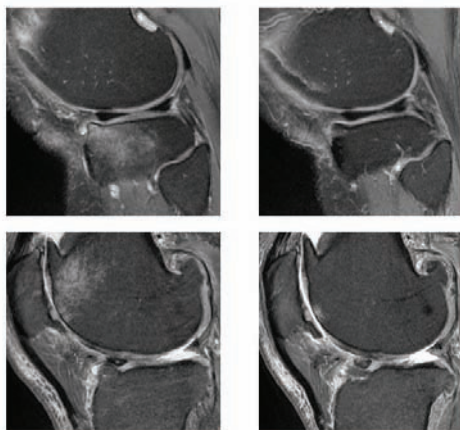


## BML Examples



MRI knee scans from two patients taken before (left) and 6 months after treatment with zoledronic acid show shrinkage of bone marrow lesions.

COURTESY, DR. GRAEME JONES

476 to 14 mm<sup>2</sup>

528 to 26 mm<sup>2</sup>

# Zoledronic Acid Shrinks Bone Marrow Lesions

BY MITCHEL L. ZOLER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

LONDON – A single 5-mg infusion of zoledronic acid, a bisphosphonate, in patients with knee osteoarthritis led to significant pain reduction and shrinkage of bone marrow lesions in a randomized,

placebo-controlled study with 59 patients.

The zoledronic acid treatment led to an average 15-point drop in pain (on a visual analog scale of 0-100) beyond what occurred in the placebo group, and the active treatment was also linked with an average 170-mm<sup>2</sup> reduction in maximal bone marrow lesion (BML) area beyond the placebo-treated patients, which was a

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

### Rx Only

#### BRIEF SUMMARY: Please consult package insert for full prescribing information

**INDICATIONS AND USAGE: Pediatric Patients:** Norditropin® is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH). Norditropin® is indicated for the treatment of children with short stature associated with Noonan syndrome. Norditropin® is indicated for the treatment of children with short stature associated with Turner syndrome. Norditropin® is indicated for the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2–4 years. **Adult Patients:** Norditropin® 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. Patients who were treated with somatropin for GHD in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for GHD adults. According to current standards, confirmation of the diagnosis of adult GHD in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

**CONTRAINDICATIONS: 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]. **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]. There have been reports of sudden death when somatropin was used in such patients [see Warnings and Precautions]. Norditropin® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome. **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. **Diabetic Retinopathy:** Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy. **Closed Epiphyses:** Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses. **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.

**WARNINGS AND PRECAUTIONS: 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]. 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. **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]. Norditropin® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome. **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. **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, 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.

**Intracranial Hypertension:** 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 may be at increased risk for the development of IH. **Fluid Retention:** Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent. **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. **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. **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. **Otitis Media and Cardiovascular Disorders in Turner Syndrome:** Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions. **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* before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults. **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. 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. **Laboratory Tests:** Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 may increase after somatropin therapy. **Pancreatitis:** Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain.

**ADVERSE REACTIONS: Most Serious and/or Most Frequently Observed Adverse Reactions:** This list presents the most serious<sup>a</sup> and/or most frequently observed<sup>b</sup> adverse reactions during treatment with somatropin: <sup>a</sup>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 and Warnings and Precautions]; <sup>b</sup>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 and Warnings and Precautions]; <sup>c</sup>Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus [see Warnings and Precautions]; <sup>d</sup>Intracranial hypertension [see Warnings and Precautions]; <sup>e</sup>Significant diabetic retinopathy [see Contraindications]; <sup>f</sup>Slipped capital femoral epiphysis in pediatric patients [see Warnings and Precautions]; <sup>g</sup>Progression of preexisting scoliosis in pediatric patients [see Warnings and Precautions]; <sup>h</sup>Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias [see Warnings and Precautions]; <sup>i</sup>Unmasking of latent central hypothyroidism [see Warnings and Precautions]; <sup>j</sup>Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) [see Warnings and Precautions]; Pancreatitis [see Warnings and Precautions]. **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*

**Major Finding:** A 5-mg infusion of zoledronic acid given to 31 patients with knee OA and associated bone marrow lesions reduced pain by 15 points more on a visual analog scale than did placebo, and reduced maximal bone marrow lesion area by 170 mm<sup>2</sup> after 6 months, compared with patients who received a placebo infusion.

**Data Source:** A single-center, randomized study with 31

patients who received a zoledronic acid infusion and 28 patients who received a placebo infusion.

