GROWTH HORMONE DEFICIENCY IN CHILDREN

CHI Formulary Indication Review

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

AH	Adult Height
CADTH	Canadian Agency for Drugs and Technologies in Health
CGHD	Child Growth Hormone Deficiency
CHI	Council for Health Insurance
DXA	Dual X-ray Absorptiometry
GCC	Gulf Cooperation Council
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GHRH	Growth Hormone-Releasing Hormone
HAS	Haute Autorité de Santé
hGH	Human Growth Hormone
IGF-1	Insulin-like Growth Factor-1
IGHD	Isolated Growth Hormone Deficiency
IQWIG	Institute for Quality and Efficiency in Healthcare
ITT	Insulin Tolerance Test
KES	Korean Endocrine Society
KSPE	Korean Society of Pediatric Endocrinology
LAGH	Long-Acting Growth Hormone
MPHD	Multiple Pituitary Hormone Deficiencies
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
QoL	Quality of Life
RhGH	Recombinant Human Growth Hormone
SCFE	Slipped Capital Femoral Epiphysis
SDS	Standard Deviation Scores
SPIGFD	Severe Primary Insulin-Like Growth Factor-1 Deficiency
TH	Target Height

Executive Summary

Growth hormone deficiency (GHD) is a rare disorder characterized by the inadequate secretion of growth hormone (GH) from the anterior pituitary gland subsequently leading to growth failure. GHD can be **congenital**, present from birth, resulting from genetic mutations or from structural defects in the brain. It can also be **acquired** later in life as a result of trauma, infection, radiation therapy, or tumor growth within the brain. A third category, **idiopathic** GHD, has no known or diagnosable cause. Childhood-onset GHD (CGHD) may be all three: congenital, acquired, or idiopathic. It results in growth retardation, short stature, and maturation delays reflected by the delay of lengthening of the bones of the extremities that is inappropriate to the chronological age of the child[1].

CGHD has an estimated prevalence between 1 in 3,500 and 1 in 10,000 children[2] and is more commonly diagnosed in boys[3]. In KSA, as of 2022, the overall prevalence rate of short stature was found to be 33.68%, and growth hormone deficiency was the most common endocrinological cause for short stature (9.7%)[4]. CGHD is usually idiopathic, but about 25% of patients have an identifiable etiology[5]. Establishing the correct diagnosis remains key in children with short stature[6].

Manifestations of growth hormone deficiency depend on the patient's age, the underlying etiology, and the specific hormone deficiencies. GHD typically manifests as growth failure, sometimes along with delay in tooth development. Height is below the 3rd percentile, and growth velocity is < 6 cm/year before age 4 years, < 5 cm/year from age 4 to 8 years, and < 4 cm/year before puberty. Skeletal maturation, assessed by bone age determination, is > 2 years behind chronologic age[5].

If left untreated, GHD may lead to short stature, delayed puberty, decreased bone mineral density, increased cardiovascular risk factors, impaired energy levels and quality of life[7].

This report compiles all clinical and economic evidence related to Child Growth Hormone Deficiency according to the relevant sources. The ultimate objective of issuing CGHD guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to CGHD patients in Saudi Arabia**. The main focus of the review was on Gulf Cooperation Council (GCC), North American and international guidelines issued within the last ten years. To elaborate, GCC guidelines detailed screening, investigation and management of GHD in children as well as in patients transitioning to adulthood. North American guidelines further emphasized on diagnosis and management of CGHD all while tackling the safety parameters of treatment approaches. Furthermore, International guidelines addressed diagnosis, benefits and risks of management as well as transitional care in depth. In addition, recent systematic reviews and meta-analyses

