Estrogen Therapy

Protecting the aging woman's brain

By **Margie Patlak***

Estrogen is once again earning accolades as the wonder hormone with potential for preventing aging diseases in women. These days, investigators are touting its ability to protect the brain from the ravages of Alzheimer's disease, Parkinson's disease, and stroke, and to aid recovery from brain injuries.

"If you talk among endocrinologists, there's no doubt that everyone believes estrogen is largely neuroprotective," neuroscientist Christian Pike, Ph.D., professor of gerontology at the University of Southern California, in Los Angeles, told ***Endocrine News.*** "The evidence for this in animals is clear," added Sarah Berga, M.D., professor of obstetrics and gynecology, reproductive endocrinology and infertility, and psychiatry at Emory University in Atlanta, Ga. Yet both noted that still under debate is whether estrogen is *clinically* neuroprotective. Clinical research is limited and often conflicting, and the hormone's reputation has been tarnished by previous disappointments with hormone therapy.

Now, however, researchers are paying close attention to the complexity of the hormone's effects, including how they vary with type of estrogen and dose, what happens when it is combined with a progestin, and its impact when taken early in menopause or much later. Researchers are also trying to develop more precisely targeted selective estrogen receptor modulators (SERMs) that can bring the benefits of estrogen while limiting its risks—which include promotion of breast and endometrial cancers. With investigative efforts on so many fronts, effective and safe hormonal therapies that help prevent or treat brain disorders in women will hopefully emerge.

y, Revisited

Panacea for the Brain?

Although it seems unlikely that one hormone could be a panacea for so many neuronal ailments, it's not far-fetched with estrogen, given its versatility and key role in basic functions such as cell regeneration, longevity, and tissue repair. Its neurocognitive role is becoming increasingly clear, with abundant animal research revealing that in females, estrogen consistently protects the brain from a wide variety of insults, including sudden drops in oxygen and glucose caused by stroke, as well as damage to neurons triggered by chemicals or inflammation. In vitro and in vivo studies also find that estrogen reduces oxidative stress and promotes the formation of new neurons and related synapses, enabling brain remodeling and repair. Estrogen also reins in levels of beta amyloid and tau phosphorylation, both associated with Alzheimer's disease, and boosts dopamine activity, which is lacking in Parkinson's disease.

… estrogen consistently protects the brain from a wide variety of insults …

Remarkably, researchers recently uncovered that at least some estrogen (and its metabolites, which seem to be driving all these neurological feats) can be made right on the spot, in the brain. This discovery has led some researchers to suggest that brain levels of estrogen are more important in determining neuroprotection than serum levels, although research on this is still scant. Studies show that in female animals, the heightened pressure caused by induced brain injury prompts astrocyte brain cells to produce aromatase, which converts androgen precursors to estrogen. Brain injury also sensitizes brain cells to estrogen's effects by up-regulating the production of estrogen receptors. Clearly, serum levels of estrogen play a role in neuroprotection as well, because when normal estrogen levels are restored in ovariectomized animals, their neurons sprout more synapses and they are better protected from neuronal harm in stroke models. In other female rodent models of stroke, estrogen appears to play a role in determining the degree of neuronal damage, with more injuries occurring during the portion of the estrous cycle when serum levels of estrogen are low.

Epidemiological studies have produced further evidence that estrogen buffers the brain. Both brain and plasma levels of estrogen are lower in female Alzheimer's disease patients aged 80 years and older than in age-matched controls, one study found. Other research has indicated that the longer women have circulating levels of estrogen dictated by menstruation or hormonal therapy, the less likely they are to develop a neurodegenerative disease.

Estrogen therapy apparently helps women with early, but not later, stages of Parkinson's disease. In human brain-imaging studies, when postmenopausal women receive estradiol, their regional brain activity increases.

Rethinking Hormone Therapy

Presumably, androgens in the male brain have similar neuroprotective effects; researchers are just starting to explore this. In the meantime, the possibility of extending estrogen's neuronal benefits in women by postmenopausal hormonal therapy is gaining currency, despite the Women's Health Initiative (WHI). This large, prospective trial of hormonal therapy for postmenopausal women found that estrogen given in combination with progestin *increased* the risk of dementia and stroke. A key suspected confounder is that most women in the trial started receiving this therapy many years after menopause, so their brain tissues may no longer have responded to estrogen and/or they may have already developed vascular disease making them prone to stroke, experts point out. Women who still had menopausal symptoms at the time they received hormonal therapy tended to reap more benefits from it, the WHI and other studies show.

Experts also point out that many women in the WHI and other trials received a mixture of estrogens. Premarin comprises mainly conjugated estrogens isolated from mares' urine, including sodium estrone sulfate, sodium equilin sulfate, and the conjugates 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin, rather than only 17β-estradiol. The last compound is the endogenous estrogen with the most activity in the brain, according to neurochemist and professor of pharmacy Therese Di Paolo, Ph.D., of Laval University in Quebec, Canada. The Premarin most of these women received is known for causing blood clots. Many took estrogen plus progestin, the latter of which decreases blood flow to the brain, some animal studies have shown. Additionally, in animals progestin is not known to be neuroprotective, unlike endogenous progesterone. Some studies suggest the combination of estrogen and progestin given continuously benefits the brain less than progesterone given cyclically—to mimic what is seen in menstruating women—or estrogen given alone. These two classes of hormones can act synergistically or antagonistically in animal models of Alzheimer's, Parkinson's, and stroke, depending on the dose, type, and timing.