**Disclosures:** The study was funded by Novartis, which markets zoledronic acid. Dr. Jones said that he has received speaker fees, travel sponsorship, and research support from Novartis and several other drug companies. Dr. Conaghan said that they had no disclosures.

cut in BML area of about 37%, compared with the starting BML area, Dr. Graeme Jones said at the meeting. Dr. Jones visualizes BMLs using MRI knee scans.

"This is the first intervention shown to work on BMLs" in patients with os-

teoarthritis (OA), said Dr. Jones, professor of rheumatology and epidemiology and head of the musculoskeletal unit at the Menzies Research Institute Tasmania, Hobart, Australia.

"This is exciting for treating existing

OA. It is one of the first positive structure modification trials," commented Dr. Philip Conaghan, professor and chairman of musculoskeletal medicine at the University of Leeds (England).

"Results from several studies have

linked BMLs with pain and cartilage damage in OA patients. The larger the BML, the faster the cartilage loss and the worse the pain," Dr. Jones said in an interview. Based on studies his group has done, about 20% of BMLs that are associated with knee OA spontaneously enlarge over the course of 3 years, another 20% shrink in size, and about 60% remain the same, he said. Their earlier research findings also showed that BMLs are independently linked with fast progression of OA and the need for knee replacement. "If you reduce BMLs, it should produce good outcomes in patients," he said.

"The next step is to show that treatment with zoledronic acid not only reduces BML size but also slows cartilage loss. Sixty patients followed for 12 months were not enough to assess cartilage. We will need about 400 patients followed for 2 years," Dr. Jones added.

Despite not yet having information on cartilage effects, he said that his results so far have convinced him that treatment with zoledronic acid is reasonable for patients with painful knee OA and BMLs.

"I use it off label. Patients need to know it's off label, and they [therefore] must be willing to pay for it, but I use it. It's been shown to work, and nothing else works. Zoledronic acid [Reclast] is available, we know about its safety, and it's been used for a long time to treat osteoporosis and cancers. If you have OA patients with BMLs, this is something to actively consider for them. Patients with OA have very limited treatment options. This can make a large difference in their pain, and it has long-lasting benefit so it can be given once a year," Dr. Jones said.

The benefits of zoledronic acid that were seen in his study might be a class effect that may be replicated by treatment with another bisphosphonate, but zoledronic acid is more potent than oral bisphosphonates and hence the drug's beneficial effect on pain and BML shrinkage may exceed the effect that other bisphosphonates might have, he said.

The pain benefit appeared to start wearing off about a year after the zoledronic acid injection. Dr. Jones said that he has a small number of patients whom he has infused a second time, which produced a second round of pain reduction.

The 59 patients who were enrolled in the study had an average age of about 60 years, with an average knee pain score of about 52 on the visual analog scale; all patients had BMLs as seen on MRI scans of their affected knees. In all, 31 patients received a 5-mg infusion of zoledronic acid and 28 patients received a placebo infusion. All patients also continued their conventional pain medication regimens.

The Food and Drug Administration has approved zoledronic acid under a number of brand names to prevent or treat osteoporosis in postmenopausal women or patients who are at risk for osteoporosis because they are taking or have taken corticosteroid therapy; to manage Paget's disease; and to prevent chemotherapy-induced bone fractures or fractures in patients with multiple myeloma or cancer that has metastasized to the bones from other locations. ■

