Somatropin GenHeal®

℞

4 IU Lyophilized Powder For Injection (Subcutaneous / Intramuscular) Growth Hormone

FORMULATION
Each vial contains:
Somatropin (recombinant Human Growth Hormone), CP ..... 4 IU (1.6mg)

PRODUCT DESCRIPTION
Somatropin (GenHeal®) is a recombinant human growth hormone (rhGH) for injection. It is a sterile, white, lyophilized powder consisting of 191 amino acid residues identical to the amino acid sequence of human growth hormone. The molecular weight is 22,125 Daltons. Each vial also contains 2 mg of glycine and 22 mg of mannitol.

PHARMACODYNAMICS
The following actions have been demonstrated for somatropin and/or human growth hormone of pituitary origin:

Tissue Growth
- Skeletal Growth: Growth hormone stimulates skeletal growth in pediatric patients with growth hormone deficiency (GHD), Prader-Willi syndrome (PWS), small for gestational age (SGA), Turner syndrome (TS), or idiopathic short stature (ISS) by its effect on the epiphyseal growth plates of long bones. An increase in IGF-1 levels (which may play a role in skeletal growth) has been shown in these patients during treatment with growth hormone therapy.
- Cell Growth: Short-statured pediatric patients with growth hormone deficiency have been shown to have fewer skeletal muscle cells compared with the normal pediatric population. Somatropin increases both the number and size of muscle cells in these patients.

Protein metabolism
- Growth hormone stimulates skeletal and soft tissue growth by promoting cell division, amino acid uptake and protein synthesis. This is reflected by nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during growth hormone therapy.

Carbohydrate metabolism
- Growth hormone modulates carbohydrate metabolism. Large doses of growth hormone may impair glucose tolerance. Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by somatropin therapy.

Lipid metabolism
- Growth hormone administration in growth hormone deficient patients causes reduction of body fat stores, mobilization of lipid stores, and an increase in plasma fatty acids.

Mineral metabolism
- Growth hormone induces sodium, potassium and phosphorus retention. Increased serum concentrations of inorganic phosphate have been observed in patients with growth hormone deficiency after growth hormone therapy. This is attributed to metabolic activity associated with bone growth and an increased tubular reabsorption of phosphate by the kidneys. Serum calcium is not significantly altered. Growth hormone could increase calciuria.

Body Composition
- A decrease in fat mass and an increase in lean body mass have been demonstrated in adult GHD patients treated with growth hormone at the recommended adult dose. When these alterations are coupled with the increase in total body water, the overall effect is to modify body composition, an effect that is maintained with continued treatment.

PHARMACOKINETICS
Subcutaneous and intramuscular pharmacokinetic profiles of rHGH are similar and subcutaneous administration usually results in a higher serum GH level but produces the same IGF-I level compared with intramuscular route.

Peak plasma levels are reached in 3-5 hours after administration; the elimination half life is 2-3 hours. The elimination takes place in the liver and kidneys which have been shown to be faster in adults than in children. There is less growth hormone detected in the urine after metabolism. Serum GH levels are not influenced by the time selected for injection in a day. However, endogenous peak GH level is reached usually after the slow-wave sleeping phase and therefore administration at night before sleep is recommended.

INDICATIONS
In Children
- ***Growth Failure***
  - Treatment of children with growth failure due to inadequate endogenous growth hormone secretion and whose epiphyses are not closed.
  - Treatment of growth retardation in prepubertal children due to chronic renal disease.
- ***Prader-Willi Syndrome (PWS)***
  Treatment of children with growth failure due to PWS (confirmed by appropriate genetic testing) ***(See Contraindications).***
- ***Small for Gestational Age (SGA)***
  Treatment of growth failure in children born SGA who fail to manifest catch-up growth by age 2 years.
- ***Turner Syndrome***
  Treatment of growth failure in girls due to gonadal dysgenesis (Turner Syndrome) whose epiphyses are not closed.
- ***Noonan Syndrome***
  Treatment of children with growth failure associated with Noonan Syndrome.
- ***Idiopathic Short Stature (ISS)***
  Treatment of children with ISS defined by:
  - Normal birth weight.
  - Careful diagnostic evaluation that excludes other known causes of short stature that should be either observed or treated by other means.
  - Height at least 2.25 standard deviation (SD) scores below the mean for age and sex.
  - Height velocity below the 25th percentile for bone age and sex over 12 months of observation and unlikely to permit attainment of adult height in the expected range.

