Growth Hormone AHM

Clinical Indications

- Growth hormone (GH) is considered medically necessary for treatment of patients in the following diagnostic categories who meet 1 or more of the following criteria
  - GH replacement is considered medically necessary for children and adolescents with the 1 or more of the following indications
    - Idiopathic growth hormone deficiency (GHD)
    - GH replacement is considered medically necessary for children and adolescents with GH deficiency, i.e. insufficient growth hormone secretion and growth failure who meet ALL of the following criteria
  - Patient has failed to respond to at least two standard GH stimulation tests, defined as a serum GH level (peak level) of less than 10 nanograms per milliliter (ng/ml) (20 mU/liter), after stimulation with insulin, levodopa, arginine, propranolol, clonidine, or glucagon. (However, one abnormal GH test is sufficient for children with defined CNS pathology, history of irradiation, multiple pituitary hormone deficiency (MPHD) or a genetic defect affecting the GH axis). For persons with thyroid deficiency, only GH secretion tests that are performed after thyroid deficiency is adequately treated because GH secretion may be subnormal merely as a result of hypothyroidism. Both stimulation tests may be performed simultaneously.
  - For children who have insufficient growth hormone secretion (fail to respond to stimulation tests), appropriate imaging (magnetic resonance imaging (MRI) or computed tomography (CT)) of the brain with particular attention to the hypothalamic-pituitary region is necessary to exclude the possibility of a tumor
  - At least 1 or more of the following criteria is met
    - Child has severe growth retardation with height standard deviation score (SDS) more than 3 SDS below the mean for chronological age and sex
    - Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex and decreased growth rate (growth velocity (GV) measured over one year below 25th percentile for age and sex). Growth velocity (GV) should be tracked over at least one year.
    - Child exhibits severe deceleration in growth rate (GV measured over 1 year -2 SDS below the mean for age and sex). Growth velocity (GV) should be tracked over at least one year.
o Child has decreasing growth rate combined with a predisposing condition such as previous cranial irradiation or tumor

o Child exhibits evidence of other pituitary hormone deficiencies or signs of congenital GHD (hypoglycemia, microphallus)

o Given the above criteria, further laboratory testing of children without classic GHD to diagnose “partial” GHD, or other abnormalities of GH secretion or bioactivity, is considered not medically necessary. This includes overnight hospitalization of children for testing of spontaneous GH secretion.

o Measurement of insulin-like growth factor I (IGF-I) is considered medically necessary to determine adequacy of growth hormone therapy in adults and children. However, the diagnosis of growth hormone deficiency should not rely solely on IGF-I measurements, but must be confirmed by provocative tests solely for growth hormone secretion. Measurement of IGF binding protein-2 (IGFBP-2), IGF binding protein-3 (IGFBP-3), and the acid labile subunit of IGF-I are considered experimental and investigational.

o **Chronic Renal Insufficiency** - GH replacement prior to renal transplantation is considered medically necessary for children with chronic renal insufficiency and growth retardation who meet **ALL** of the following criteria
  - Child's nutritional status has been optimized, metabolic abnormalities have been corrected, and steroid usage has been reduced to a minimum
  - At least **1 or more** of the following criteria is met
    - Child has severe growth retardation with height SDS more than 3 SDS below the mean for chronological age and sex
    - Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex and decreased growth rate (GV measured over one year below 25th percentile for age and sex)
    - Child exhibits severe deceleration in growth rate (GV measured over one year -2 SDS below the mean for age and sex)

o Consistent with established guidelines for children with chronic renal insufficiency after renal transplantation, resumption of growth hormone therapy is not considered medically necessary until at least 1 year after the transplant to allow time to ascertain whether catch-up growth will occur.

o **Turners Syndrome** - GH replacement is considered medically necessary for children with Turner's syndrome and growth retardation who meet **ALL** of the following criteria
  - The diagnosis of Turner's syndrome is confirmed by chromosome analysis
  - At least **1 or more** of the following criteria is met
    - Child has severe growth retardation with height SDS more than 3 SDS below the mean for chronological age and sex
• Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex and decreased growth rate (GV measured over one year below 25th percentile for age and sex)
• Child exhibits severe deceleration in growth rate (GV measured over one year -2 SDS below the mean for age and sex)

○ Prader Willi Syndrome- GH replacement is considered medically necessary for children with Prader Willi syndrome and growth retardation who meet ALL of the following criteria
  ▪ The diagnosis of Prader Willi syndrome is confirmed by appropriate genetic testing
  ▪ At least 1 or more of the following criteria is met
    • Child has severe growth retardation with height SDS more than 3 SDS below the mean for chronological age and sex
    • Child has moderate growth retardation with height SDS between -2 and -3 SDS below the mean for chronological age and sex and decreased growth rate (GV measured over one year below 25th percentile for age and sex)
    • Child exhibits severe deceleration in growth rate (GV measured over one year -2 SDS below the mean for age and sex)

○ SGAt children- GH supplementation is considered medically necessary for children born small for gestational age, and who meet ALL of the following criteria
  ▪ Child was born small for gestational age, defined as birth weight or length 2 or more standard deviations below the mean for gestational age
  ▪ Child fails to manifest catch up growth by age 2 years, defined as height 2 or more standard deviations below the mean for age and sex

  • Growth curves plotting growth from birth through age 3 should be submitted for evaluation

○ Noonan Syndrome- GH therapy is considered medically necessary for prepubertal children with short stature associated with Noonan syndrome who meets ALL of the following criteria
  ▪ Height 2 SDS or more below the mean for chronological age and sex
  ▪ GV measured over one year prior to initiation of therapy of 1 or more SDS below the mean for age and sex

○ GH therapy is considered medically necessary for the treatment of short stature or growth failure in children with SHOX deficiency whose epiphyses are not closed

○ Weight loss related to HIV -GH supplementation is considered medically necessary for HIV-infected persons with involuntary weight loss of greater than 10% of pre-illness baseline body weight or body mass index (BMI) less than 20 kg/m2, in the absence of a concurrent illness or medical condition other than HIV infection that would explain these findings, and who have failed to adequately respond or are intolerant to anabolic steroids (e.g., Megace)

• In children and adolescents, GH therapy will be considered not medically necessary if any of the discontinuation criteria is met
  ○ Expected final adult height has been reached
If there is a poor response to treatment, generally defined as an increase in growth velocity of less than 50% from baseline, in the first year of therapy. In children with Prader-Willi syndrome, evaluation of response to therapy should also take into account whether body composition (i.e., ratio of lean to fat mass) has significantly improved.

- Increase in height velocity is less than 2 cm total growth in one year of therapy.
- There are persistent and uncorrectable problems with adherence to treatment.

At completion of linear growth (that is, growth rate less than 2 cm/year), available guidelines indicate that GH treatment should be stopped for at least 3 months, and GH status should be re-assessed to determine whether continued GH treatment into adulthood is necessary. The patient should be reevaluated three or more months after discontinuation of GH therapy to determine if the patient fulfills medical necessity criteria for GH treatment at adult doses as set forth below.

**GH replacement is considered medically necessary for adults who meet ALL of the following**

- GH treatment of adults with documented GHD is considered medically necessary when **ALL** of the following criteria are met:
  - Patient has GH deficiency as a result of hypothalamic or pituitary disease (e.g., panhypopituitarism, pituitary adenoma, trauma, cranial irradiation, pituitary surgery) and at least one other hormone deficiency diagnosed (except for prolactin deficiency).
  - Patient is already receiving adequate replacement therapy for any other pituitary hormone deficiencies.
  - Patient has a severe GH deficiency, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test (growth hormone releasing hormone, arginine, or glucagon).
  - Patient has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire.

- Treatment is considered medically necessary for an initial 9 months, allowing for an initial 3-month period of GH dose titration, followed by a 6-month therapeutic trial period. Subsequent GH treatment is considered medically necessary only if, upon subsequent testing of the effect of this treatment, the patient demonstrates a QoL improvement of 7 or more points in QoL-AGHDA score.

- **Adults who were growth hormone deficient as children or adolescents** who meet **1 or more** of the following:
  - For adolescents and adults younger than age 25 years with childhood-onset growth hormone deficiency (including idiopathic isolated growth hormone deficiency [IIGHD] or multiple pituitary hormone deficiencies, including growth hormone [MPHD]) who have completed linear growth (growth rate less than 2 cm per year), GH treatment at adult doses is considered medically necessary only in those who have failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH stimulation test.
test (growth hormone releasing hormone, arginine, or glucagon). For adults having a low IGF-1 (a marker of insulin response) concentration (standard deviation score less than -2), failure to respond to only one standard GH stimulation test is required. In these patients, GH supplementation at adult doses is considered medically necessary until adult peak bone mass is achieved (between 25 and 30 years of age)

- Consistent with available guidelines, as a condition of continued authorization of GH therapy at adult doses, that GH therapy be stopped for at least 3 months after completion of linear growth (that is, growth rate less than 2 cm/year), and that GH status should be reassessed. As a condition of continued authorization, reassessment of GH status after GH treatment is stopped for at least 3 months before initiating GH supplementation at adult doses. The patient will be reevaluated three or more months after discontinuation of GH therapy to determine if the patient fulfills medical necessity criteria for GH treatment at adult doses

- For adults over age 25 years with childhood onset growth hormone deficiency (IIGHD or MPHD), GH treatment at adult doses is considered medically necessary if they meet ALL of the following criteria
  - Patient has failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). For patients having a low IGF-1 (a marker of insulin response) concentrations (SDS less than -2), failure to respond to only one standard GH stimulation test is required
  - Patient has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of Life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire (see Figure 4 below)

- Adults who develop growth hormone deficiency in early adulthood meet 1 or more of the following
  - GH treatment at adult doses is considered medically necessary for selected patients who develop isolated GH deficiency (IIGHD or MPHD) in adolescence or early adulthood, after linear growth is completed but before the age of 25 years
  - GH treatment at adult doses is considered medically necessary only in those who have failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). For adults having a low IGF-1 (a marker of insulin response) concentration (SDS less than -2), failure to respond to only one standard GH stimulation test is required. In these patients, GH supplementation at adult doses is
considered medically necessary until adult peak bone mass is achieved (between 25 and 30 years of age)

