
Mannitol	60 mg	60 mg	58 mg
HCl/NaOH	as needed	as needed	as needed
Water for Injection	up to 1.5 mL	up to 1.5 mL	up to 1.5 mL

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Somatropin (as well as endogenous GH) binds to a dimeric GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by IGF-I produced in the liver and also locally (e.g., skeletal growth, protein synthesis), while others are primarily a consequence of the direct effects of somatropin (e.g., lipolysis) *[see Clinical Pharmacology (12.2)]*.

12.2 Pharmacodynamics

Tissue Growth

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

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 (IGFs). The somatomedins, among them IGF-I, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-I levels are low in the serum of hypopituitary dwarfs and hypophysectomized humans or animals, and increase after treatment with somatropin.

Cell Growth

It has been shown that the total number of skeletal muscle cells is markedly decreased in children with short stature lacking endogenous GH 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

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. Administration of human growth hormone to normal adults and patients with growth hormone deficiency results in increases in mean serum fasting and postprandial insulin levels, although mean values remain in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A_{1C} levels remain in the normal range.

Lipid Metabolism

Somatropin stimulates intracellular lipolysis, and administration of somatropin leads to an increase in plasma free fatty acids and triglycerides. Untreated GHD is associated with increased body fat stores, including increased abdominal visceral and subcutaneous adipose tissue. Treatment of growth hormone deficient patients with somatropin results in a general reduction of fat stores, and decreased serum levels of low density lipoprotein (LDL) cholesterol.

Mineral Metabolism

Administration of somatropin results in an increase in 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 children with GHD 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 sulfate and collagen, and increases the urinary excretion of hydroxyproline.

12.3 Pharmacokinetics

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

In a study conducted in 18 GHD adult patients, where a SC dose of 0.024 mg/kg or 3 IU/m^2 was given in the thigh, mean (±SD) C_{max} values of 13.8 (±5.8) and 17.1 (±10.0) ng/mL were observed 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.

The aqueous Norditropin cartridge formulation is bioequivalent to the lyophilized Norditropin vial formulation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin.

14 CLINICAL STUDIES

14.1 Short Stature in Children with Noonan Syndrome

A prospective, open label, randomized, parallel group trial with 21 children was conducted for 2 years to evaluate the efficacy and safety of Norditropin treatment for short stature in children with Noonan

syndrome. An additional 6 children were not randomized, but did follow the protocol. After the initial two-year trial, children continued on Norditropin until final height. Retrospective final height and adverse event data were collected from 18 of the 21 subjects who were originally enrolled in the trial and the 6 who had followed the protocol without randomization. Historical reference materials of height velocity and adult height analyses of Noonan patients served as the controls.

The twenty-four (24) (12 female, 12 male) children 3 – 14 years of age received either 0.033 mg/kg/day or 0.066 mg/kg/day of Norditropin subcutaneously which, after the first 2 years, was adjusted based on growth response.

In addition to a diagnosis of Noonan syndrome, key inclusion criteria included bone age determination showing no significant acceleration, prepubertal status, height SDS <-2, and HV SDS <1 during the 12 months pre-treatment. Exclusion criteria were previous or ongoing treatment with growth hormone, anabolic steroids or corticosteroids, congenital heart disease or other serious disease perceived to possibly have major impact on growth, FPG >6.7 mmol/L (>120 mg/dL), or growth hormone deficiency (peak GH levels <10 ng/mL).

Patients obtained a final height (FH) gain from baseline of 1.5 and 1.6 SDS estimated according to the national and the Noonan reference, respectively. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at 18 years of age, while a height gain of 1.6 SDS (Noonan) corresponds to a mean height gain of 11.5 cm in boys and 11.0 cm in girls at 18 years of age.

A comparison of HV between the two treatment groups during the first two years of treatment for the randomized subjects was 10.1 and 7.6 cm/year with 0.066 mg/kg/day versus 8.55 and 6.7 cm/year with 0.033 mg/kg/day, for Year 1 and Year 2, respectively.