were tackled; thereby providing an in-depth understanding of the different CGHD characteristics.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in Child Growth Hormone Deficiency were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The management of CGHD involves a **multidisciplinary approach**. **Drug therapy is an integral component for the management of Child Growth Hormone Deficiency.** The major goal for the CGHD pharmacological approach is acceleration of growth velocity to promote normalization of growth and stature during childhood and attainment of normal adult height (AH) appropriate for the child's genetic potential.[8] The standard pharmacological interventions include daily injections of synthetic growth hormone. Results are often seen as soon as 3 to 4 months after treatment starts. The treatment lasts several years, usually until late puberty when growth is completed.[9] Newer agents for the treatment of CGHD include SFDA registered agents as Somapacitan, Mecasermin and Somatrogon-ghla. Non-SFDA registered agents include Lonapegsomatropin-tcgd as well as Vosoritide, a newly approved agent for patients with achondroplasia.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of Child Growth Hormone Deficiency.

Major recommendations for suggested drug therapies are summarized in tables 1 and 2.

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Table 1. SFDA-Registered Drugs for the Treatment of Growth Hormone Deficiency in Children

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Somatropin	Treatment of children with growth failure due to growth hormone deficiency	**1st**	Strong Recommendation[10]	Positive Recommendation from HAS[11].
Somapacitan	For the replacement of endogenous growth hormone in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency	**1st**	Strong Recommendation[12]	Positive Recommendation from PBAC[13].
Somatrogon-ghla	Treatment of pediatric patients aged 3 years and older who have growth failure due to an inadequate secretion of endogenous growth hormone	**1st**	Strong Recommendation[14]	Positive Recommendation from NICE[15], CADTH[16], HAS[17], IQWIG[18] and PBAC[19].
Mecasermin	Treatment of growth failure in pediatric patients ≥ 2 years of age with severe primary insulin-like growth factor-1 (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH	**1st**	Strong Recommendation[20]	Positive Recommendation from CADTH[21], HAS[22] and PBAC[23].

Table 2. Non-SFDA-Registered Drugs for the Treatment of Growth Hormone Deficiency in Children

Medication	Indication	Line of Therapy	Level of Evidence/Recommendation
Lonapegsomatropin-tcgd	Treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone	**1st**	Strong Recommendation[24]
Vosoritide	To increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses	**Alternative**	Strong Recommendation[25]

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

1.1.1 Diagnosis and Management of Growth Disorders in Gulf Cooperation Council (GCC) Countries: Current Procedures and Key Recommendations for Best Practice [2016]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

This review article was published in 2016 in the International Journal of Pediatrics and Adolescent Medicine. It tackles current clinical procedures, identify important challenges and, where possible, use evidence-based data to provide key recommendations for best practice in the management of growth disorders[26]. The main recommendations (ungraded) are detailed below:

Height Screening for Short Stature in Primary Care

- To detect children with failure to thrive or growth failure during the first two years of life, the Saudi growth charts established in 2007 would generally be preferable to the WHO charts for use in Saudi Arabia.
- Auxological criteria are required for referral of short stature from primary to secondary care and are found below:

Table 3. Criteria for Referral of Short Children from Primary to Secondary Care

Infants from birth to three years of age: • Height Standard Deviation Score (SDS) ≤ 3 or • Height SDS ≤ 2 (3rd percentile) on two or more occasions within one year
Children aged three to 10 years: A combination of: • Height that is short for parental target height (TH), i.e., height SDS > 1.6 below TH SDS • Height SDS ≤ 2.5 • Change in height SDS > 1 over an undetermined time interval (minimum four months)

Investigation of Short Stature in Secondary Pediatric Care

- The clinical assessment and baseline investigations recommended in children referred to secondary care for short stature are found below:

Table 4. Clinical Assessment and Laboratory Investigations Recommended in Children Referred to Secondary Care for Short Stature

Clinical Assessment: • History: family history, inquiry about consanguinity, parental heights, birth weight, length of gestation, systematic inquiry for chronic symptoms • Accurate height measurement using wall stadiometer, weight, BMI, plotting of height on growth chart compared with parental height percentiles • Physical examination of systems • Examination for dysmorphic features
Laboratory Investigations: • Complete blood count • Renal function • Liver function • ESR • Calcium, phosphorus • Alkaline phosphatase • Bone age • Skeletal X-rays (when body disproportion is present) • Tissue transglutaminase • IgA • IGF-1 (when available) • Free T4, TSH • Karyotype or FSH (9 years) if not available (in females only)