- Following achievement of peak bone mass between 25 and 30 years of age, continued GH treatment is considered medically necessary for adults who meet ALL of the following criteria
  - Patient has a severe GH deficiency: GH treatment at adult doses is considered medically necessary only in those who have failed to respond to at least two standard GH stimulation tests, defined as a peak GH response of less than 9 mU/liter (3 ng/ml) during an insulin tolerance test and one other cross-validated GH test (growth hormone releasing hormone, arginine, or glucagon). (For adults having a low IGF-1 (a marker of insulin response) concentration (SDS less than -2), failure to respond to only one standard GH stimulation test is required)
  - Patient has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire
  - According to available guidelines, for the first 2-3 months dosage adjustments should be made after monthly assessments of serum levels of IGF-1, and in response to the presence of adverse effects, until a maintenance dose is achieved. As a condition of continued authorization, an annual reassessment of serum levels of IGF-1 in adults is required and appropriate dosage adjustments, as GH requirements in adults may decrease with age
  - **Continued Therapy** - The continued medical necessity of growth hormone therapy is reviewed at least annually to determine whether growth hormone therapy continues to be medically necessary. The annual medical necessity review focuses on ALL of the following documentation
    - Response to therapy
    - Discontinuation criteria are not met
    - Documentation of any major changes in clinical status affecting the medical necessity of growth hormone supplementation
    - Documentation that the person continues to follow up with the provider and receive appropriate reevaluations and care
  - GH supplementation is considered medically necessary for persons with short bowel syndrome who depend on intravenous parenteral nutrition for nutritional support
    - Growth hormone treatment of short bowel syndrome for more than four weeks duration is considered investigational as administration of growth hormone for more than four weeks duration has not been adequately studied for this indication. There is insufficient evidence of the effectiveness of repeat courses of growth hormone for short bowel syndrome
  - Pegvisomant (Somavert) is considered medically necessary for the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are inappropriate
There are several brands of growth hormone on the market. There is a lack of reliable evidence that any one brand of growth hormone is superior to other brands for medically necessary indications. Humatrope, Nutropin, Nutropin AQ, Saizen and Tev-Tropin brands of growth hormone ("preferred growth hormones") are less costly. Consequently, because other brands (e.g., Genotropin, Norditropin and Omnitrope) of growth hormone are more costly than these preferred growth hormones, and preferred growth hormones are at least as likely to produce equivalent therapeutic results, no other growth hormones will be considered medically necessary unless the patient has a contraindication or intolerance to at least two of the preferred growth hormones. If the preferred growth hormones do not have the labeled indication, then it is considered medically necessary to use another brand of growth hormone that has the required labeling indication.

Growth hormone therapy will be considered medically necessary for persons who meet medical necessity criteria; even if they are also diagnosed with a co-morbid medical condition for which growth hormone therapy is considered not medically necessary or experimental and investigational. For example, growth hormone therapy would be considered medically necessary for a child with cystic fibrosis (an experimental and investigational indication) if the child was also severely growth hormone deficient according to the criteria set forth above.

Indications considered Not Medically Necessary

- GH growth hormone therapy is considered investigational in persons with the following contraindications for which the safety of growth hormone therapy has not been established
  - Benign intracranial hypertension (BIH)
  - Critically ill persons (e.g., after complications following open heart or abdominal surgery, multiple trauma, acute respiratory failure or similar conditions)
  - Diabetic retinopathy
  - Persons with evidence of tumor activity. In persons with tumors, anti-tumor therapy must be completed before initiating GH therapy
  - Persons with known hypersensitivity to GH or to any of its excipients
  - Women who are pregnant or lactating
- GH growth hormone therapy is considered investigational in persons with the following contraindications for which the safety of growth hormone therapy has not been established
  - Amyotrophic lateral sclerosis
  - Anabolic therapy to enhance body mass or strength for professional, recreational or social reasons
  - Anti-aging
  - Burn injuries
  - Cerebral palsy
  - CHARGE (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) syndrome
- Chondrodystrophy
- Chronic catabolic states, including inflammatory bowel disease, pharmacologic glucocorticoid administration, and respiratory failure
- Chronic fatigue syndrome
- Congestive heart failure
- Constitutional delay of growth and development
- Corticosteroid-induced pituitary ablation
- Crohn's disease
- Cystic fibrosis
- Depression
- Down syndrome and other syndromes associated with short stature and increased susceptibility to neoplasms (e.g., Bloom syndrome, Fanconi syndrome)
- Fibromyalgia
- Fracture healing
- Glucocorticoid-induced growth failure
- Growth hormone insensitivity (partial or complete)
- Growth retardation due to amphetamines (e.g., Adderall, Ritalin)
- HIV lipodystrophy
- Hypertension
- Hypochondroplasia
- Hypophosphatemia (e.g., hypophosphatemic rickets)
- Infertility/in-vitro fertilization
- Intra-uterine growth restriction not meeting diagnostic criteria for small for gestational age children
- Ischemic heart disease
- Juvenile rheumatoid arthritis
- Kabuki syndrome
- Muscular dystrophy
- Neurosecretory growth hormone dysfunction
- Non-classic congenital adrenal hyperplasia
- Obesity/morbid obesity
- Osteogenesis imperfecta
- Osteoporosis
- Post bariatric surgery
- Post-traumatic stress disorder
- Precocious puberty
- Russell-Silver syndrome (that does not result in small for gestational age)
- Skeletal dysplasias (e.g., achondroplasia, kyphomelic dysplasia)
- "Somatopause" in older adults
Evidence Summary

- **Background**
  - These criteria are based on evidence-based guidelines on growth hormone supplementation from the National Institute of Clinical Excellence (NICE, 2002). Growth hormone (GH) has been approved by the U.S. Food and Drug Administration (FDA) for treatment of GH deficiency (GHD) in both children and adults, short stature associated with chronic renal insufficiency (CRI) before renal transplantation, short stature in patients with Turner syndrome (TS), HIV-associated wasting syndrome in adults, idiopathic short stature, treatment of children with short stature associated with Noonan syndrome, short stature homeobox–containing gene deficiency, and treatment of children born small for gestational age (SGA) who fail to manifest catch-up growth. There are several brands of growth hormone (somatropin) on the market, and there is a lack of reliable evidence that any brand of growth hormone is more effective than others for any indication.
  - Studies have shown that over 90 percent of adults diagnosed with growth hormone deficiency have overt pituitary disease, which is usually caused by a pituitary adenoma or by surgery or radiation therapy for a pituitary adenoma.
  - The syndrome of GHD characteristically manifests with deficiencies in bone density, reduction in muscle strength and exercise tolerance, decreases in vitality and energy, emotional lability, feelings of social isolation, and increases in body fat and higher serum lipid concentrations.
  - The usefulness of GH treatment in adults with pituitary disease who have completed their statural growth is based on the role of GH in increasing bone density and in improving mood and motivation. There is some evidence to suggest that growth hormone therapy improves cardiovascular risk factors and increases bone mineral density (Ball, 2002). A Committee convened by the National Institute of Clinical Excellence (2003) concluded, however, that it was uncertain what impact GH treatment had on the longer-term clinical outcomes and mortality related to cardiovascular risk factors and changes in bone mineral density. In addition, there are other more effective, better established and less costly therapies to reduce cardiovascular risk factors and increase bone mineral density.
  - The NICE Committee concluded that a trial of GH treatment could be recommended for adults with GH deficiency who have a severe perceived impairment of QoL as demonstrated by a reported score of at least 11 in QoL-AGHDA (NICE, 2003). The Committee agreed that the QoL-AGHDA questionnaire (see Figure 4 of Appendix) is the best available evaluation tool for the assessment of both baseline QoL and the effect of treatment in adults with GH deficiency.

- According to this guideline tesamorelin (Egrifta) is considered cosmetic for the reduction of excess abdominal fat in HIV-infected persons with lipodystrophy, and is considered experimental and investigational for other indications.
examination of available evidence, the Committee found that the subgroup of adults with GH
deficiency for whom treatment may be clinically justified are those who have an improvement in
QoL equivalent to an absolute change in their baseline QoL-AGHDA score of at least 7 points. The
Committee stated that reassessment of the need for GH replacement should take place after a
trial treatment period of 9 months (3 months for dose titration and 6 months for assessment of
response). For GH treatment to continue after this trial period, it should be necessary to
demonstrate a sustained improvement in QoL.

• NICE recommended that adults with childhood GHD must be retested as adults before long-term
  GH replacement is instituted, because some GH-deficient children are found to be GH sufficient in
  adulthood (NICE, 2003).

• Growth hormone levels continue to decline through adulthood, and the proportion of adults who
  may be considered growth hormone deficient increases with age. Some investigators have
  claimed that idiopathic growth hormone deficiency in adults is common and that most cases of
  idiopathic adult-onset growth hormone deficiency go undetected. These investigators have
  promoted growth hormone supplementation as a “rejuvenation” treatment for aging adults with
  age-related declines in growth hormone levels. Clinical studies of elderly persons with relatively
  low levels of endogenous growth hormone have shown small increases in lean body mass and
  bone mass, as well as improvements in plasma lipid profile with growth hormone
  supplementation. However, the long-term oncogenic effects and other potential adverse
  consequences of growth hormone supplementation in adults with idiopathic growth hormone
  deficiency are unknown. In addition, improvements in lean body mass, bone mass, and plasma
  lipid profile may be better achieved with other treatments in adults with idiopathic growth
  hormone deficiency.

• According to NICE, the diagnosis of GHD in adult patients requires provocative testing of GH
  secretion (NICE, 2003). Random samples of GH are usually meaningless. In most academic
  medical centers, the insulin tolerance test (ITT) has been the validated study of choice. However,
  the literature indicates the test has an inherent risk of profound hypoglycemia, and is
  contraindicated in patients with abnormal electrocardiographic findings, with a history of
  ischemic heart disease or cerebrovascular disease, or with seizure disorders. According to
  available guidelines, the ITT is not generally recommended for patients older than 65 years of
  age.

• In adults, the GH response to insulin-induced hypoglycemia is dependent on age, weight, and sex
  hormones, but most normal adults tested will have a peak GH secretion above 3 ng/mL (when GH
  is measured in a polyclonal competitive radioimmunoassay). Thus, values less than 3 ng/mL are
  considered indicative of GHD. In children and adolescents, in whom secretion may be more
  robust and GH effects on growth may require higher levels of secretion than in older patients,
  values below 10 ng/mL are considered inadequate.

• In patients in whom insulin-induced hypoglycemia is contraindicated or unsafe or where
  appropriate testing arrangements are unavailable, the literature states that alternatives to ITT
should be used. Information is now emerging that intravenously administered arginine, either alone or in combination with GH-releasing hormone (GHRH), may be useful. When only intravenously administered arginine is used, cutoff values for a normal response are similar to those expected with ITT. When it is used in combination with GHRH, the response may be augmented and the cutoff level is somewhat higher (9 to 10 ng/mL). Available literature suggests tests that use of glucagon, propranolol, or levodopa has a lesser established diagnostic value in comparison to ITT. Although useful as a diagnostic procedure in children, the literature states that a test that uses clonidine is of dubious value for the diagnosis of GH deficiency in adults. In adults with a history of hypothalamic pituitary disease or cranial irradiation, generally only one provocative test of GH secretion is needed (NICE, 2003). In adults with childhood onset isolated GH deficiency (no evidence of hypothalamic pituitary abnormality or cranial irradiation), two diagnostic tests should be recommended, except for those having low insulin-like growth factor-1 (IGF-1) (a marker of GH response) concentrations (standard deviation score less than -2) who may be considered for one test (NICE, 2003).