  Use only in ISS patients whose epiphyses are not closed.
- ***Short Stature Homeobox-containing Gene (SHOX) Deficiency***

Treatment of short stature or growth failure in children with SHOX whose epiphyses are not closed.

In Adults
- ***Somatropin Deficiency Syndrome***
  Replacement of endogenous growth hormone in adults with growth hormone deficiency, who meet the following two criteria:
  - ***Adult Onset:*** Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiency (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
  - ***Childhood Onset:*** Patients who were growth hormone-deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

  To confirm the diagnosis of adult growth hormone deficiency in both groups, appropriate growth hormone stimulation test (i.e., insulin tolerance test or combined arginine-growth hormone releasing hormone) is usually required. However, this may not be necessary in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic disease.
- ***Management of AIDS Wasting or Cachexia***
- ***Short bowel syndrome in patients receiving specialized nutritional support***
  Used to increase intestinal absorption of water, electrolytes, and nutrients from specialized nutritional care.

DOSAGE AND ADMINISTRATION
Patients receiving somatropin should be under the supervision of a physician experienced in the diagnosis and management of patients with growth hormone deficiency, Turner syndrome, ISS, SHOX deficiency, or adult patients with either childhood-onset or adult-onset growth hormone deficiency. The dose of somatropin should be ***individualized*** based on the patient's clinical and biochemical response to therapy.
Response to treatment in children treated with somatropin should be assessed by regular measurements by a specialist in child growth.
IGF-I concentrations should be monitored and maintained within the normal range for age and sex.

Usual Recommended Dose
Subcutaneous (SC) injection
- 0.1-0.2 IU/kg body weight once daily, or 2-3 IU/m^2 body surface area 3 times a week. It is usually given in the evening before sleep, preferably in the abdominal area. The injection site should change regularly to prevent lipoatrophy.

Intramuscular (IM) injection
- 0.2-0.24 IU/kg body weight or 4-6 IU/m^2 body surface area per dose given 3 times a week.

Note: A lower starting dose may be required in adult patients with growth hormone deficiency. A higher dosage requirement may be needed in patients suffering from other indications (i.e., Turner syndrome, Prader-Willi syndrome, SHOX-deficiency, and others). The actual starting dose may be determined by a trained endocrinologist and titrated according to response of each patient.

Preparation of the Dosage Form:
1. Using aseptic technique, push the needle through the rubber closures and draw up to 2 mL of the diluent.
2. Inject the diluent aiming the stream of liquid against the glass wall of the vial of the dry powder.
3. Slowly dissolve the lyophilized somatropin powder with sterile water for injection by gently turning the vial upside down several times. It takes about 2 minutes for the powder to dissolve completely. **DO NOT SHAKE VIAL.**

Storage procedures:
Before and after reconstitution, refrigerate at temperatures between 2-8°C. Do not freeze. Protect from light. Vials reconstituted with Sterile Water for Injection should be used within 72 hours. Dispose used needles and syringes in a puncture-proof hard plastic or glass container

CONTRAINDICATIONS
- Hypersensitivity to somatropin or any component of the product.
- Patients with acute critical illness due to complications after an open heart surgery, abdominal surgery or multiple accidental trauma or those with acute respiratory failure. *(See Warnings and Precautions)*
- Children with Prader-Willi syndrome who are severely obese, have a history of upper respiratory obstruction or sleep apnea, or have severe respiratory impairment.
- Evidence of tumor activity or active neoplasia (intracranial neoplasm must be inactive and antitumor therapy completed prior to instituting therapy). Somatropin must be discontinued if there is evidence of tumor activity.
- Patients with active proliferative or severe non-proliferative diabetic retinopathy
- Children with closed epiphysis
- Pregnancy and lactation
- Discontinue treatment with somatropin at renal transplantation in children with chronic renal disease