Investigation of the Growth Hormone-IGF-1 Axis:

- A low serum IGF-1 for age (≤ 2 SDS) in the presence of auxological abnormalities would indicate a relatively high likelihood of GH deficiency, which should then be confirmed by a GH stimulation test.
- An international consensus has recommended that a cut-off of 6.7 μg/L is appropriate throughout childhood and early adolescence.
- The Growth Hormone Research Society consensus statement recommends two GH stimulation tests to confirm the diagnosis of GH deficiency.

- Most pediatric endocrinologists use sex steroid priming immediately before the GH stimulation tests in boys who are older than 11 years of age and girls who are older than 10 years of age who are not in advanced puberty.
- Choices for priming are a depot testosterone injection 100-125 mg five days before the GH test, ethinylestradiol 100 µg daily for three days, or stilboestrol 1 mg twice daily for the two days before the test.
- An MRI scan of the hypothalamic-pituitary region should be performed in patients diagnosed with GH deficiency.

Growth Hormone Therapy

- The starting dose of hGH should follow EMA and US Pediatric Endocrine Society guidelines of 23-39 µg/kg/day, i.e., 0.18-0.25 µg/kg/week.
- Patients with severe GH deficiency, i.e., peak GH < 3 µg/L require hGH doses at the lower end of the recommended range, whereas patients with mild or partial GH deficiency require doses at the upper end of the range.
- The increase of hGH dose during puberty is not recommended.
- A change in height SDS > 0.5 during the first year of therapy generally indicates that the patient is experiencing catch-up growth. In contrast, a change in height SDS < 0.3 indicates a poor response.
- Measurement of IGF-1 concentration is recommended for children with GH deficiency treated with hGH, with the aim of normalizing serum IGF-1 concentrations. However, evidence is lacking that supports the value of IGF-1 monitoring for safety in children and the lack of any data to indicate a safe upper limit for serum IGF-1 concentrations.

Transitional Care of the GH-Deficient Patient After Completion of Linear Growth

- Continued hGH replacement until the age of acquisition of peak bone mass and full physical maturity, i.e., at approximately 25 years of age, is necessary to complete physiological somatic development.
- Following completion of linear growth, GH secretion needs to be reassessed, ideally using an insulin or glucagon stimulation test.
- Growth hormone replacement will be limited to patients with severe GH deficiency, i.e., a peak GH level < 3-5 µg/L.
- The following table tackles the principles and requirements of transitional care to meet the needs of the GH-deficient patient following completion of linear growth:

Table 5. Transitional Care of the GH-Deficient Patient After Completion of Linear Growth

Requirements: • Development of an amicable and collaborative working relationship between the pediatric and adult endocrinologist • Clinical and academic interest of the adult endocrinologist to take responsibility for the young adult patient with severe GH deficiency • Understanding that somatic and skeletal development is not complete until the age of 25 years and that the GH-IGF-1 axis is necessary to achieve this
Organization: • Joint consultations in either the pediatric or adult setting to agree on priorities for investigations, e.g., DEXA scan, reassessment of GH secretion • Following demonstration of GH deficiency, an agreed protocol for reintroduction of hGH therapy • Assessment of pituitary function, both hormonal and imaging, to ensure optimal puberty, thyroid and adrenal function • Ideally, close liaison between pediatric and adult endocrinology specialist nurses
Benefits: • Seamless patient care with transfer to the adult service at an agreed age and following an agreed protocol of care • Educational advantages for both pediatrician and adult specialist with opportunities for productive collaborative research

- It is of utmost importance to emphasize the adherence to the treatment regimens instated to generate the best possible clinical outcomes.