- Although serum IGF-I concentrations are related to GH adequacy, accepted guidelines state that the diagnosis of GHD should not rely simply on IGF-I measurements but should be confirmed by provocative tests solely for GH secretion.
- In adults with GHD, the FDA-approved labeling states that the starting dosage of GH should be very low (0.1 to 0.4 mg/day). The product labeling further states that this dose should be increased gradually on the basis of clinical and biochemical responses assessed at monthly intervals. The biochemical marker generally relied upon for GH is the IGF-I level in serum. Values of IGF-I should be maintained in the normal age- and sex-adjusted range. The literature indicates that the dose may be increased, on the basis of individual patient requirements, to a maximum of 1.75 mg daily in patients younger than 35 years of age, and to a maximum of 0.875 mg daily in patients older than 35 years of age. Of note, this dose is substantially less than GH replacement doses in children and adolescents, in whom the dose is based on weight.
- The FDA has approved the use of growth hormone (Zorbtive, Serono Inc., Rockland, MA) for the treatment of short bowel syndrome in patients receiving specialized nutritional support. According to the FDA-approved labeling, Zorbtive should be used in conjunction with optimal management of short bowel syndrome. Specialized nutritional support may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences. Nutritional supplements may be added according to the discretion of the treating physician. Optimal management of short bowel syndrome may include dietary adjustments, enteral feedings, parenteral nutrition, fluid and micronutrient supplements, as needed. The FDA approval of Zorbtive was based on the results of a randomized, double-blind, controlled, parallel-group Phase III clinical study of growth hormone in subjects with short bowel syndrome (SBS) who were dependent on intravenous parenteral nutrition (IPN) for nutritional support. The primary endpoint was the change in weekly total IPN volume defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid. Subjects received either
placebo with the nutritional supplement, glutamine (n=9), growth hormone without glutamine (n=16) or growth hormone with glutamine (n=16). All 3 groups received a specialized diet. Following a two-week equilibration period, treatment was administered in a double-blind manner over a further period of four weeks. The dosing of growth hormone was approximately 0.1 mg/kg/day for 4 weeks. Mean reductions in IPN volume in each patient group were significantly greater in both the group treated with growth hormone (reduction of 2.1 liter per week compared to placebo plus glutamine) and the group treated with growth hormone plus glutamine (reduction of 3.9 liter per week compared to placebo plus glutamine) than in group treated with placebo plus glutamine. According to the FDA-approved labeling, Zorbtive should be administered to patients with short bowel syndrome (SBS) at a dose of approximately 0.1 mg/kg subcutaneously daily to a maximum of 8 mg daily. Administration at doses higher than 8 mg per day or for more than 4 weeks has not been adequately studied. According to the FDA-approved labeling, injections should be administered daily for 4 weeks. The FDA notes that the safety and effectiveness of Zorbtive in pediatric patients with short bowel syndrome has not been established.

- According to available guidelines, GH therapy is contraindicated in patients with active malignant disease, benign intracranial hypertension (BIH), and proliferative or pre-proliferative diabetic retinopathy. Potential for childbearing is not a contraindication, but accepted guidelines caution that GH therapy should be discontinued when pregnancy is confirmed. The guidelines further caution that GH should not be used in critically ill patients who have acute catabolism. GH therapy is also contraindicated in persons with hypersensitivity to GH or its excipients.
- The FDA has approved GH for use in the following pediatric conditions: growth hormone deficiency, Turner syndrome, chronic renal insufficiency before transplantation, and children born small for gestational age. An advisory committee to the FDA also recommended approval of growth hormone for children with idiopathic short stature.
- An assessment conducted for the National Institute of Clinical Excellence (2001) suggests the following criteria be used to define subnormal growth in children with growth hormone deficiency: decreasing growth rate combined with a predisposing condition such as previous cranial irradiation; or evidence of other pituitary hormone deficiencies or signs of congenital GHD (hypoglycemia, microphallus); or moderate growth retardation with height SDS for sex and chronological age between -2 and -3 SDS below the mean and decreased growth rate (growth velocity (GV) below 25th percentile for age and sex); or severe deceleration in growth rate (GV below 3rd percentile for age and sex); or severe growth retardation with height standard deviation score (SDS) for sex and chronological age less than 3 SDS below the mean. In addition, retardation of bone maturation is found in most cases of subnormal growth.
- Diagnosis of GHD in children is confirmed by measurements of GH secretion, commonly in several samples following stimulation by a provocative agent such as insulin or clonidine (NICE, 2001). The literature states that the standard method of assessing growth hormone secretion in children is to measure the serum growth hormone response to insulin and other stimuli. Another method
is to make frequent measurements of serum growth hormone during the day and night, but this is no more effective than the standard method for detecting growth hormone deficiency. Formerly, the diagnosis of growth hormone deficiency in children was based on a peak serum growth hormone concentration of 5 ng/mL or less in response to a provocative test, but a peak serum growth hormone concentration of less than 10 ng/mL is now considered abnormal. However, because the available growth hormone assays have not been standardized, the literature states that the cutoff value of less than 10 ng/mL is of limited usefulness, especially in borderline cases. Instead, accepted guidelines indicate the diagnosis should be based on very short height, as defined by the standard-deviation score (more than 2.0 standard deviations below the mean height for normal children of the same age), delayed bone age, poor growth velocity (less than the 25th percentile), and predicted adult height substantially below the mean parental height. When used in conjunction with these measures, however, the guidelines suggest a peak serum growth hormone value of less than 10 ng/mL in response to stimulation is a reasonable definition of growth hormone deficiency, with values less than 5 ng/mL reflecting the most severe deficiency.

- If thyroxine is insufficient, then the literature indicates tests of GH secretion should be postponed until the thyroid deficiency is adequately replaced because GH secretion may be subnormal merely as a result of the hypothyroidism. If GHD is suspected in a peripubertal person with a growth pattern that resembles constitutional delay of growth and development, sex steroid priming before testing of GH secretion has been recommended by some investigators.

- Other markers of growth hormone secretion, such as concentrations of serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3), are not consistently abnormal in children with growth hormone deficiency.

- Available literature states that growth hormone stimulation tests and indirect measures of determining endogenous growth hormone secretion (measurement of serum IGF-1 and IGFBP-3 or urinary GH) are often subject to questionable specificity, false failure rates, and lack of published age- and sex-specific normal ranges. Due to the inadequacies of these tests, a subnormal growth velocity often becomes the deciding factor in choosing to initiate growth hormone therapy. However, available literature indicates that measurement of short-term growth velocity is unreliable in predicting future growth. Growth velocity during the autumn and winter may be lower than that during the rest of the year by more than 2 cm/yr. and may be normal if less than 2.5 cm/year during these cooler seasons. Therefore, for valid measurements, accepted guidelines provide that growth velocity should be tracked over an entire year.

- Because of its pronounced anabolic effects, GH is contraindicated in children with an active malignant condition. There is controversy over whether it is safe to administer growth hormone to children in the year or two following treatment for leukemia, medulloblastomas, ependymomas, or other tumors.

- GH treatment in children with childhood-onset GHD is generally begun with a dosage of GH of 0.15 to 0.3 mg/kg per week given six or seven times weekly. A maintenance dosage of up to 0.30
mg/kg of body weight is frequently recommended. Treatment is continued until the handicap of short stature is ameliorated, until epiphyseal closure has been recorded, or until the patient is otherwise no longer responding to GH treatment.

- Turner syndrome (TS), which occurs in 1 in every 2000 live born girls, is due to abnormalities or absence of an X chromosome and is frequently associated with short stature, which may be ameliorated with GH treatment. Because growth in height is variable in patients with Turner syndrome, literature suggest that the decision whether to treat with GH and the timing of such treatment should be made on the basis of each patient’s height and growth velocity. Treatment is often initiated when the standard deviation score for height decreases to less than 2 standard deviations below the mean.

- Growth failure associated with TS is thought to be multifactorial, with one of the factors being reduced sensitivity to GH, rather than decreased GH levels. Therefore, supra-physiological doses of GH are required for treatment in children with TS (NICE, 2002). According to the available literature, treatment is often initiated with GH doses higher than those used in treating GHD; the usual dose of GH for TS is 0.045-0.050 mg/kg/day. Several studies suggest that statural growth may be optimized by concomitant treatment with oxandrolone in a daily dose of 0.0625 mg/kg.

- Prader-Willi syndrome (PWS) consists of hypothalamic obesity, short stature, developmental delay, hypogonadotropic hypogonadism, small hands and feet, and hypotonia. The hypothalamic disorder may result in impaired GH secretion in some patients. Studies have shown that GH appears to have beneficial effects on growth velocity of pediatric patients with Prader-Willi syndrome. Clinical studies have also shown that growth hormone supplementation in PWS has a positive impact on body composition, with increases in lean mass and decreases in percent body fat. The FDA has approved Genotropin brand of growth hormone for the “long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome.” A number of randomized controlled clinical studies have reported significant increases in height velocity in PWS children treated with growth hormone. One uncontrolled study has reported on final height in a small group of treated children with PWS. The study reported final height of 170 cm in males and 159 in females. These heights are well within the normal range. Presuming a treatment effect based on the change in standard deviation (SD) from the start of treatment to the completion of treatment, there was a change of 1.64 SD. Converting this SD improvement to cm in adult height, this corresponds to treated males being approximately 11 cm and treated females being approximately 9.8 cm taller than the presumptive height of untreated children.

- Children with Prader-Willi syndrome are considered to have a hypothalamic disorder, and thus GH therapy is intended to replace physiological levels of GH. The recommended dose of GH therapy for children with Prader-Willi syndrome is 0.035 mg/kg/day.

- According to the FDA-approved labeling, GH should only be used in the long-term treatment of pediatric patients with genetically confirmed Prader-Willi syndrome. The FDA has received reports of fatalities after the initiation of somatropin therapy in pediatric patients with Prader-Willi syndrome and having one or more risk factors, including severe obesity, history of upper
airway obstruction or sleep apnea, and unidentified respiratory infection. Male sex may confer added risk to those with one or more of these risk factors. The FDA-approved labeling of Humatrope (Eli Lilly Co.) was revised to state that GH is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment. The FDA recommends that patients with Prader-Willi syndrome be evaluated for signs of upper airway obstruction and sleep apnea prior to therapy initiation. Treatment should be interrupted in patients showing signs of upper airway obstruction (including onset of increased snoring) and/or sleep apnea. All patients with Prader-Willi syndrome being treated with GH should be managed effectively for weight control and monitored for signs of respiratory infection. The FDA emphasizes the need for early diagnosis and aggressive treatment of these infections.