**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 were 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 [see *Warnings and Precautions*]. 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 Children with Turner Syndrome:** In two clinical studies wherein children with Turner syndrome were treated until final height with various doses of Norditropin®, the most frequently reported adverse events were common childhood diseases including influenza-like illness, otitis media, upper respiratory tract infection, otitis externa, gastroenteritis and eczema. Otitis media adverse events in Study 1 were most frequent in the highest dose groups (86.4% in the 0.045–0.067–0.089 mg/kg/day group vs. 78.3% in the 0.045–0.067 mg/kg/day group vs. 69.6% in the 0.045 mg/kg/day group) suggesting a possible dose-response relationship. Of note, approximately 40–50% of these otitis media adverse events were designated as "serious" [see *Warnings and Precautions*]. No patients in either study developed clearcut overt diabetes mellitus; however, in Study 1, impaired fasting glucose at Month 48 was more frequent in patients in the 0.045–0.067 mg/kg/day group (n=4/18) compared with the 0.045 mg/kg/day group (n=1/20). Transient episodes of fasting blood sugars between 100 and 126 mg/dL, and, on occasion, exceeding 126 mg/dL also occurred more often with larger doses of Norditropin® in both studies [see *Warnings and Precautions* and *Adverse Reactions*]. Three patients withdrew from the 2 high dose groups in Study 1 because of concern about excessive growth of hands or feet. In addition, in Study 1, exacerbation of preexisting scoliosis was designated a serious adverse reaction in two patients in the 0.045 mg/kg/day group [see *Warnings and Precautions*]. **Clinical Trials in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2–4 Years: Study 1 (Long-Term):** In a multi-center, randomized, double-blind study, 53 non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) to final height for up to 13 years (mean duration of treatment 7.9 and 9.5 years for girls and boys, respectively). The most frequently reported adverse events were common childhood diseases including influenza-like illness, upper respiratory tract infection, bronchitis, gastroenteritis, abdominal pain, otitis media, pharyngitis, arthralgia, and headache. Adverse events possibly/probably related to Norditropin® were otitis media, arthralgia, headaches (no confirmed diagnoses of benign intracranial hypertension), gynecomastia, and increased sweating. One child treated with 0.067 mg/kg/day for 4 years was reported with disproportionate growth of the lower jaw, and another child treated with 0.067 mg/kg/day developed a melanocytic nevus [see *Warnings and Precautions*]. There were no clear cut reports of exacerbation of preexisting scoliosis or slipped capital femoral epiphysis. No apparent differences between the treatment groups were observed. In addition, the timing of puberty was age-appropriate in boys and girls in both treatment groups. Therefore, it can be concluded that no novel adverse events potentially related to treatment with Norditropin® were reported in long-term Study 1. **Study 2 (Short-Term):** In a multi-center, randomized, double-blind, parallel-group study, 98 Japanese non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) for 2 years or were untreated for 1 year. The most frequently reported adverse events were common childhood diseases almost identical to those reported above for Study 1. Adverse events possibly/probably related to Norditropin® were otitis media, arthralgia and impaired glucose tolerance. No apparent differences between the treatment groups were observed. However, arthralgia and transiently impaired glucose tolerance were only reported in the 0.067 mg/kg/day treatment group. Therefore, it can also be concluded that no novel adverse events potentially related to treatment with rhGH were reported in short-term Study 2. As with all protein drugs, some patients may develop antibodies to the protein. Eighteen of the 76 children (~24%) treated with Norditropin® developed anti-rhGH antibodies. However, these antibodies did not appear to be neutralizing in that the change from baseline in height SDS at Year 2 was similar in antibody positive and antibody negative children by treatment group. In both Study 1 and Study 2, there were no clear cut cases of new onset diabetes mellitus, no children treated for hyperglycemia, and no adverse event withdrawals due to abnormalities in glucose tolerance. In Study 2, after treatment with either dose of Norditropin® for 2 years, there were no children with consecutive fasting blood glucose levels between 100 and 126 mg/dL, or with fasting blood glucose levels > 126 mg/dL. Furthermore, mean hemoglobin A<sub>1c</sub> levels tended to decrease during long-term treatment in Study 1, and remained normal in Study 2. However, in Study 1, 4 children treated with 0.067 mg/kg/day of Norditropin® and 2 children treated with 0.033 mg/kg/day of Norditropin® shifted from normal fasting blood glucose levels at baseline to increased levels after 1 year of treatment (100 to 126 mg/dL or > 126 mg/dL). In addition, small increases in mean fasting blood glucose and insulin levels (within the normal reference range) after 1 and 2 years of Norditropin® treatment appeared to be dose-dependent [see *Warnings and Precautions* and *Adverse Reactions*]. In both Study 1 and Study 2, there was no acceleration of bone maturation. A dose-dependent increase in mean serum IGF-I SDS levels within the reference

range (but including a substantial number of children with serum IGF-1 SDS > +2) was observed after both long-term (Study 1) and short-term (Study 2) Norditropin® 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 [see *Warnings and Precautions* and *Adverse Reactions*]. 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**

Adverse Reactions	Norditropin® (N=53)		Placebo (N=52)	
	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. **Post-Marketing Experience** 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 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 and Warnings and Precautions*]. Pancreatitis: cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain [see *Warnings and Precautions*]. The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children).

**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.

**More detailed information is available upon request.**

For information contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, USA, 1-888-NOVO-444 (1-888-668-6444)

Date of Issue: December 7, 2010

**Version: 13**

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

*Novo Nordisk®* is a registered trademark of Novo Nordisk A/S. Norditropin®, FlexPro®, NordiPen®, and Norditropin NordiFlex® are registered trademarks of Novo Nordisk Health Care AG.

© 2011 Novo Nordisk 143532 Jan 2011



**norditropin®**  
somatropin (rDNA origin) injection