1.2 North American Guidelines

1.2.1 Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency [2016]

The Drug and Therapeutics, and Ethics Committees of the Pediatric Endocrine Society has issued guidelines for the management of growth hormone deficiency in children and adolescents using growth hormone and IGF-1 treatment; the following grades of recommendation/level of evidence were opted:

In brief, the quality of the evidence was judged as very low (⬤ ◯ ◯ ◯), low (⬤ ⬤ ◯ ◯), moderate (⬤ ⬤ ⬤ ◯), or high (⬤ ⬤ ⬤ ⬤), reflecting the reviewers' assessment of the quality of the evidence according to GRADE guidelines.

Recommendations were assessed as strong (denoted by "We recommend") or conditional (denoted by "We suggest").

In accordance with GRADE guidelines, strong recommendations reflect confidence that providing such care will afford patients, on balance, more good than harm, while conditional recommendations require more individualized consideration of the risk-benefit assessment for a given patient.

On occasion, the taskforce made statements that are marked as "ungraded good practice statements." These are recommendations without direct supporting evidence that are usually non contestable and are important to include in the guideline to emphasize certain aspects of care such as providing counseling and education to patients.

The recommendations are detailed below[8]:

Efficacy of GH Treatment for GHD

- The use of GH is recommended to normalize AH and avoid extreme shortness in children and adolescents with GHD. (Strong recommendation, ⬤ ⬤ ⬤ ⬤)
- The use of routine cardiac testing, dual X-ray absorptiometry (DXA) scanning, and measurement of lipid profiles is suggested against in children and adolescents treated with GH. (Conditional recommendation, ⬤ ⬤ ◯ ◯)

Consideration and Diagnosis of GHD

- It is suggested to establish a diagnosis of GHD without GH provocative testing in patients possessing all of the following three conditions: auxological criteria, hypothalamic-pituitary defect (such as major congenital malformation, tumor or irradiation), and deficiency of at least one additional pituitary hormone. (Conditional recommendation, ⬤ ⬤ ◯ ◯)
- It is suggested that GHD due to congenital hypopituitarism be diagnosed without formal GH provocative testing in a newborn with hypoglycemia who does not attain a serum GH concentration above 5 µg/L and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk). (Conditional recommendation, ⬤ ⬤ ◯ ◯)
- A low GH concentration at the time of spontaneous hypoglycemia is insufficient to diagnose GHD alone.

GH Provocative Testing

- It is recommended against the reliance on GH provocative test results as the sole diagnostic criterion of GHD. (Strong recommendation, ⬤⬤⬤⬤)
- Given the substantial number of healthy, normally growing children who test below accepted limits, inadequate response to two different provocative tests is required for diagnosis of GHD.
- Sex steroid priming prior to provocative GH testing is suggested in prepubertal boys older than 11 and in prepubertal girls older than 10 years with AH prognosis within –2 SD of the reference population mean in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty. (Conditional recommendation, ⬤⬤◯◯)
- GH-naïve boys and girls are to be started on 2 mg (1 mg for body weight < 20 kg) of β-estradiol (not ethinyl estradiol) orally on each of the 2 evenings preceding the test. Alternatively, boys can be primed with intramuscular testosterone (50–100 mg of a depot formulation administered 1 week before the test).
- The use of spontaneous GH secretion in the diagnosis of GHD in a clinical setting is recommended against. (Strong recommendation, ⬤⬤◯◯)

Dosing of GH Treatment for Patients with GHD

- In children with GHD, the use of weight-based or body surface area (BSA)-based GH dosing is recommended. (Strong recommendation, ⬤⬤⬤◯)
- An initial GH dose of 0.16–0.24 mg/kg/week (22–35 µg/kg/day) is recommended with individualization of subsequent dosing. (Strong recommendation, ⬤⬤◯◯)
- Measurement of serum IGF-1 levels is suggested as a tool to monitor adherence and IGF-1 production in response to GH dose changes.
- It is suggested that the GH dose be lowered if serum IGF-1 levels rise above the laboratory-defined normal range for the age or pubertal stage of the patient. (Conditional recommendation, ⬤◯◯◯)
- During puberty, it is not recommended to routinely increase the GH dose to 0.7 mg/kg/week in every child with GHD. (Strong recommendation, ⬤⬤◯◯)
- GH treatment at pediatric doses is not recommended to be continued beyond attainment of a growth velocity below 2–2.5 cm/year. The decision to

discontinue pediatric dosing prior to attainment of this growth velocity should be individualized. (Strong recommendation, ●●○○)