- Growth delay in children with Chronic renal insufficiency (CRI) may result from numerous physiologic derangements, including acidosis, secondary hyperparathyroidism, malnutrition, or zinc deficiency. Before initiation of GH treatment in patients with CRI, existing metabolic derangements (such as acidosis, secondary hyperparathyroidism, and malnutrition) should be corrected. Growth failure in children with chronic renal insufficiency is thought to be due to be multifactorial, with one of the factors being reduced sensitivity to GH rather than GH insufficiency. The dose of growth hormone generally recommended for children with chronic renal insufficiency (0.045-0.050 mg/kg/day) is higher than that for children with classic GH deficiency.

- In July 2001, Genotropin received approval as an orphan by the FDA for “long-term treatment of growth failure in children who were born small for gestational age (SGA) who fail to manifest catch-up growth by age 2.” Studies that were presented to the FDA and published controlled clinical trials have been relatively short term (2 to 6 years) and show, as would be expected, some normalization (“catch up”) of growth of children born small for gestational age. Short term clinical studies have shown that, while growth hormone administration induces catch-up growth in SGA children, it also increases skeletal maturation, so that little or no gain in final adult height would be expected (Stanhope, et al., 1991; Zeghir, et al., 1996; Coutant, et al., 1998; Vance & Mauras, 1999).

- The first randomized controlled clinical trial of GH treatment for SGA children reporting on final adult height showed that GH supplementation had induced catch-up growth, but a relatively small increase in final adult height that was less than the child’s genetic potential. Carel, et al. (2003) reported on a study of 168 short children born SGA who were randomized to receive either growth hormone supplementation until attainment of adult height or no treatment. The investigators report that this study differs from previous published studies of GH therapy for SGA children in that this is the first published randomized controlled clinical study that reports on final adult heights. In addition, this study differs from previous studies in that SGA children with GH deficiency were excluded.

- The investigators reported that the adult heights of GH-treated SGA patients were greater than those of control patients, with a difference of 0.6 standard deviation score (SDS) units (95%
confidence interval (CI), 0.2-0.9) between groups (Carel, et al., 2003). Although the gain in height statistically significant, it is small and treated SGA children remain relatively short compared to peers of normal stature. In this study, the difference observed between treated and control children was 2.7 cm [1.06 inches] in boys and 4.2 cm [1.65 inches] in girls.

- The observed effect of growth hormone supplementation on final adult height in patients born small for gestational age was no greater than the reported effect growth hormone supplementation on the final adult height of patients with idiopathic short stature (Carel, et al., 2003). The investigators summarize published studies of growth hormone supplementation in children with idiopathic short stature that show differences in adult height between treated and untreated children ranging from 0.6 SDS to 1.3 SDS.

- SGA children in this study initiated growth hormone treatment at a mean age of 10.5 years in girls and 12.5 years in boys, and the duration of treatment varied between 6 months and 3.5 years (Carel, et al., 2003). The investigators reported that although the treatment duration was shorter than in other studies of growth hormone supplementation for SGA children, the dose of GH supplementation was about 50% higher than used in most other studies, the effects of GH supplementation tend to decrease with duration of therapy, and the overall results were similar to other studies of GH supplementation of SGA children. The investigators concluded that although growth hormone supplementation increases final adult height in SGA children, the children remain short relative to their peers, and the clinical significance of this relatively small increase in height in improving the child's functional capacity, self perception and self-esteem is unclear.

- In addition, the long-term effects of growth hormone supplementation children born small of gestational age are unknown. Root (2002) explained that children born small for gestational age are at greatly increased risk for the development of insulin resistance and hyperinsulinism, which is associated with the “metabolic syndrome” of impaired carbohydrate tolerance progressing to type 2 diabetes mellitus, dyslipidemia, hypertension, increased mortality due to coronary artery disease, and in female hyperandrogenism and the polycystic ovarian syndrome. Growth hormone administration is also associated with insulin resistance and hyperinsulinism in IUGR children and other subjects, although these effects may be reversible. “Interestingly, the development of type 2 diabetes mellitus is not only related to subnormal fetal growth but also to increased rates of linear growth between 7 and 15 years of age. It is precisely at this age that [growth hormone] is to be administered to subjects with IUGR to increase the rate of linear growth, potentially increasing still further their risk for development of type 2 diabetes mellitus.”

- In an editorial, Silverstein and Shulman (2003) explained: “The use of [growth hormone] has only recently been approved for use in SGA children with short stature and normal growth hormone responses; hence, its use will likely increase in this population. Its effect on long-term insulin sensitivity in an already at-risk population and later development of type 2 diabetes is not yet known. In a study of more than 23,000 children registered in a pharmaco-epidemiological survey of GH-treated patients, Cutfield, et al. (2000) found an increase in type 2 diabetes (using
American Diabetes Association criteria) 6-fold greater than expected for the background populations. This risk may be even greater, more than 20-fold, when ethnically similar populations are used for comparison, and the less stringent World Health Organization criteria for abnormality are applied. These observations are cautionary in light of the now well-established risk of adult type 2 diabetes in low-birth-weight-for-age. Several studies have demonstrated an increased risk of insulin resistance and type 2 diabetes in adults who were small at birth. One study of 23,000 healthy U.S. men found a 2-fold increased risk of type 2 diabetes if they were SGA."

- The authors concluded that “[l]onger-term studies comparing the risk of type 2 DM and associated co-morbidities in rhGH-treated SGA children to untreated SGA children will be needed” and “[o]nly with extended follow-up can we be assured that the structural benefits outweigh the possible long-term risks” (Silverstein & Shulman, 2003).

- Stanhope (2000) commented on the use of growth hormone in children born small for gestational age and intrauterine growth retardation (IUGR) children: "More than any other condition associated with short stature and treated with GH particular caution should be applied to the long-term sequelae of children with IUGR. There is now convincing evidence that IUGR is a predisposing factor to the development of hypertension, diabetes and cardiovascular disease in adult life. As the dose of administered GH needs to be pharmacological, and in the order of two or three times replacement dose, long-term follow-up of such treated children into old age will be required for absolute reassurance that high dose GH treatment throughout childhood and adolescence is safe."

- Rapaport (2002) has noted, however, that the concern about insulin resistance has been shown not to result in abnormal glucose level or diabetes after as long as 6 years of treatment. Rapaport (2002) cited the results of a study that showed that insulin sensitivity parameters adversely affected during treatment with growth hormone revert to normal within 3 months of treatment. Rapaport also noted that growth hormone treatment of up to 6 years has not been shown to increase lipid levels or substantially increase blood pressure.

- Root (2002) noted that the benefits of growth hormone supplementation on the psychological well-being of person's growth small for gestational age are unknown. "There are as yet no data demonstrating any beneficial effect of treatment on their psychological well-being, educational advancement, or vocational attainment” (Root, 2002).

- According to the FDA-approved labeling for Genotropin brand of growth hormone, the recommended dose of growth hormone for SGA patients is 0.48mg/kg body weight per week (Pharmacia, 2003). Van Pareren, et al. (2003), however, reported on the results of a randomized controlled dose-ranging study of growth hormone in SGA children, and found no significant differences in outcomes of adult height SDS or gain in height between patients assigned to GH at the recommended dose of 0.48 mg/kg per week and patients assigned to GH therapy at half the usual recommended dose or 0.24 mg/kg per week.
• The FDA has approved growth hormone for the treatment of children with short stature associated with Noonan syndrome. The FDA approval was based upon the results of a two-year long prospective, open label, randomized, parallel group trial of growth hormone in 21 children with short stature associated with Noonan syndrome. An additional 6 children were not randomized, but did follow the protocol. After the initial two-year trial, children continued on Norditropin until final height. Retrospective final height and adverse event data were collected from 18 of the 21 subjects who were originally enrolled in the trial and the 6 who had followed the protocol without randomization. Historical reference materials of height velocity and adult height analyses of Noonan patients served as the controls. The 24 children (12 female, 12 male) ages 3 to 14 years received either 0.033 mg/kg/day or 0.066 mg/kg/day of growth hormone subcutaneously which, after the first 2 years, was adjusted based on growth response. In addition to a diagnosis of Noonan syndrome, key inclusion criteria included bone age determination showing no significant acceleration, prepubertal status, height SDS less than or equal to 2, and height velocity SDS less than 1 during the 12 months pre-treatment. Exclusion criteria were previous or ongoing treatment with growth hormone, anabolic steroids or corticosteroids, congenital heart disease or other serious disease perceived to possibly have major impact on growth, fasting plasma glucose greater than 120 mg/dL, or growth hormone deficiency. Patients obtained a final height gain from baseline of 1.5 and 1.6 SDS estimated according to the national and the Noonan reference, respectively. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at 18 years of age, while a height gain of 1.6 SDS (Noonan) corresponds to a mean height gain of 11.5 cm in boys and 11.0 cm in girls at 18 years of age. A comparison of height velocity between the two treatment groups during the first two years of treatment for the randomized subjects was 10.1 and 7.6 cm/year with 0.066 mg/kg/day versus 8.55 and 6.7 cm/year with 0.033 mg/kg/day, for year 1 and year 2, respectively. Age at start of treatment was a factor for change in height SDS (national reference). The younger the age at start of treatment, the larger the change in height SDS. Examination of gender subgroups did not identify differences in response to growth hormone. The FDA-approved labeling for Norditropin brand of growth hormone indicates that not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. Therefore, the FDA-approved labeling recommends that, prior to initiating growth hormone for a patient with Noonan syndrome, establish that the patient does have short stature. The FDA-approved labeling for Norditropin recommends a dosage of growth hormone of up to 0.066 mg/kg/day for pediatric patients with short stature associated with Noonan syndrome.

• Short stature homeobox-containing gene (SHOX) deficiency: SHOX is located on the distal ends of the X and Y chromosomes encoding a homeodomain transcription factor responsible for a significant proportion of long-bone growth. Children with mutations or deletions of SHOX, including those with TS who are haplo-insufficient for SHOX have variable degrees of growth impairment, with or without a spectrum of skeletal anomalies consistent with dyschondrosteosis.
• Blum et al (2007) examined the effectiveness of GH therapy in treating short stature associated with SHOX deficiency (SHOX-D). A total of 52 pre-pubertal children (24 male, 28 female; age of 3.0 to 12.3 years) with a molecularly proven SHOX gene defect and height below the 3rd percentile for age and gender (or height below the 10th percentile and height velocity below the 25th percentile) were randomized to either a GH-treatment group (n = 27) or an untreated control group (n = 25) for 2 years. To compare the GH treatment effect between patients with SHOX-D and those with TS, a third study group, 26 patients with TS aged 4.5 to 11.8 years, also received GH. Between-group comparisons of 1st-year and 2nd-year height velocity, height sd score, and height gain (cm) were performed using analysis of co-variance accounting for diagnosis, sex, and baseline age. The GH-treated SHOX-D group had a significantly greater 1st-year height velocity than the untreated control group (mean +/- se, 8.7 +/- 0.3 versus 5.2 +/- 0.2 cm/year; p < 0.001) and similar 1st-year height velocity to GH-treated subjects with TS (8.9 +/- 0.4 cm/year; p = 0.592). GH-treated subjects also had significantly greater 2nd-year height velocity (7.3 +/- 0.2 versus 5.4 +/- 0.2 cm/year; p < 0.001), 2nd-year height sd score (-2.1 +/- 0.2 versus -3.0 +/- 0.2; p < 0.001) and 2nd-year height gain (16.4 +/- 0.4 versus 10.5 +/- 0.4 cm; p < 0.001) than untreated subjects. The authors noted that patients with SHOX-D demonstrated marked, highly significant, GH-stimulated increases in height velocity and height SDS during the 2-year study period. The effectiveness of GH therapy in children with SHOX-D was equivalent to that observed in children with TS. They concluded that GH is effective in improving the linear growth of patients with various forms of SHOX-D.