Age at start of treatment was a factor for change in height SDS (national reference). The younger the age at start of treatment, the larger the change in height SDS.

Examination of gender subgroups did not identify differences in response to Norditropin.

Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, prior to initiating Norditropin for a patient with Noonan syndrome, establish that the patient does have short stature.

14.2 Adult Growth Hormone Deficiency (GHD)

A total of six randomized, double-blind, placebo-controlled studies were performed. Two representative studies, one in adult onset (AO) GHD patients and a second in childhood onset (CO) GHD patients, are described below.

Study 1

A single center, randomized, double-blind, placebo-controlled, parallel-group, six month clinical trial was conducted in 31 adults with AO GHD comparing the effects of Norditropin® [somatropin (rDNA origin) for injection] and placebo on body composition. Patients in the active treatment arm were treated with Norditropin 0.017 mg/kg/day (not to exceed 1.33 mg/day). The changes from baseline in lean body mass (LBM) and percent total body fat (TBF) were measured by total body potassium (TBP) after 6 months.

Treatment with Norditropin produced a significant (p=0.0028) increase from baseline in LBM compared to placebo (Table 3).

Table 3 – Lean Body Mass (kg) by TBP

	Norditropin (n=15)	Placebo (n=16)
Baseline (mean)	50.27	51.72
Change from baseline at 6 months (mean)	1.12	-0.63
Treatment difference (mean) 95% confidence interval p-value	1.74 (0.65, 2.83) p=0.0028	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0004) in the Norditropin-treated group compared to the placebo group (Table 4).

Table 4 – Total Body Fat (%) by TBP

	Norditropin	Placebo

	(n=15)	(n=16)
Baseline (mean)	44.74	42.26
Change from baseline at 6 months (mean)	-2.83	1.92
Treatment difference (mean) 95% confidence interval p-value	-4.74 (-7.18, -2.30) p=0.0004	

Fifteen (48.4%) of the 31 randomized patients were male. The adjusted mean treatment differences on the increase in LBM and decrease in percent TBF from baseline were larger in males compared to females.

Norditropin also significantly increased serum osteocalcin (a marker of osteoblastic activity).

Study 2

A single center, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, six month clinical trial was conducted in 49 men with CO GHD comparing the effects of Norditropin and placebo on body composition. Patients were randomized to placebo or one of three active treatment groups (0.008, 0.016, and 0.024 mg/kg/day). Thirty three percent of the total dose to which each patient was randomized was administered during weeks 1-4, 67% during weeks 5-8, and 100% for the remainder of the study. The changes from baseline in LBM and percent TBF were measured by TBP after 6 months.

Treatment with Norditropin produced a significant (p=0.0079) increase from baseline in LBM compared to placebo (pooled data) (Table 5).

Table 5 – Lean Body Mass (kg) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	48.18	48.90
Change from baseline at 6 months (mean)	2.06	0.70
Treatment difference (mean) 95% confidence interval p-value	1.40 (0.39, 2.41) p=0.0079	

Analysis of the treatment difference on the change from baseline in percent TBF revealed a significant decrease (p=0.0048) in the Norditropin-treated groups (pooled data) compared to the placebo group (Table 6).

Table 6 – Total Body Fat (%) by TBP

	Norditropin (n=36)	Placebo (n=13)
Baseline (mean)	34.55	34.07
Change from baseline at 6 months (mean)	-6.00	-1.78
Treatment difference (mean) 95% confidence interval p-value	-4.24 (-7.11, -1.37) p=0.0048	

Norditropin also significantly reduced intraabdominal, extraperitoneal and total abdominal fat volume, waist/hip ratio and LDL cholesterol, and significantly increased serum osteocalcin.

Forty four men were enrolled in an open label follow up study and treated with Norditropin for as long as 30 additional months. During this period, the reduction in waist/hip ratio achieved during the initial six months of treatment was maintained.

16 HOW SUPPLIED/STORAGE AND HANDLING

Norditropin Cartridges *[somatropin (rDNA origin) injection] 5 mg/1.5 mL and 15 mg/1.5 mL:*

Norditropin is individually cartoned in 5 mg/1.5 mL or 15 mg/1.5 mL cartridges which must be administered using the corresponding color-coded NordiPen delivery system.