Safety Issues of GH Treatment for Patients with GHD

- GH recipients are recommended to be monitored for potential development of intracranial hypertension, SCFE, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated. (Strong recommendation, ●●●●)
- Reassessment of both the adrenal and thyroid axes is recommended after initiation of GH therapy in patients whose cause of GHD is associated with possible multiple pituitary hormone deficiencies (MPHD). (Strong recommendation, ●●○○)

Transitional Care after Childhood GH Treatment

- Patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect except ectopic posterior pituitary are to be diagnosed with persistent GHD. (Strong recommendation, ●●●○)
- The measurement of the serum IGF-1 concentration is suggested to be the initial test of the somatotropic axis if re-evaluation of the somatotropic axis is clinically indicated. (Conditional recommendation, ●○○○)
- GH provocative testing is recommended to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-1 level. (Strong recommendation, ●●●○)
- GH treatment is to be initiated in individuals with persistent GHD in the transition period (The transition period is the time from late puberty to establishment of adult muscle and bone composition and encompasses attainment of AH.) (Conditional recommendation, ●●○○)

1.3 European Guidelines

There have been no European guidelines issued in the past ten years for the management of Child Growth Hormone Deficiency.

1.4 International Guidelines

1.4.1 Diagnosis and Treatment of Growth Hormone Deficiency: A Position Statement from Korean Endocrine Society and Korean Society of Pediatric Endocrinology [2020]

The Korean Endocrine Society (KES) and Korean Society of Pediatric Endocrinology (KSPE) have issued a position statement for the diagnosis and management of Growth Hormone Deficiency; the following grades of recommendation and levels of evidence were opted:

Table 6. KES & KSPE Grade of Recommendation/Level of Evidence

Recommendation Level	Definition
A	When there is a clear rationale for the recommendations: When manifold randomized controlled trials that can be generalized because they have sufficient test or meta-analysis results support a recommendation.
B	When there is a reliable basis for the recommendations: When reasonable grounds support this through well-performed cohort studies or patient—control group studies.
C	When there is a possible basis for the recommendations: When relevant grounds are seen through randomized clinical studies or case reports and observational studies carried out in a small institution, despite their inherent unreliability.
E	Expert recommendations: There is no basis to support the recommendations, but they are supported by expert opinion or expert clinical experience.

The recommendations are detailed below[27]:

Potential causes of growth hormone deficiency are listed in table 7.

Table 7. Causes of Growth Hormone Deficiency

Congenital	Acquired
Genetic: • Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2) • GHRH receptor gene defects • GH secretagogue receptor gene defects • GH gene defects • GH receptor/post receptor defects **Associated with brain structural defects:** • Agenesis of corpus callosum • Septo-optic dysplasia • Empty sella syndrome • Holoprosencephaly • Encephalocele • Hydrocephalus • Arachnoid cyst **Associated with midline facial defects:** • Single central incisor • Cleft lip/palate	**Neoplastic:** • Pituitary adenoma • Craniopharyngioma • Rathke's cleft cyst • Glioma/astrocytoma • Germinoma • Metastatic **Infiltrative/granulomatous disease:** • Langerhans cell histiocytosis • Sarcoidosis • Hypophysitis **Vascular damage:** • Head injury • Pituitary tumor apoplexy • Sheehan's syndrome • Subarachnoid hemorrhage **Treatment of pituitary and hypothalamic diseases:** • Cranial irradiation • Surgery of the pituitary or hypothalamus **Central nervous system infection:** • Idiopathic

Diagnosis and Treatment of Growth Hormone Deficiency in Children and Adolescents

- Two or more GH stimulation tests should be administered when GH deficiency is suspected in children **(A)**.
- Repeated GH stimulation tests are not required in GH patients with pituitary lesions or a proven genetic cause of GH deficiency **(C)**.
- GH replacement should be continued in children and adolescents until the epiphyseal plates close or their full height is reached **(C)**.
- GH replacement should be resumed as soon as possible in patients with GH deficiency during transition **(B)**.