• According to this guideline GH treatment for HIV patients with lipodystrophy syndrome is considered to be experimental and investigational. Even though preliminary observations suggest that recombinant human GH may lead to partial regression of fatty Buffalo humps and to a decrease in waist size secondary to truncal obesity, there is no definitive evidence of effectiveness of growth hormone for this indication.

• Constitutional delay of growth is characterized by normal prenatal growth followed by growth deceleration during infancy and childhood, which is reflected by declining height percentiles at this time. Children with constitutional delay have later timing of puberty than do their peers, allowing a longer period during which they are able to grow. Most commonly, these patients achieve normal adult height if no treatment is given. Although constitutional delay may be treated with GH, other effective and less costly treatments are available. In male patients, the literature shows testosterone or anabolic steroids are effective, and in female patients, low dose estrogens may be used.

• GH has been tried in several skeletal dysplasias associated with short stature, most notably achondroplasia. Although GH treatment of patients with achondroplasia has induced some growth acceleration, the literature shows the growth velocities achieved have been insufficient to produce catch-up growth. Thus, the height of these patients is not sufficiently altered so that it can approach the normal range for height.
- Kyphomelic dysplasia is a bone dysplasia with severe rhizomelic limb shortening, bowed extremities and dimples over the bowing. Other reported features include truncal shortening, short stature, and micrognathia. Intelligence is normal. There is spontaneous improvement of the bowing with growth. There is a lack of evidence on the use of GH in kyphomelic dysplasia.

- Osteogenesis imperfecta is caused by mutations in the gene for type I collagen. It is associated with bone demineralization and, in many instances, with retarded bone growth. GH has not been proven to be consistently effective in improving bone growth and mineralization in patients with this condition.

- Because short stature is characteristic of many syndromes, GH therapy has been attempted in several conditions, including Down syndrome, Fanconi syndrome, and Bloom syndrome. The high basal risk of malignant tumor or leukemia in these syndromes, however, has led many pediatric endocrinologists to recommend against the use of GH because the potential for GH to increase the risk of malignancy.

- GH is not recommended for treatment of acute catabolism, including preoperative and postoperative treatment, critically ill patients, and burn patients. The results of two clinical trials of GH therapy for critically ill patients showed a significantly higher mortality in GH-treated patients.

- Short-term acceleration of growth as a result of growth hormone therapy has also been reported in children with spinal cord defects, hypophosphatemic rickets, and cystic fibrosis; some of these children had impaired growth hormone production. However, no studies have prospectively assessed linear growth until achievement of final height. A discordance between stimulated and spontaneous GH secretion gave rise to the belief that GH neurosecretory dysfunction might exist in children, especially in those who had received low-dose cranial irradiation. Current guidelines do not recommend growth hormone for children with these conditions. Growth hormone treatment has been proposed for children with "partial" growth hormone insensitivity. However, there are no established criteria for diagnosis of partial growth hormone insensitivity, and there are no studies of the effectiveness of growth hormone for this condition.

- A systematic evidence review of interventions for chronic fatigue syndrome prepared by the UK National Health Service Centre for Reviews and Dissemination (2002) identified one small clinical trial of GH for chronic fatigue syndrome (Moorkens, et al., 1998), and found that “no conclusions regarding the effect of [growth hormone] treatment can be drawn from this trial.” An assessment prepared for the Agency for Healthcare Quality and Research also concluded that there is insufficient evidence of the effectiveness of GH as a treatment for chronic fatigue syndrome (Mulrow, et al., 2001).

- Limited data are available on the effectiveness of GH in an array of conditions in adult patients, including chronic catabolic states, older men and women, postoperative patients, those with states associated with excessive glucocorticoids, obese/morbid obese patients, osteoporosis, muscular dystrophy, and those with infertility, but no consistent benefit has been shown. Until
more data are available, however, guidelines do not recommend long-term GH therapy in these conditions.

- Growth failure often complicates Crohn's disease in childhood. Abnormalities in the GH/insulin-like growth factor-1 axis may occur. In a randomized controlled study, Calenda et al (2005) examined the effects of administered GH on growth in these patients. A total of 7 children (6 boys and 1 girl; age of 11.9 to 16 years) with Crohn's disease and growth failure were enrolled. In phase 1, patients were randomized to either GH (0.05 mg/kg per day) or placebo; in phase 2, patients who received placebo during the first year received GH for various time periods. Follow-up was every 3 months for up to 2 years. During placebo treatment (4 patients), mean height-for-age z score (haz) increased 0.23 in the first half year and 0.55 in the second half year. The mean improvement in haz during the first half year of GH treatment (7 patients) was 0.13; during the second half year (5 patients), haz decreased 0.01. Effects of GH varied among patients; 2 patients grew only when nutritional supplementation was added. Observed changes were not statistically significant. Serum insulin-like growth factor-1 levels correlated with height velocity. Only 2 patients later reached expected adult height. These investigators concluded that GH treatment at the dose given did not stimulate growth in children with Crohn's disease and short stature. Whether or not GH plus nutritional therapy would be effective in promoting sustained catch-up growth remains to be determined.

- Liu et al (2007) stated that human GH is widely used as an anti-aging therapy, although its use for this purpose has not been approved by the FDA and its distribution as an anti-aging agent is illegal in the United States. The authors evaluated the safety and effectiveness of GH therapy in the healthy elderly. They found that the literature published on randomized, controlled trials evaluating GH therapy in the healthy elderly is limited but suggests that it is associated with small changes in body composition and increased rates of adverse events. The authors concluded that, based upon this evidence, GH cannot be recommended as an anti-aging therapy. Furthermore, in an editorial on the use of GH secretagogues to prevent and treat the effects of aging, Blackman (2008) stated that many questions regarding the potential utility and safety of an oral GH secretagogue in older individuals remain unanswered. The clinical use of GH axis manipulation in the elderly should be restricted to carefully controlled clinical trials.

- While it has been documented that GH secretion is impaired in patients with ALS (Morselli et al, 2006), there is a lack of evidence to support the use of GH in these patients. Based on the known trophic effects of GH on nerve and muscle, Smith et al (1993) treated 75 patients with ALS for up to 18 months with synthetic human GH (hGH) or a placebo. The course of ALS was assessed serially using a quantitative (TQNE) neuromuscular and manual examination (MRC) and laboratory chemistries. Average insulin-related growth factor values increased from 1.2 to 2.3 U/ml in the treated group. Surprisingly, serum insulin levels did not increase. Hyperglycemia was noted in only 2 patients of the 38 patients receiving hGH, and this resolved with cessation of treatment. Over the 12-month treatment there were 11 deaths (6 controls, 5 treated). Survival analysis, performed approximately 12 months following cessation of treatment, did not reveal a
difference between the treatment and placebo group. The TQNE scores declined inexorably in both the control and treated group. Retrospective analysis of the TQNE data indicated a poor prognosis for patients who lost arm strength early. A correlation between the TQNE and MRC scores was evident at early stages of motor unit loss, less so when muscle weakness was advanced.

- In a meta-analysis, Tritos and Danias (2008) examined the safety effectiveness of rhGH therapy in congestive heart failure (CHF). These investigators searched 3 literature databases (MEDLINE, EMBASE, and the Cochrane Register) for clinical studies of rhGH therapy in CHF due to systolic dysfunction. Therapy with rhGH appears to have beneficial clinical effects (weighted mean difference [95 % CI] in CHF including improved exercise duration (1.9 mins [1.1 to 2.7]), maximum oxygen consumption (2.1 ml x kg(-1) x min(-1) [1.2 to 3.0]), and New York Heart Association class (-0.9 [-1.5 to -0.3]). There were salutary hemodynamic effects of rhGH therapy, including increased cardiac output (0.4 L x min(-1) [0.1 to 0.6]) and decreased systemic vascular resistance (-177 dyn x s x cm(-5) [-279 to -74]). Among rhGH-treated patients, left ventricular (LV) ejection fraction improved (4.3 % [2.2 to 6.4]). Despite increases in LV mass and wall thickness, there were no adverse effects on diastolic function. Subgroup analyses suggest that study design and treatment duration may influence some of the treatment effects. Most of the beneficial effects were driven by either uncontrolled or longer duration studies. Administration of rhGH therapy slightly increased the risk for ventricular arrhythmia; however, this finding was driven by a single small study. The authors concluded that rhGH therapy may have beneficial cardiovascular effects in CHF caused by LV systolic dysfunction. The possibility of pro-arrhythmia associated with rhGH therapy requires further study. They stated that larger randomized trials with longer treatment duration are needed to fully elucidate the safety and effectiveness of rhGH therapy in this patient population.

