

## I. ALL CLAIMS: HEALTH CARE PROFESSIONALS

### 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.

Fundusoscopic 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.

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 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD-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.

## II. ALL CLAIMS: CONSUMERS

### Indications and Usage:

Norditropin® (somatropin [rDNA origin] injection) is used to treat: children who have growth failure because of low or no growth hormone; children who are short (in stature) and who have Noonan syndrome or Turner syndrome; children who are short (in stature) because they were born small (small for gestational age-SGA) and have not caught-up in growth by age 2 to 4 years; and adults who do not make enough growth hormone.

### Important Safety Information:

Do not use Norditropin® if: you have a critical illness caused by certain types of heart or stomach surgery, trauma or breathing (respiratory) problems; you are a child with Prader-Willi syndrome who is severely obese or has breathing problems including sleep apnea; you have cancer or other tumors; your healthcare provider tells you that you have certain types of eye problems caused by diabetes; you are a child with closed bone growth plates (epiphyses) or you are allergic to any of the ingredients in the medicine.

Before you take Norditropin®, tell your healthcare provider if you: have diabetes; had cancer or any tumor; have any other medical condition; are pregnant or plan to become pregnant; are breast-feeding or plan to breast-feed.

Norditropin® can cause serious side effects, including: high risk of death in people who have critical illnesses because of heart or stomach surgery, trauma or serious breathing (respiratory) problems; high risk of death in children with Prader-Willi syndrome who are severely obese or have breathing problems including sleep apnea; return of tumor or cancerous growths; high blood sugar (hyperglycemia); increase in pressure in the skull (intracranial hypertension); swollen hands and feet due to fluid retention; decrease in thyroid hormone levels; hip and knee pain or a limp in children (slipped capital femoral epiphysis); worsening of pre-existing curvature of the spine (scoliosis); middle ear infection, hearing problems or ear problems in patients with Turner syndrome.

Patients with Noonan syndrome and Turner syndrome should be closely monitored by their doctors as they are more likely to have congenital heart disease.

The most common side effects of Norditropin® include: headaches, muscle pain, joint stiffness, high blood sugar (hyperglycemia), sugar in your urine (glucosuria), swollen hands and feet due to fluid retention, and redness and itching in the area you inject. If you have headaches, eye problems, nausea or vomiting (these may be symptoms of raised pressure in the brain), contact your healthcare provider right away.

Norditropin® may affect how other medicines work, and other medicines may affect how Norditropin® works so be sure to tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take: glucocorticoid medication, thyroid hormone, insulin or other medicine for diabetes, medicines that are metabolized by

the liver (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine), or oral estrogen replacement medicine.

### III. CLAIM SPECIFIC SAFETY INFORMATION: HEALTH CARE PROFESSIONALS & CONSUMERS

Storage Flexibility for <b>NordiFlex®</b>	All Norditropin® products must be refrigerated prior to first use. Do not freeze. After initial use, Norditropin NordiFlex® 5 mg/1.5 mL and 10 mg/1.5 mL delivery pens can either be stored outside of the refrigerator (at up to 77°F) for use within 3 weeks or in the refrigerator (between 36° and 46°F) for use within 4 weeks. These storage flexibility guidelines also apply to Norditropin® cartridge 5 mg/1.5 mL. Norditropin NordiFlex® 15 mg/1.5 mL and Norditropin NordiFlex® 30 mg/3 mL delivery pens must always be refrigerated (between 36° and 46°F) – both prior to and after the initial injection – for use within 4 weeks. These guidelines for continuous refrigerated storage also apply to Norditropin® cartridge 15 mg/1.5 mL.
Storage Flexibility for <b>FlexPro®</b>	All Norditropin® products must be refrigerated prior to first use. Do not freeze. After initial use, FlexPro® 5 mg/1.5 mL and 10 mg/1.5 mL delivery pens can either be stored outside of the refrigerator (at up to 77°F) for use within 3 weeks or in the refrigerator (between 36°F and 46°F) for use within 4 weeks. The FlexPro® 15 mg/1.5 mL delivery pen must always be refrigerated (between 36°F and 46°F)—both prior to and after the initial injection—for use within 4 weeks.
Needle statement	Needles are sold separately and may require a prescription in some states.