Benefits of Growth Hormone Treatment

- GH treatment improves body composition, exercise capacity, and bone mineral density in patients with GH deficiency **(A)**.
- GH treatment lowers the risk of cardiovascular disease in patients with GH deficiency, but there is insufficient evidence regarding its effects on mortality reduction **(B)**.
- GH treatment improves quality of life in patients with GH deficiency **(A)**.

Risks and Side Effects of Growth Hormone Treatment

- GH treatment is contraindicated in patients with an active malignancy (except basal cell or squamous cell skin cancers) **(A)**.
- Changes in blood glucose levels should be observed during GH treatment in patients with diabetes mellitus, who may require their antidiabetic medication to be adjusted **(B)**.
- Thyroid and adrenal gland function should be monitored during GH treatment in patients with hypopituitarism **(B)**.

1.4.2 Review Article: Advances in Differential Diagnosis and Management of Growth Hormone Deficiency in Children [2021]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The recommendations detailed below were obtained from a thorough 2021 review article discussing the advances in differential diagnosis and management of CGHD[6]:

Diagnosis

- The diagnosis of GHD in children is based on medical history, auxological and biochemical investigation, radiological skeletal maturation assessment and neuroimaging of the pituitary region.
- Genetic analysis is indicated in selected patients.
- In children with suspected GHD, an accurate history includes measured parental heights.
- Physical examination involves measuring the weight, head circumference and standing height, or supine length if < 2 years old.
- Body proportion, BMI, fontanels, dentition, external genitalia, pubertal status, and presence of dysmorphic features should be assessed.

- Furthermore, height velocity should be determined through serial measurements with a minimum interval of 6 months.
- Skeletal maturity reflects the child's biological age and provides an important contribution to the diagnostic work-up.

Table 8 describes the criteria to initiate immediate investigation for GHD:

Table 8. Criteria to Initiate Investigation for Childhood Growth Hormone Deficiency

Height • 3SD below the mean • 1.5SD below the midparental height • 2SD below the mean and a height velocity per year that is 1SD below the mean for chronological age
Height velocity • 2 SD below the mean over 1 year • 1.5 SD below the mean sustained over 2 years
Other signs • Intracranial lesion • MPHD • Neonatal GHD
GHD: growth hormone deficiency; MPHD: multiple pituitary hormone deficiency; SD: standard deviation

Laboratory Investigations

- The clinical suspicion of neonatal GHD can be confirmed by a single GH measurement, preferably obtained during a hypoglycemic episode, from plasma, serum, or newborn blood screening cards within the first week of life.
- Most guidelines suggest a 5 µg/l cut-off in neonates with additional pituitary hormone deficiencies, or with the triad of ectopic posterior pituitary, anterior pituitary hypoplasia and abnormal pituitary stalk.
- In infancy and childhood, in the absence of signs and symptoms indicative of GHD, other causes of short stature should be ruled out.
- GH stimulation tests might be required to assess GH secretory capacity.
- A diagnosis of GHD without GH provocative testing is suggested only in patients who satisfy all the following criteria: auxological characteristics, presence of hypothalamic–pituitary defects on neuroimaging (congenital or acquired) and one additional pituitary hormone deficiency.