- In a review on the potential of cytokines and growth factors in the treatment of ischemic heart disease, Beohar et al (2010) stated that cytokine therapy promises to provide a non-invasive treatment option for ischemic heart disease. Several cytokines mobilize progenitor cells from the bone marrow or are involved in the homing of mobilized cells to ischemic tissue. The recruited cells contribute to myocardial regeneration both as a structural component of the regenerating tissue and by secreting angiogenic or anti-apoptotic factors, including cytokines. To date, RCTs have not reproduced the efficacy observed in pre-clinical and small-scale clinical investigations. Nevertheless, the list of promising cytokines continues to grow, and combinations of cytokines, with or without concurrent progenitor cell therapy, warrant further investigation. In particular, the authors noted that the effect of GH on myocardial growth, cardiac function, and IGF-1 levels in patients with non-ischemic or ischemic cardiomyopathy, and in mixed patient populations, has been examined in several small studies. Overall, the findings suggested that more research with GH or IGF-1 are needed, despite concerns regarding retinopathy and other potential long-term side effects.
• In a pilot study, Savastano et al (2009) examined if GH treatment prevents lean body mass (LBM) loss in the early post-operative period. A total of 24 women (body mass index: 44.4 +/- 7.6 kg/m\(^2\), aged 36.8 +/- 11.7 yrs) undergoing laparoscopic-adjustable silicone gastric banding (LASGB) and with GH deficiency after LASGB was included in the study. Group A (n = 12) included a standardized diet regimen and exercise program plus recombinant human GH (0.5 +/- 0.13 mg every day), and group B (n = 12) included a standardized diet regimen and exercise program. The follow-up duration was 6 months. The excess of body weight loss did not differ between groups A and B after 3 and 6 months. At 3 months, LBM loss was lower (p < 0.0001) and fat mass (FM) loss was higher (p = 0.02) in group A than group B. At 3 and 6 months, appendicular skeletal muscle mass loss was lower (p = 0.000) in group A than group B. At 3 (p = 0.0003 and 0.0005, respectively) and 6 months (p < 0.0001 and 0.0002, respectively), the percent changes of FM and LBM were significantly higher in group A than group B. In both groups, fasting and post-glucose area under the plasma concentration-time curve insulin significantly reduced. The homeostasis model assessment of insulin and insulin sensitivity indexes and total to high-density lipoprotein cholesterol ratio improved only in group A. The authors concluded that GH therapy for 6 months after LASGB reduces loss in LBM and appendicular skeletal muscle mass during a standardized program of low-calorie diet and physical exercise program, with improvement of lipid profile and without a deterioration of glucose tolerance. These preliminary findings need to be validated with well-designed studies.

• Idiopathic short stature is not considered to be a disease. A heterogeneous group of otherwise apparently normal children who are two or more standard deviations below the mean for height, but who have normal serum growth hormone responses to stimuli are classified as having genetic short stature, normal-variant familial short stature if their parents are short, constitutional delay of growth if there is a delay in skeletal maturation, idiopathic short stature, or neurosecretory growth hormone dysfunction. Treatment of these children with growth hormone is controversial with regard to both efficacy and ethics. Although GH therapy initially causes growth acceleration, it also accelerates pubertal development and advances bone age so that the duration of growth during puberty is shortened.

• One randomized controlled clinical trial (RCT) reported near final height (NFH) in of girls with idiopathic short stature. Two published studies reporting final height were prospective non-randomised controlled trials, one in peripubertal boys with subnormal integrated GH concentration and one in short, normal children. Results from the RCT including NFH found that treated girls were approximately 7.5 cm taller than randomised control girls and 6 cm taller than girls who refused consent. Other long term studies also suggest that final height is increased by GH treatment. However, the increase is between 2 cm to 7 cm, and treated individuals remain relatively short when compared with peers of normal stature.

• Short stature does not result in disease or functional limitation. Therefore, the use of growth hormone for this condition considered an enhancement of human performance or appearance rather than as a medically necessary treatment of disease. All normal and healthy populations
have genetic variation that will give rise to individuals with short stature. In a position statement, the American Academy of Pediatrics (1997) has noted that, by definition, children with short stature relative to their peers will always exist and targeting the current cohort for medical intervention will merely replace them with another cohort.

- Studies have demonstrated that the use of growth hormone in children with ISS increases growth rate and height and may minimally increase final height, as compared with baseline predicted values, but generally does not increase final height to normal levels. Some argue, however, that the major criterion for the use of GH in ISS should be improvement in the individual patient’s quality of life, regardless of whether final height is improved or not. But, whether short stature itself (with no pathological basis) correlates with psychosocial dysfunction of any kind is debated. An assessment conducted by NICE stated that “Most studies concur that shortness alone does not necessarily result in negative psychological consequences. Many studies have found no relation between degree of shortness and psychological problems.”

- In addition, there is no adequate evidence from randomized prospective clinical studies demonstrating clinically significant improvements in functional status or reductions in psychological dysfunction in children with idiopathic short stature who are treated with growth hormone. In addition, some experts maintain, however, that psychological dysfunction may be better addressed by psychological intervention and counseling than by the use of growth hormone.

- In a position statement on the use of growth hormone in children, the American Academy of Pediatrics (1997) has stated: “In many other instances, the use of GH has been justified on the grounds that persons with short stature (defined as more than 2 SDs below the mean for age and sex) experience stigma in an affluent society. These children are often teased in school about their short stature; moreover, empiric evidence indicates that numerous social benefits are linked to tall stature. In some children, short stature may be part of an acquired or inherited disorder. For these children, growth augmentation is viewed as an avenue to normalcy. Despite these concerns and the fairly extensive use of recombinant human GH in these patient groups, no objective current data demonstrate the psychosocial benefits of hormonal therapy in this group of children and few physiologic data demonstrate an effect on final adult height. The above considerations have led some to question whether research on the use of human GH to attempt to increase the final adult height of non-GH-deficient children is warranted.”

- “It is also unclear whether GH therapy reduces the psychosocial problems that very short children may experience. Indeed, there is evidence that GH therapy exacerbates these problems in some children owing to unrealistic expectations concerning the therapeutic outcome and enhanced feelings that something is ‘wrong’ with them.”

- “There is also the question of how to define treatment ‘success.’ Short stature is a characteristic that must be defined relative to the general population in which people will always be of different heights. Thus, even if GH therapy were available to and effective in all 'short' stature children, a
population of short children will still exist; they will simply be a few inches taller than those in the former population.”

- Root (2002) stated that “[m]any studies document the psychological good health and normal educational progress of healthy children with idiopathic short stature. In fact, short children with behavioral problems and learning disabilities are referred more frequently for endocrine evaluation than are their normally achieving age and height peers. Furthermore, it is quite possible that the extensive testing, daily injections, and frequent medical visits needed during [growth hormone] administration may imprint upon the child (and reinforce to the parent) a negative concept of his/her self worth.”

- There is no adequate evidence that short stature, in and of itself, is associated with functional limitations. A systematic evidence review prepared for the Agency for Healthcare Research and Quality evaluated the relationship of short stature in childhood with functional limitations, including intelligence, academic achievement, behavior, visual-motor perception, and psychomotor development (Wheeler, et al., 2003). The assessment concluded that there was no evidence that short stature in children is associated with severe functional limitations.

- Acromegaly is a potentially life-threatening disease triggered by an excess of GH. Symptoms include headaches, profuse sweating, swelling, joint disorders, changes in facial features, as well as enlarged hands, feet and jaw. If untreated, patients with acromegaly often have a shortened life-span because of heart and respiratory diseases, diabetes mellitus and cancer.

- In 2003, the FDA approved pegvisomant (Somavert) for the treatment of acromegaly in patients who have had an inadequate response to existing therapies. Pegvisomant, a polyethylene glycol derivative of human GH, is the first in a new class of drugs called GH receptor antagonists. It competes with endogenous GH for the receptor and results in suppression of serum insulin-like growth factor (IGF-1). Clinical studies have shown that pegvisomant normalized concentrations of IGF-I in more than 90 % of patients by blocking the effects of GH. The most commonly reported adverse effects with pegvisomant were injection site reactions, sweating, headache and fatigue.

- Subcutaneous atrophy and central fat accumulation are common among human immunodeficiency virus (HIV)-infected patients receiving anti-retroviral therapy (ART), and may be accompanied by dyslipidemia and insulin resistance. These fat changes, although commonly referred to together as lipodystrophy, are best considered as separate disorders, with distinct pathogeneses and treatment approaches. These morphological and metabolic abnormalities first appeared after introduction of protease inhibitors more than 10 years ago, but research has demonstrated that their pathogenesis is multi-factorial, with contributions from other ART, patient-related factors, and HIV itself. Switching to a less toxic highly active ART regimen has shown partial effectiveness for the management of fat atrophy and lipid abnormalities. Lifestyle modification or surgical approaches are the treatment of choice for lipohypertrophy, although novel therapies targeting the GH axis show promise (Brown, 2008).

- Tesamorelin, a synthetic GH releasing factor analog (GHRH[1-44]), has been developed as a potential treatment for a variety of conditions that may be associated with a relative deficiency of
GH including HIV-related lipodystrophy, a condition in which excess fat develops in different areas of the body, most notably around the liver, stomach, and other abdominal organs (known as visceral adipose tissue [VAT]); and is often associated with many ART used to treat HIV.

- Falutz and colleagues (2008) evaluated long-term safety and effects of tesamorelin in the treatment of HIV patients with abdominal fat accumulation. These patients with central fat accumulation in the context of ART were randomized to tesamorelin 2 mg (n = 273) or placebo (n = 137) subcutaneously daily for 26 weeks. At week 26, patients originally on tesamorelin were re-randomized to 2 mg tesamorelin (T-T group, n = 154) or placebo (T-P group, n = 50), whereas patients originally on placebo were switched to tesamorelin (P-T group, n = 111). Tesamorelin was generally well-tolerated. The prevalence of adverse events and serious adverse events during the extension phase was comparable with the initial phase. Changes in glucose parameters over 52 weeks were not clinically significant and similar to those after 26 weeks. The change in VAT was sustained at -18% over 52 weeks of treatment (p < 0.001 versus baseline) as was the change in triglycerides (-51 mg/dl, p < 0.001 versus baseline). Similar sustained beneficial effects were seen for total cholesterol, but high-density lipoprotein decreased minimally over 52 weeks. Upon discontinuation of tesamorelin, VAT re-accumulated. The authors concluded that treatment with tesamorelin was generally well-tolerated and resulted in sustained decreases in VAT and triglycerides over 52 weeks without aggravating glucose. Although effects on VAT are sustained during treatment for 52 weeks, these effects do not last beyond the duration of treatment.