WARNINGS AND PRECAUTIONS
Acute Critical Illness
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. The potential benefit should be weighed against the potential risk since the safety of continuing somatropin replacement therapy who concurrently develop these illness have not been established.
Prader-Willi Syndrome in Children
Deaths, more commonly seen in males than in females, have been reported in children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment and are treated with somatropin. Check for signs and symptoms of upper airway obstruction and sleep apnea prior to initiation of treatment and discontinue in those who show signs of upper airway obstruction including onset of or increased snoring, and/or new onset of sleep apnea. All patients with Prader-Willi syndrome using somatropin should also have an effective weight control program and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively.
Neoplasms
Monitor patients with preexisting tumors or growth failure secondary to an intracranial lesion for recurrence or progression of underlying disease. An increased risk of a second neoplasm has been reported in childhood cancer survivors treated with somatropin; the most common second neoplasms were meningiomas in patients treated with radiation to the head for their first neoplasm. Monitor patients for any malignant transformation of skin lesions.
Glucose Intolerance
Blood glucose levels should be monitored periodically as insulin resistance may be induced by growth hormone, especially at higher doses in susceptible patients. Doses of insulin or oral agents may need to be adjusted for patients with diabetes on somatropin therapy.
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. These symptoms usually occur within the first 8 weeks of therapy which generally resolve after termination of therapy or a reduction of the dose. Fundoscopic examination is recommended before and periodically during the course of growth hormone therapy to exclude the presence of preexisting papilledema. Discontinue the use of somatropin if papilledema is observed; somatropin may be restarted at a lower dose after IH-associated signs and symptoms have resolved. An increased risk for developing intracranial hypertension has been observed in patients with Prader-Willi and Turner syndrome.
Fluid Retention
Fluid retention (clinical manifestations are usually transient and dose dependent) may occur in adult patients receiving somatropin replacement therapy.
Hypopituitarism
Closely monitor hormonal replacement treatments in patients with hypopituitarism (multiple pituitary hormone deficiencies) during somatropin treatment.
Hypothyroidism
Changes in thyroid hormone laboratory measurements may develop during treatment in children who lack adequate endogenous growth hormone secretion. Untreated hypothyroidism prevents optimal response to therapy. Therefore, periodically test thyroid function and treat with thyroid hormone when indicated.
Slipped Capital Femoral Epiphyses in Children
Slipped capital epiphysis may occur more frequently in patients with endocrine disorders or in patients during rapid growth. Any child having onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.
Progression of Preexisting Scoliosis in Children
Progression of scoliosis can occur in patients who experience rapid growth. Somatropin has not been shown to increase the occurrence of scoliosis. Signs and symptoms of scoliosis should be monitored during treatment.
Otitis Media and Cardiovascular Disorders in Turner Syndrome
Since patients with Turner syndrome have an increased risk of ear and hearing disorders, these patients receiving somatropin should be evaluated carefully for otitis media at least on a yearly basis. Closely monitor patients with Turner syndrome for cardiovascular disorders such as stroke, aortic aneurysm/dissection, hypertension as these patients are at risk for these conditions.
Local and Systemic Reactions
Since tissue atrophy may result when somatropin is administered subcutaneously at the same site over a long period of time, rotate the injection site to avoid this complication. *(See Dosage and Administration)*
Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and IGF-1 may increase with somatropin therapy.

INTERACTION WITH OTHER MEDICAMENTS
Inhibition of 11ß-Hydroxysteroid Dehydrogenase Type 1 (11ßHSD-1)
Somatropin inhibits 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD-1) in adipose/hepatic tissue which may interfere with the metabolic conversion of cortisol and cortisone to their active metabolites. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance doses since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11ßHSD-1 enzyme.
Glucocorticoid Therapy
Concomitant glucocorticoid therapy may inhibit the growth promoting effects of somatropin. Carefully adjust the glucocorticoid replacement dose in patients with coexisting ACTH deficiency to avoid an inhibitor effect for growth.
Drugs metabolized by Cytochrome P450 System: Somatropin may alter the clearance of drugs metabolized by CYP liver enzymes.
Oral Estrogens: A larger dose of somatropin may be required to achieve the defined treatment goal in patients receiving concomitant estrogen therapy.
Insulin and Oral Hypoglycemic Agents (OHA): Antagonisms of the effects of insulin and/or OHAs may necessitate an increase or adjustment of insulin and/or OHA dosage.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy
It is not known whether somatropin can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Somatropin should be used only if clearly needed and if the benefits outweigh the risk to the pregnant woman.
Lactation
It is not known whether somatropin is excreted in human milk. Since many drugs are excreted in the human milk, somatropin should be used with caution in breastfeeding women.
Elderly
There is no clinical experience on the use of somatropin in patients more than 65 years old. However, some older individuals have greater sensitivity to somatropin and therefore may be at an increased risk in developing adverse events. Dosage adjustment may be necessary in elderly patients starting at a lower initial dose and smaller dose increments.
Obese Patients
Patients who are obese are more likely to manifest adverse effects when treated with a weight-based treatment regimen.