- Many stimulation tests to evaluate GH secretion exist; Clonidine, glucagon, arginine, and the insulin tolerance test are the most routinely used.
- The insulin tolerance test is considered the gold standard and is used to assess GH secretion in response to hypoglycemia.
- The most recent guidelines of the Paediatric Endocrine Society published in 2016[8] recommend the use of sex steroid priming before GH testing in prepubertal male individuals > 11 years of age and prepubertal female individuals > 10 years of age.
- The steroid preparation used is mostly oral 17β-estradiol or stilboestrol for two to seven evenings preceding the test, or 50–100mg intramuscular testosterone enanthate administered 1 week ahead.
- Owing to poor accuracy, confirmation of a GHD diagnosis requires two failed tests.
- The provocative tests should be performed after an overnight fast using a standardized protocol under the supervision of an expert team, preferably on two different days.
- A peak GH concentration below 7 µg/l has been suggested; however, the diagnostic GH peak cut-off is still a matter of discussion and ranges from 5µg/l to 10µg/l.
- The best assays should measure the 22kDa isoform, as it most accurately reflects pituitary GH secretion.
- Other biochemical parameters such as IGF-1 and IGFBP3 are positively correlated with GH secretion.
- A single IGF-1 and IGFBP3 measurement is more reliable than a single GH measurement; for this reason, both IGF-1 and IGFBP3 have been investigated as alternatives to GH stimulation testing and proposed as markers of GH treatment.

Treatment with recombinant human growth hormone (rhGH)

- The established treatment for GHD in children is rhGH, also known as somatropin.
- The recommended daily GH dosage based on weight is 0.16–0.24 mg/kg per week (0.022–0.035 mg/kg per day) with a maximum dose that should not exceed 0.3 mg/kg per week.
- The dose might be increased at puberty, although this change is not recommended routinely.

- An approach that is broadly used is to adjust the GH dose based on serum concentrations of IGF-1.
- The optimal response to therapy is monitored after the first year via height velocity parameters; these are height velocity and/or change in height SDS that both intrinsically correct for age and sex.
- Following a year of GH therapy, the medication response is considered poor if the height SDS improvement is lower than 0.4.

Transitional Care

- The current guidelines for GH testing during transition all agree on the need for retesting patients with isolated growth hormone deficiency (IGHD) after stopping rhGH for at least 1 month.
- Patients with idiopathic IGHD and an IGF-1 of ≥ 0 SDS probably do not have persistent GHD, and hence transition therapy might not need to be considered.
- Repeating a GH stimulation test is not necessary in patients with any of the following factors: MPHD (three or more hormonal deficiencies), low serum concentrations of IGF-1 (less than –2.0 SDS), documented genetic defects affecting pituitary function and/or hypothalamic–pituitary structural brain defects. In these patients, rhGH therapy can be continued without interruption, although the dose needs to be reduced to adult age dosing, which is lower than weight-based dosing in children.
- The insulin tolerance test remains the gold standard. An appropriate hypoglycemic stimulus is considered when glucose drops below 2.78 mmol/l (50 mg/dl) and is associated with symptoms.
- The insulin tolerance test is contraindicated in patients with a history of seizures, and cardiovascular or cerebrovascular disease.
- Depending on the availability, other tests can be used, such as GHRH in combination with arginine, glucagon, or the Macimorelin stimulation test.
- For glucagon, a GH cut-off of < 3 µg/l is recommended in those with a normal BMI (18.5–24.9kg/m2) and decreases to < 1µg/l in those with a BMI of > 30kg/m2 and low pretest probability.
- For the GHRH and arginine test, the cut-off peak values vary widely between studies from 5.6µg/l to 20.3µg/l.
- For the Macimorelin stimulation test, a GH cut-off of 2.8µg/l was recommended by the FDA.

Treatment with rhGH During Transition

- During transition, patients are treated with daily subcutaneous rhGH similarly to the pediatric population.
- For patients younger than 30 years, most guidelines recommend initiating a dose of 400–500 µg per day, with a mildly increased dose during transition, that is, an increase in daily dosing by 100–200µg per day every 1–2 months based on the individual's response.
- During transition, serum concentrations of IGF-1 should be monitored every 4 to 6 weeks until the optimal maintenance dose of rhGH is achieved.
- A repeat follow-up IGF-1 should be measured every 6 to 12 months.