"When we thought that all women were the same and all estrogens and progesterones were the same, we were barking up the wrong tree," said Dr. Berga, a WHI investigator. She added that figuring out the right dose of estrogen is critical, given the U-shaped curve that typifies responses to hormones. She added that studies show that the estrogen patch, which delivers a smaller amount of estrogen more akin to natural circulating levels, is not linked to increased stroke risk. "You have to find the sweet spot. If I give you too much or too little insulin, for example, I can kill you. We haven't paid enough attention to how much estrogen we should be giving," she explained.

Avoiding the increased risk of breast and other cancers is also critical. Researchers are finding that the same biochemical pathways that estrogen stimulates to further brain repair and plasticity are also known to have involvement in various cancers, including breast cancer. "Some of the activities you want are those you don't want when it comes to cancer," noted Dr. Di Paolo.

A Kinder, Gentler SERM

The risk of cancer might be limited by using compounds that do not operate in the body sites most likely to develop tumors fueled by estrogen, such as the breast and endometrium. Researchers continue to devise and test more SERMs with scopes of action narrow enough that hormonal therapy's benefits are reaped without many of the risks. Other investigators are trying to develop synthetic versions of estrogen that act only in the brain. As for those SERMs already on the market, clinical findings are conflicting as to whether they help prevent Alzheimer's disease and other cognitive deficits. The widely used tamoxifen can both block and stimulate the estrogen receptor, so it is possible that results might depend on dosing and whether estrogen is present, researchers say. A newer SERM, raloxifene, might not reach the brain in sufficient amounts. Rat studies suggest that only 1%–2% of the drug crosses the blood-brain barrier.

Some investigators are pursuing non-feminizing estrogen derivatives such as 17α-estradiol and estratriene derivatives, which are known to have potent neuroprotective effects but do not activate estrogen receptors in the reproductive tract. These compounds are naturally produced at high levels in brain tissue and don't decline following gonadectomy. Research on these compounds is still preliminary.

Impatient Patients

In the meantime, how should doctors advise perimenopausal or newly menopausal women who are considering estrogen therapy? Should physicians tell patients that the hormone might help protect their minds as well as relieve their hot flashes?

"We have to take into account the age of the person, her family and personal medical history, and the type of estrogen used," said Dr. Berga. "It's a much more complicated and nuanced discussion than yes or no. If you didn't tell her neuroprotection is a possibility, you probably wouldn't be doing an adequate job. If you told her in a dogmatic yes-or-no fashion, you also probably would not be doing a very good job."

Dr. Pike added, "My best guess, based on the animal data, is that there are probably benefits as long as women start taking it soon after menopause. I feel pretty good about that recommendation now, but I expect doctors may not feel comfortable recommending estrogen for all patients without more data."

As Dr. Berga pointed out, "The decision you make is always based on the best information that you can gather today. I don't tell women to go or not to go on estrogen, but rather tell them here's the data for and against, and you have to choose whether or not to go on hormonal therapy as well as continually revisit your choice, because it's a renewable decision that may change as more evidence files in." ■

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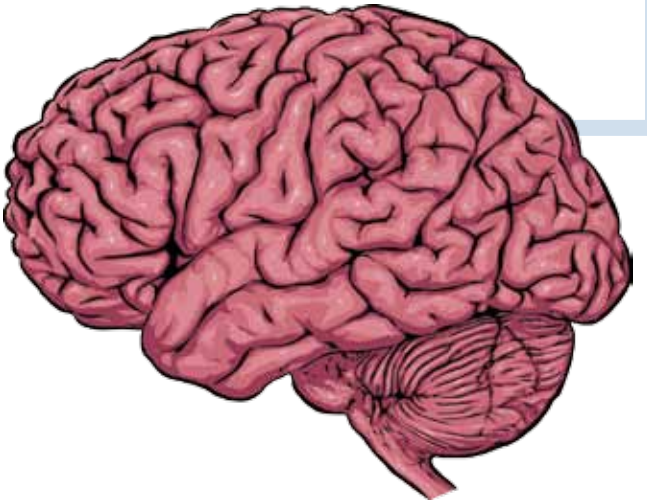
* Margie Patlak is a free-lance science writer, living in the Philadelphia area.