UNDESIRABLE EFFECTS
The most serious and/or most frequently observed adverse reactions during somatropin therapy include:
- 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)*
- 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)*
- Glucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus *(see Warnings and Precautions)*
- Intracranial hypertension *(see Warnings and Precautions)*
- Significant diabetic retinopathy *(see Contraindications)*
- Slipped capital femoral epiphysis in pediatric patients *(see Warnings and Precautions)*
- Progression of preexisting scoliosis in pediatric patients *(see Warnings and Precautions)*
- Fluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paresthesias *(see Warnings and Precautions)*
- Unmasking of latent central hypothyroidism *(see Warnings and Precautions)*
- Injection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) *(see Warnings and Precautions)*

Injection Site Reactions: Injection site reactions, including pain or burning associated with the injection, fibrosis, nodules, rash, inflammation, pigmentation, or bleeding; lipoatrophy; mild and transient edema (either localized or generalized); asthenia
CNS Effects: Headache, dizziness, drowsiness, syncope, aggressiveness, benign intracranial hypertension, altered mood, myalgia, paresthesia, dry mouth, and hypesthesia have been reported.
Cardiovascular Effects: Palpitations, hypertension, and hyperlipidemia.
Vascular Effects: Hematuria, postural hypotension and peripheral edema. Leukemia has been reported in a small number of growth hormone-deficient children treated with somatropin.
Endocrine/Metabolic Effects: Hypothyroidism, mild transient hyperglycemia, glucosuria, abnormal ejaculation, priapism, and gynecomastia have been reported.
Development of diabetes mellitus of which all had predisposing factors, e.g., elevated glycated hemoglobin levels and/or marked obesity prior to receiving somatropin, have also been reported. Decrease in serum thyroxin levels have been reported rarely. Increased blood alkaline phosphatase level may be seen during treatment with somatropin. A patient developed carbohydrate metabolism abnormalities which resolved upon discontinuation of somatropin.
Respiratory Effects: Respiratory illnesses such as influenza, tonsillitis, otitis, sinusitis, rhinitis, and nasopharyngitis. Dyspnea and sleep apnea have been reported frequently.
Gastrointestinal Effects: Constipation, diarrhea, nausea, vomiting, gastroenteritis, increased appetite, and pancreatitis.
Musculoskeletal Effects: Arthralgia, arching joints, arthrosis, hip pain, fracture, aggravation of preexisting scoliosis, scoliosis, muscle pain, joint pain and disorder, and back pain, localized muscle pain, weakness, and pain and stiffness of the extremities have been reported. Slipped capital femoral epiphysis (occurs more frequently in patients with endocrine disorders) and Legg-Calve-Perthes disease (occurs more frequently in patients with short stature), which may present as the development of a limp or complaints of hip or knee pain, have been reported in children treated with growth hormone. Symptoms of carpal tunnel syndrome, which lessened after dosage reduction or treatment interruption or surgery, have also been reported.
Skin Reactions: Rash, pruritus, urticaria, and angioedema.
Anti-hGH Antibodies: As with other protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. Growth hormone antibody binding capacities <2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been observed. In general, growth hormone antibodies are not neutralizing and do not interfere with the growth response. In addition to an evaluation of compliance with the prescribed treatment program and thyroid status, test for antibodies to human growth hormone in any patient who fails to respond to therapy.
Anti-hGH antibodies were not detected in any of the patients treated with somatropin.
Other Effects: Increased risk of ear disorders (e.g., otitis media), eye disorders [e.g., blurred vision, intraoperative floppy iris syndrome (IFIS)], hair loss, jaw prominence, increased growth of hands and feet, urinary tract infection, pyrexia, central precocious puberty, fatigue, edema, generalized edema, peripheral edema, mild to moderate symptoms of fluid retention, including peripheral swelling, excessive number of cutaneous nevi, and progression of pigmented nevi have also been reported.

OVERDOSAGE AND MANAGEMENT
Specific information on somatropin overdosage is not available. However, acute overdosage may initially result in hypoglycemia and subsequently to hyperglycemia. Long-term overdosage may result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

STORAGE
Store at temperatures between 2-8°C.
Do not freeze.
Protect from light.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Type I, clear glass vial, box of 1.

DATE OF REVISION OF PACKAGE INSERT: March 2017
DATE OF RENEWAL OF THE AUTHORIZATION: June 2015

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For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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