- Norditropin Cartridges 5 mg/1.5 mL (orange) NDC 0169-7768-11
- Norditropin Cartridges 15 mg/1.5 mL (green) NDC 0169-7770-11

Non-injected/unused Norditropin cartridges must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

5 mg/1.5 mL (orange) cartridges:
After a Norditropin cartridge (5 mg/1.5 mL) has been inserted into its NordiPen delivery system (NordiPen 5), it may be **EITHER** stored in the pen in the refrigerator (2-8ºC/36-46ºF) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25ºC (77ºF). Discard unused portion.

15 mg/1.5 mL (green) cartridges:
After a Norditropin cartridge (15 mg/1.5 mL) has been inserted into its NordiPen delivery system (NordiPen 15), it must be stored in the pen in the refrigerator (2-8ºC/36-46ºF) and used within 4 weeks. Discard unused portion after 4 weeks.

Norditropin NordiFlex prefilled pens *[somatropin (rDNA origin) injection] 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL:*

Norditropin NordiFlex is individually cartoned in 5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL prefilled pens.

- Norditropin NordiFlex 5 mg/1.5 mL (orange) NDC 0169-7704-11
- Norditropin NordiFlex 10 mg/1.5 mL (blue) NDC 0169-7705-11
- Norditropin NordiFlex 15 mg/1.5 mL (green) NDC 0169-7708-11

Non-injected/unused Norditropin NordiFlex prefilled pens must be stored at 2-8°C/36-46°F (refrigerator). Do not freeze. Avoid direct light.

5 mg/1.5 mL (orange) and 10 mg/1.5 mL (blue) prefilled pens:
After the initial injection, a Norditropin NordiFlex (5 mg/1.5 mL or 10 mg/1.5 mL) prefilled pen may be **EITHER** stored in the refrigerator (2-8ºC/36-46ºF) and used within 4 weeks **OR** stored for up to 3 weeks at not more than 25ºC (77ºF). Discard unused portion.

15 mg/1.5 mL (green) prefilled pens:
After the initial injection, a Norditropin NordiFlex 15mg/1.5 mL prefilled pen must be stored in the refrigerator (2-8ºC/36-46ºF) and used within 4 weeks. Discard unused portion after 4 weeks.

Table 7 – Storage Options

Norditropin Product Formulation	**Before Use**	**In-use (After 1st injection)**	
	Storage requirement	**Storage Option 1 (Refrigeration)**	**Storage Option 2 (Room temperature)**
5 mg	2-8 ºC/ 36-46 ºF Until exp date	2-8 ºC/36-46 ºF 4 weeks	Up to 25ºC/77ºF 3 weeks
10 mg		2-8 ºC/36-46 ºF 4 weeks	Up to 25ºC/77ºF 3 weeks
15 mg		2-8 ºC/36-46 ºF 4 weeks	Does Not Apply

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Patients being treated with Norditropin Cartridges or Norditropin NordiFlex prefilled pens (and/or their parents) should be informed about the potential risks and benefits associated with somatropin treatment *[in particular, see Adverse Reactions (6.1) for a listing of the most serious and/or most frequently observed adverse reactions associated with somatropin treatment in children and adults].* This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer Norditropin Cartridges or Norditropin NordiFlex prefilled pens should receive appropriate training and instruction on proper use from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in

the importance of proper disposal, and cautioned against any reuse of needles. This information is intended to aid in the safe and effective administration of the medication.

If patients are prescribed Norditropin Cartridges (to be inserted into color-coded NordiPen delivery systems), physicians should instruct patients to read the NordiPen INSTRUCTION booklet provided with the NordiPen delivery systems.

If patients are prescribed Norditropin NordiFlex, physicians should instruct patients to read the PATIENT INFORMATION and INSTRUCTIONS FOR USE leaflets provided with the Norditropin NordiFlex prefilled pens.

Version 8

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