- In a randomized, placebo-controlled trial with a safety extension, Falutz and associates (2010a) examined the effects of tesamorelin in HIV-infected patients with central fat accumulation. A 12-month study of 404 HIV-infected patients with excess abdominal fat in the context of ART was conducted between January 2007 and October 2008. The study consisted of 2 sequential phases. In the primary efficacy phase (months 0 to 6), patients were randomly assigned to receive tesamorelin [2 mg subcutaneous (SC) every day] or placebo in a 2:1 ratio. In the extension phase (months 6 to 12), patients receiving tesamorelin were rerandomized to continue on tesamorelin (2 mg SC every day) or switch to placebo. Patients initially randomized to placebo switched to tesamorelin. Patients and investigators were blinded to treatment assignment throughout the study. The primary end point was VAT. Secondary end points included body image, IGF-I, safety measures, including glucose, and other body composition measures. Visceral adipose tissue decreased by -10.9% (-21 cm²) in the tesamorelin group versus -0.6% (-1 cm²) in the placebo group in the 6-month efficacy phase, p < 0.0001. Trunk fat (p < 0.001), waist circumference (p = 0.02), and waist-hip-ratio (p = 0.001) improved, with no change in limb or abdominal SC fat. Insulin-like growth factor-1 increased (p < 0.001), but no change in glucose parameters was observed. Patient rating of belly appearance distress (p = 0.02) and physician rating of belly profile (p = 0.02) were significantly improved in the tesamorelin versus placebo-treated groups. The drug was well-tolerated. Visceral adipose tissue was reduced by approximately 18% (p < 0.001) in patients continuing tesamorelin for 12 months. The initial improvements over 6 months in VAT were rapidly lost in those switching from tesamorelin to placebo. The authors concluded
Falutz et al (2010b) performed a pooled analysis of 2 phase-III studies of tesamorelin in ART-treated HIV patients with excess abdominal fat. The 2 multi-center, international studies were a 26-wk randomized, placebo-controlled primary intervention phase that was followed by a 26-wk safety extension. A total of 806 ART-treated HIV patients with excess abdominal fat were randomized in a 2:1 fashion to receive tesamorelin 2 mg (n = 543) or placebo (n = 263) SC daily. At wk 26, patients initially on tesamorelin were re-randomized to 2 mg tesamorelin (T-T group, n = 246) or placebo (T-P, n = 135) for an additional 26 weeks, whereas patients on placebo were switched to tesamorelin (P-T, n = 197). Tesamorelin at a dose of 2 mg or identical placebo, SC, was given daily. Main outcome measure was percent change in VAT by computed tomography scan at week 26. At week 26, VAT decreased significantly in tesamorelin-treated patients (-24 +/- 41 versus 2 +/- 35 cm²), tesamorelin versus placebo, p < 0.001; treatment effect, -15.4 %). No significant changes were observed in abdominal SC adipose tissue (-2 +/- 32 versus 2 +/- 29 cm²), p = 0.08; treatment effect, -0.6 %). Treatment with tesamorelin resulted in significant decreases in triglycerides (-37 +/- 139 versus 6 +/- 112 mg/dl, p < 0.001; treatment effect, -12.3 %) and cholesterol to high-density lipoprotein ratio (-0.18 +/- 1.00 versus 0.18 +/- 0.94, p < 0.001; treatment effect, -7.2 %) versus placebo. Tesamorelin improved body image [belly appearance distress (p = 0.002)], patient rating of belly profile (p = 0.003), and physician rating of belly profile (p < 0.001). Mean IGF-I increased 108 +/- 112 versus -7 +/- 64 ng/ml (p < 0.001 versus placebo). At week 52, decreases in VAT [-35 +/- 50 cm² (-17.5 +/- 23.3%), waist circumference (-3.4 +/- 6.0 cm), triglycerides (-48 +/- 182 mg/dl), cholesterol (-8 +/- 38 mg/dl), and non-high-density lipoprotein (-7 +/- 38 mg/dl) were maintained (all p < 0.001 versus original baseline) in the T-T group. Treatment with tesamorelin was generally well-tolerated. No clinically meaningful differences were observed between groups in glucose parameters at weeks 26 and 52. The authors concluded that treatment with tesamorelin reduces VAT and maintains the reduction for up to 52 weeks, preserves abdominal sc adipose tissue, improves body image and lipids, and is overall well-tolerated without clinically meaningful changes in glucose parameters.

On November 10, 2010, the FDA approved tesamorelin (Egrifta) to treat HIV patients with lipodystrophy. Egrifta was approved to induce and maintain a reduction of excess visceral abdominal fat in HIV-infected patients with lipodystrophy. Tesamorelin, the first FDA-approved treatment for lipodystrophy, is administered in a once-daily injection. The recommended dose of Egrifta is 2 mg injected subcutaneously once a day. The most commonly reported side effects associated with the use of tesamorelin included joint pain (arthralgia), skin redness and rash at the injection site (erythema and pruritus), stomach pain, swelling, and muscle pain (myalgia). Worsening blood sugar control occurred more often in patients treated with tesamorelin than with placebo.
• The product labeling of Egrifta states: "There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking Egrifta." The product labeling also states that Egrifta has a weight-neutral effect, and is not indicated for weight loss management. The labeling states that the long term cardiovascular effects of Egrifta have not been studied.

• Sivakumar et al (2011) noted that HIV-associated lipodystrophy is a disorder of fat metabolism that occurs in patients with HIV infection. It can cause metabolic derangements and negative self-perceptions of body image, and result in non-compliance with highly active anti-retroviral therapy (HAART). Growth hormone axis drugs have been evaluated for treatment of this disorder, but no systematic review has been conducted previously. These investigators compared the effects of GH axis drugs versus placebo in changing visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and lean body mass (LBM) in patients with HIV-associated lipodystrophy. They searched MEDLINE (1996 to 2009), CENTRAL (Issue 4, 2009), Web of Science, Summons, Google Scholar, the FDA website, and Clinicaltrials.gov from October 13, 2009 to June 7, 2010. These researchers excluded newspaper articles and book reviews from the Summons search; this was the only search limitation applied.

• They also manually reviewed references of included articles. Inclusion criteria were as follows: RCT; study participants with HIV-associated lipodystrophy; intervention consisting of GH, GHRH, tesamorelin or IGF-1; study including at least 1 primary outcome of interest: change in VAT, SAT or LBM. Two independent reviewers extracted data and assessed study quality using a standardized form. The authors of one study were contacted for missing information. The main effect was calculated as a summary of the mean differences in VAT, SAT and LBM between the intervention and placebo groups in the included studies. Subgroup analyses were performed to assess different GH axis drug classes. A total of 10 RCTs including 1,511 patients were included in the review. All had a low risk of bias and passed the test of heterogeneity for each primary outcome.

• Compared with placebo, GH axis treatments decreased VAT [weighted mean difference (WMD) -25.20 cm(2); 95% CI: -32.18 to -18.22 cm(2); p < 0.001] and increased LBM (WMD 1.31 kg; 95% CI: 1.00 to 1.61 kg; p < 0.001], but had no significant effect on SAT mass (WMD -3.94 cm(2); 95% CI: -10.88 to 3.00 cm(2); p = 0.27]. Subgroup analyses showed that GH had the most significant effects on VAT and SAT, but none on LBM. The drugs were well-tolerated but statistically significant side effects included arthralgias and edema.

• The authors concluded that the findings of this review indicated that, based on the findings of the 10 included studies, GH axis treatments were effective in reducing VAT and increasing LBM in patients with HIV-associated lipodystrophy. However, clinicians must decide whether the attributed benefits are clinically significant, considering the costs and potential risks of GH axis treatments. A limitation of this study was the small number of studies available of each GH axis drug class.

• Also, an UpToDate review on "Treatment of HIV-associated lipodystrophy" (Glesby, 2013) states that "Recombinant human growth hormone (rhGH) is known to be lipolytic; patients with AIDS-
related wasting treated with supraphysiologic doses of rhGH (Serostim) lost body fat while gaining lean body mass. This observation provided the rationale for studying the efficacy of rhGH in the treatment of patients with fat accumulation initially in pilot studies and ultimately in randomized, placebo-controlled trials....The major side effects of rhGH are fluid retention, arthralgias, myalgias, and, less commonly, carpal tunnel syndrome and diabetes mellitus.

- Of note, studies of rhGH for increased truncal fat have generally excluded patients with impaired fasting glucose and impaired glucose tolerance on a standard, 75 gram 2-hour oral glucose tolerance test, since these patients may be at increased risk of developing rhGH-induced hyperglycemia and diabetes. While maintenance therapy with rhGH after an induction phase was superior to placebo in the phase III trial, the optimal strategy for maintaining visceral fat reduction that may be achieved from rhGH induction is uncertain. rhGH is not currently indicated for the treatment of HIV-associated truncal obesity and its clinical development for this indication appears to be on hold”.

- Le Corvoisier et al (2007) systematically reviewed and analyzed all RCTs and open studies of sustained GH treatment in patients with congestive heart failure (CHF). A total of 12 trials were identified in 3 databases. These researchers conducted a combined analysis of GH effects on cardiovascular parameters using the overall effect size to evaluate significance and computing the weighted mean differences with and without treatment to assess effect size.

- Growth hormone treatment significantly modified morphological cardiovascular parameters [inter-ventricular septum thickness, +0.55 (S.D., 0.43) mm (p < 0.001); posterior wall thickness, +1.01 (0.44) mm (p < 0.01); left ventricle (LV) end-diastolic diameter, -2.02 (1.22) mm (p < 0.01); and LV end-systolic diameter, -5.30 (2.33) mm (p < 0.05)]; LV and systemic hemodynamics [LV end-systolic wall stress, -38.9 (13.3) dynes/cm(2) (p < 0.001); LV ejection fraction (LVEF), +5.10 (1.74) % (p < 0.05); and systemic vascular resistance, +195.0 (204.5) dyn x sec(-1) x cm(-5) (p < 0.01)]; and functional parameters [New York Heart Association (NYHA) class, -0.97 (0.23) (p < 0.01); exercise duration, +103.7 (37.6) sec (p < 0.001); and maximal oxygen uptake, +2.48 (1.76) ml/kg x min (p < 0.01)]. Subgroup analysis and meta-regression showed significant relationships between the IGF-I response and GH treatment effects.

- The authors concluded that the findings of this meta-analysis suggested that GH treatment improves several relevant cardiovascular parameters in patients with CHF. However, these results must be confirmed by a large randomized placebo-controlled trial on hemodynamic, morphological, and functional parameters during long-term high-dose GH treatment of patients with CHF.

- Kemp and Frindik (2011) noted that GH was first used to treat a patient in 1958. For the next 25 years it was available only from cadaver sources, which was of concern because of safety considerations and short supply. In 1985, GH produced by recombinant DNA techniques became available, expanding its possible uses. Since that time there have been 3 indications approved by the FDA for GH-deficiency states and 9 indications approved for non-GH-deficiency states. In 2003 the FDA approved GH for use in ISS, which may indirectly cover other diagnoses that have short
stature as a feature. However, coverage for GH therapy is usually more reliably obtainable for a specific indication, rather than the ISS indication. Possible future uses for GH therapy could include the treatment of syndromes such as Russell-Silver syndrome or chondrodystrophy.

- Other non-short-stature indications could include wound healing and burns. Other uses that have been poorly studied include aging and physical performance, in spite of the interest already shown by elite athletes in using GH. The safety profile of GH developed over the past 25 years has shown it to be a very safe hormone with few adverse events associated with it. The challenge for the future is to follow these patients into adulthood to determine whether GH therapy poses any long-term risks.

- Kirk (2012) stated that GH therapy has now been available for over 5 decades, with all GH now biosynthetically produced, and administered by daily injection. In the United Kingdom, pediatric GH is currently licensed in 6 different conditions: (i) GHD, (ii) TS, (iii) SGA, (iv) PWS, (v) CRI, and (vi) short stature due to SHOX deficiency; all of these have been ratified by the most recent (2010) NICE review. While the primary purpose of pediatric GH therapy in most indications is to improve short and long-term growth, in others (e.g., PWS) it has a role in improvement of body composition.