References:

* Rosario ER, Chang L, Head EH, Stanczyk FZ, Pike CJ. Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease, *Neurobiology of Aging*, 2011; 32:604–613.
* Carroll JC, Rosario ER, Villamagna A, Pike CJ. Continuous and cyclic progesterone differentially interact with estradiol in the regulation of Alzheimer-like pathology in female 3xtransgenic-Alzheimer's disease mice. *Endocrinology*, 2010;151:2713–2722.
* Cosimo Melcangi R, Garcia-Segura LM. Sex-specific therapeutic strategies based on neuroactive steroids: In search for innovative tools for neuroprotection. *Horm Behav*, 2010;57:2–11.
* Pike CJ, Carroll JC, Rosario ER, Barron AM. Protective actions of sex steroid hormones in Alzheimer's disease. *Front Neuroendocrinol*, 2009;30:239–258.
* Loucks TL, Berga SL. Does postmenopausal estrogen use confer neuroprotection? *Semin Reprod Med*, 2009;27:260–274.
* Morissette M, Al Sweidi S, Callier S, Di Paolo T. Estrogen and SERM neuroprotection in animal models of Parkinson's disease, *Mol Cell Endocrinol*, 2008;290:60–69.

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Please see important safety information and Brief Summary of the Prescribing Information on the adjacent pages.

References: 1. Fuchs GS, Mikkelsen S, Knudsen TK, Kappelgaard A-M. Ease of use and acceptability of a new pen device for the administration of growth hormone therapy in pediatric patients: an open-label, uncontrolled usability test. *Clin Ther.* 2009;31:2906-2914. **2.** Norditropin® FlexPro® [Instructions for Use]. Princeton, NJ: Novo Nordisk Inc; 2010. **3.** Data on file. PDS290 pen-injector for Norditropin® SimpleXx® container closure system: comparison to Norditropin NordiFlex®. Princeton, NJ: Novo Nordisk Inc; 2009.

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Indications and Usage

Norditropin® (somatropin [rDNA origin] injection) is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone, the treatment of children with short stature associated with Noonan syndrome or Turner syndrome, the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2-4 years, and for the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) who meet either of the following two criteria: 1. Adult Onset: 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 2. Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Important Safety Information

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure as increased mortality may occur.

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. There have been reports of sudden death when somatropin was used in such patients. Norditropin® is not indicated for the treatment of patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Somatropin should not be used or should be discontinued with any evidence 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. Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence. In childhood cancer survivors, an increased risk of a second neoplasm, particularly meningiomas in patients treated with radiation to the head for their first neoplasm, has been reported in patients treated with somatropin.

Somatropin should not be used in patients with active proliferative or severe non-proliferative diabetic retinopathy, for growth promotion in pediatric patients with closed epiphyses, or in patients with known hypersensitivity to somatropin or any of its excipients.

Somatropin may decrease insulin sensitivity particularly at higher doses in susceptible patients. Glucose levels should be monitored periodically, including close monitoring of patients with preexisting diabetes or glucose intolerance. Doses of anti-hyperglycemic drugs (insulin or oral agents) may require adjustment for patients with diabetes on somatropin therapy.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting, usually occurring within the first eight (8) weeks after initiation of somatropin therapy, has been reported in a small number of patients. In all reported cases, rapid resolution has occurred after therapy cessation or a reduction of dose. Funduscopic examination should be performed routinely before and during somatropin therapy. If papilledema is observed, somatropin treatment should be discontinued.

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

In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Periodic thyroid function tests are recommended and thyroid hormone replacement therapy should be initiated or adjusted as needed.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or with rapid growth. Onset of a limp or complaints of hip or knee pain in somatropin patients should be carefully evaluated. Rapid growth may also result in progression of preexisting scoliosis. Patients with a history of scoliosis or skeletal abnormalities, which may be present in untreated Noonan, Turner or Prader-Willi syndrome, should be monitored.

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. Somatropin may also increase the risk of IH in Turner patients. 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.

Congenital heart disease is an inherent component of Noonan syndrome. Though a clinical study in Noonan syndrome reported no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography), the safety of Norditropin® in children with Noonan syndrome and significant cardiac disease is not known.

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. 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.

Other somatropin-related adverse reactions include injection site reactions/rashes, lipoatrophy and headaches. Subcutaneous injection of somatropin at the same site repeatedly may result in tissue atrophy and can be avoided by rotating the injection site.

Somatropin inhibits 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD-1) in adipose/hepatic tissue, and may significantly impact the metabolism of cortisol and cortisone. 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, especially with cortisone acetate and prednisone, for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses.

Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine) as limited published data suggest somatropin may alter clearance of these compounds.

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal.

The safety and effectiveness of Norditropin® in patients age 65 years and older has not been evaluated in clinical studies. Elderly patients may be more sensitive to the actions of somatropin and may be more prone to develop adverse reactions.

Please see Brief Summary of Prescribing Information on the following pages.

norditropin®
somatropin (rDNA origin) injection

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-I 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[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 and Warnings and Precautions]*; [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 and Warnings and Precautions]*; [a,b]Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus *[see Warnings and Precautions]*; [b]Intracranial hypertension *[see Warnings and Precautions]*; [b]Significant diabetic retinopathy *[see Contraindications]*; [b]Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions]*; [b]Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions]*; [a]Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias *[see Warnings and Precautions]*; [a]Unmasking of latent central hypothyroidism *[see Warnings and Precautions]*; [a]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*

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 *[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_{1c} 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

	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. **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.

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somatropin (rDNA origin) injection