- Khadilkar et al (1999) stated that growth failure and anterior pituitary dysfunction are clinical features of the CHARGE and VATER associations. These researchers investigated pituitary dysfunction as a potential cause of poor growth in a series of 4 and 3 patients with the CHARGE and VATER associations, respectively, who had height SDS less than -2. Five of the 7 patients had associated subnormal growth velocity SDS. Patients were investigated with a combination of dynamic and basal endocrine tests. All patients were found to be normo-natremic and to have normal basal thyrotroph and stimulated corticotroph function. The 1 peri-pubertal patient had evidence of biochemical gonadotroph dysfunction. Although 2 patients had marginally low stimulated serum GH responses to glucagon stimulation testing, this was associated with either normal growth velocity or normal serum IGFBP-3 concentrations.

- Thus, somatotroph dysfunction could not be demonstrated unequivocally in any patient. The authors concluded that poor childhood linear growth in the CHARGE and VATER associations does not appear to be associated with pituitary dysfunction.

- Kanaka-Gantenbein (2001) noted that skeletal dysplasias are genetic disorders of bone and cartilage development, mainly characterized by disproportionate short stature. Achondroplasia is the commonest and best described form of skeletal dysplasia, leading to a mean final height of 131 +/- 5.6 cm for males and 124 +/- 5.9 cm for females. Growth hormone has been used in different studies in patients with achondroplasia in order to ameliorate their height, and short-term results ranged from rather positive to moderate. However, disproportionate advancement of bone age has been observed that can compromise the positive effect of such treatment. Furthermore, concern exists about the aggravation of body disproportion necessitating a later leg-lengthening procedure in order to achieve proportionate adult stature. In hypochondroplasia, GH treatment seems to give better results when administered at puberty.
No data on final height yet exist, however, so that more studies with greater numbers of patients need to be performed before a consensus on GH use in achondroplasia and hypochondroplasia can be reached. Other forms of skeletal dysplasias are quite rare, so that no conclusion on GH use in such patients can be drawn. Finally, in osteogenesis imperfecta, GH administration significantly ameliorates bone density but does not clearly seem to affect final height positively.

Francomano (2005), Chief of the Medical Genetics Branch of the National Human Genome Research Institute/National Institutes of Health stated that "Trials of growth hormone (GH) therapy in hypochondroplasia have shown mixed results. Several reports indicate that some individuals respond well with increased proportional height velocity, others respond with increased disproportionate growth, and some do not respond [Appan et al 1990, Mullis et al 1991, Bridges et al 1991]. These differences in individual responses may result from genetic heterogeneity and indicate a need for stratification of affected individuals with regard to genetic etiology (e.g., those with FGFR3 mutations and those without). While a response to GH has been sustained in some individuals for as long as 6 years [Bridges & Brook 1994], data about final adult height in these individuals are not yet available and the ultimate success of this approach remains uncertain.

Meyer et al [2003] emphasized the importance of considering pubertal development in assessing the response to GH stimulation testing. Tanaka et al [2003] reported data suggesting that children with hypochondroplasia may have a greater response to GH therapy than children with achondroplasia. Kanazawa et al [2003] also reported a response to GH among children with hypochondroplasia. Growth hormone therapy is still considered experimental and controversial”.


In a pilot study, Rothenbuhler et al (2012) evaluated the growth promoting effect of a recombinant growth hormone (rGH) treatment protocol adjusted on IGF-1 dosing in children affected by the most severe forms of FGFR3 N540K-mutated hypochondroplasia. This study included 6 children (mean age, 2.6 +/- 0.7 years; mean height SDS, -3.0 +/- 0.5) with the N540K mutation of FGFR3 gene who received an rGH dosage titrated to an IGF-1 level close to 1.5 SDS of the normal range. Recombinant GH therapy was interrupted 1 day per week, 1 month per year, and 6 months every 2 years. The mean height SDS increased by 1.9 during the 6.1 +/- 0.9-year study period, reaching -0.8 to -1.3 at age 8.7 +/- 1 years. The mean +/- SDS baseline IGF-1 value was -1.6 +/- 0.5 before rGH treatment and 1.4 +/- 0.3 during the last year of observation. The average cumulative rGH dose was 0.075 +/- 0.018 mg/kg/day (range of 0.059 to 0.100 mg/kg/day).

Trunk/leg disproportion was improved. The authors concluded that IGF-1-dosing rGH treatment durably improves growth and reduces body disproportion in children with severe forms of hypochondroplasia. The findings of this small, non-randomized study need to be validated by well-designed studies with long-term follow-up.

In a review on "Novel agents and approaches for stem cell mobilization in normal donors and patients", Bakanay and Demirer (2012) listed GH as one of the investigational agents. They noted
that in the future, thrombopoietin-receptor agonists may be potential adjuncts to granulocyte colony-stimulating factor in poor mobilizers.

- Non-classic congenital adrenal hyperplasia (NCCAH), also termed as late onset of CAH, is a very mild form of 21-hydroxylase deficiency. The incidence of disease is estimated at 0.1% of population (Jesic et al, 2004). Ghizzoni and colleagues (1996) reported that NCCAH is associated with "slight" alterations in GH secretion. The Endocrine Society's clinical practice guideline on "Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency" (Speiser et al, 2010) and an UpToDate review on "Diagnosis and treatment of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency" (Nieman, 2012) did not mention the use of GH therapy.

- Allen et al (1998) stated that growth failure is common during long term treatment with glucocorticoids (GC) due to blunting of GH release, IGF-I bioactivity, and collagen synthesis. These effects could theoretically be reversed with GH therapy. The National Cooperative Growth Study database (n = 22,005) was searched for children meeting the following criteria: (i) pharmacological treatment with GC and GH for more than 12 months, (ii) known type and dose of GC, and (iii) height measurements for more than 12 months. A total of 83 patients were identified. Monitoring of glucose, insulin, IGF-I, IGF-binding protein-3, type 1 procollagen, osteocalcin, and glycosylated hemoglobin levels was performed in a subset of patients. Stimulated endogenous GH levels were less than 10 microg/L in 51% of patients, and less than 7 microg/L in 37% of patients. The mean GC dose, expressed as prednisone equivalents, was 0.5 +/- 0.6 mg/kg day.

- Baseline evaluation revealed extreme short stature (mean height SD score = -3.7 +/- 1.2), delayed skeletal maturation (mean delay of 3.1 yrs), and slowed growth rates (mean of 3.0 +/- 2.5 cm/yr). After 12 months of GH therapy (mean dose of 0.29 mg/kg x weeks), mean growth rate increased to 6.3 +/- 2.6 cm/yr, and height SD score improved by 0.21 +/- 0.4 (p < 0.01). During the second year of GH therapy (n = 44), the mean growth rate was 6.3 +/- 2.0 cm/yr. Prednisone equivalent dose and growth response to GH therapy were negatively correlated (r = -0.264; p < 0.05). Plasma concentrations of IGF-I, IGF-binding protein-3, procollagen, osteocalcin, and glycosylated hemoglobin increased with GH therapy, whereas glucose and insulin levels did not change.

- The authors concluded that the growth-suppressing effects of GC were counter-balanced by GH therapy; the mean response is a doubling of baseline growth rate. However, responsiveness to GH is negatively correlated with GC dose. Glycosylated hemoglobin levels increased slightly, but glucose and insulin levels were not altered by GH therapy.

- An UpToDate review on "Treatment of fibromyalgia in adults not responsive to initial therapies" (Goldenberg, 2013) lists GH as one of the investigational approaches for the treatment of fibromyalgia. It notes that "Growth hormone, both as monotherapy and as adjunctive therapy, improves symptoms of fibromyalgia, although cost concerns and the need for long-term efficacy and safety data are considerations limiting its use".
Intrauterine growth restriction (IUGR) refers to a condition in which a fetus is unable to achieve its genetically determined potential size (Ross, 2013). This functional definition seeks to identify a population of fetuses at risk for modifiable but otherwise poor outcomes. This definition intentionally excludes of fetuses that are small for gestational age (SGA) but are not pathologically small. Not all fetuses that are SGA are pathologically growth restricted and, in fact, may be constitutionally small. Similarly, not all fetuses that have not met their genetic growth potential are SGA.

In a Cochrane review, Say and colleagues (2003) evaluated the effects of hormone administration for suspected impaired fetal growth and perinatal outcome. These investigators searched the Cochrane Pregnancy and Childbirth Group trials register (November 1, 2002). Acceptably controlled trials of hormone administration for suspected impaired fetal growth which report fetal, perinatal or maternal outcomes were selected for analysis. Eligibility and trial quality were assessed. No studies were included since none of the potentially relevant trials reported clinical outcomes. The authors concluded that there is insufficient evidence to evaluate the clinical use of hormone administration for suspected impaired fetal growth. Furthermore, an UpToDate review on "Fetal growth restriction: Evaluation and management" (Resnik, 2013) does not mention the use of GH as a management tool.

Gabrielli et al (2000) noted that Kabuki syndrome is characterized by mental retardation (mild-to-moderate), skeletal anomalies, typical facial appearance and post-natal growth deficiency. The researchers described 2 patients with Kabuki syndrome and proven GH deficiency. The 1st patient has been on GH replacement therapy for 4 years; the 2nd for 11 years. There is insufficient evidence to support the use of GH for the treatment of patients with Kabuki syndrome.

**FDA-Approved Indication Brands**
- Growth failure associated with chronic renal insufficiency Nutropin, Nutropin AQ
- Growth failure associated with Noonan syndrome Norditropin
- Growth failure associated with Prader-Willi syndrome Genotropin
- Growth failure associated with Turner syndrome Genotropin, Humatrope, Norditropin, Nutropin, and Nutropin AQ
- Growth failure in children due to inadequate secretion of endogenous growth hormone Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, and Tev-Tropin
- Children born small for gestational age (SGA) who fail to manifest catch-up growth Genotropin, Norditropin, Humatrope
- Growth hormone deficiency in adults Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, and Saizen
- Idiopathic short stature* Genotropin, Humatrope, Nutropin, and Nutropin AQ
- Short bowel syndrome Zorbutive
- Short stature homeobox-containing gene deficiency Humatrope
- Wasting or cachexia associated with HIV Serostim

**Normal Results of a GH Stimulation Test:**
ActiveHealth Management  
Medical Management Guidelines

- Normal peak value -- at least 10 ng/ml
- Indeterminate -- 5 to 10 ng/ml
- Subnormal -- 5 ng/ml

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Footnotes

[A] (Note: A normal value rules out hGH deficiency; in some laboratories, the normal level is 7 ng/ml.) [ A in Context Link 1 ]

Codes

CPT® or HCPCS: 38205, 38206, J2940, J2941, S9558