1.4.3 Brazilian Society of Pediatrics: Growth Hormone Deficiency and the Transition from Pediatric to Adult Care [2021]

The Brazilian Society of Pediatrics has issued a review article discussing the approach to patients diagnosed with growth hormone deficiency (GHD) in childhood during the transition period from puberty to adulthood; the recommendations are detailed below[28]:

- Resuming, rhGH replacement therapy in patients with confirmed persistent GHD during the transition period after the achievement of final height is recommended, as most studies have reported long-term improvement in body composition, bone health, QoL, and lipid metabolism in adulthood.
- The most frequently used criteria for interrupting rhGH use in adolescence are growth velocity less than 2 cm/year, and bone age above 16 years in boys and 14-15 years in girls.
- Patients with multiple (≥ 3) pituitary hormone deficiencies (MPHD) regardless of etiology, and low serum IGF-1 (<−2.0 SDS), or GHD with a documented causal genetic mutations or specific pituitary/hypothalamic structural defect, except ectopic posterior pituitary, can be diagnosed with persistent GHD.
- Patients who should be reevaluated through a GH provocative testing in the transition phase:
    - Patients with idiopathic isolated GHD and low-normal (> −2 and < 0 SDS) or low (< −2 SDS) serum IGF-1 levels
    - Patients with GHD and deficiency of only 1 or 2 additional pituitary hormones
    - Patients with isolated GHD with pituitary hypoplasia or ectopic posterior pituitary

    - Previous history of cranial irradiation
- It is mandatory to discontinue rhGH for 1-3 months in patients who will be retested.
- The gold-standard test for the evaluation of GH IGF-1 axis in adults is the insulin tolerance test (ITT).
- Alternative tests are growth hormone-releasing hormone (GHRH)-arginine test, Macimorelin test and glucagon stimulation test.
- Magnetic resonance imaging (MRI) is another helpful tool to establish the diagnosis of permanent GHD.
- At the moment of rhGH interruption and GH reevaluation, the patient must have a full evaluation which includes body composition, bone mineral density, lipid, and glucose profile, and QoL appraisal.
- Patients with confirmed GHD in the transition period should restart rhGH replacement at a dose of 0.4–0.5 mg/day.
- The dose adjustment of rhGH may be done according to IGF-1 levels, which must be measured every 4-8 weeks until the achievement of levels within but not exceeding the upper normal range (IGF-1 between 0 and +2 SD) and subsequently, every 6 months.
- Dose titration must be done with increases by 0.1–0.2 mg every month until adequate levels of IGF-1 are achieved.
- The adequate replacement of the other pituitary deficiencies, if present, is important.
- Monitoring should also include clinical evaluation (side effects, blood pressure, pulse rate, body mass index, waist circumference) and assessment of fasting glucose, hemoglobin A1c, lipid profile, serum-free T4, and early morning cortisol if clinically indicated, at approximately 6-month intervals, and QoL measurements annually.
- Bone mineral density may be reevaluated through dual-energy X-ray absorptiometry (DXA) every 18–24 months.
- If a pituitary lesion is present, baseline and periodic MRIs should be undertaken for regular follow up.
- If there are no subjective or objective benefits of treatment after 12-18 months of therapy, interrupting rhGH replacement can be discussed with the patient.

1.4.4 Growth Hormone Research Society International Perspective: Diagnosis, Genetics, and Therapy of Short Stature in Children (2019)

The Growth Hormone Research Society (GRS) convened a Workshop in March 2019 to evaluate the diagnosis and therapy of short stature in children. Recommendations (ungraded) issued by the GRS are similar to those listed in the guidelines above and will not be detailed[29].

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in **2022 and 2023** for child growth hormone deficiency.

Table 9. Systematic Review and Meta-Analysis for Child GHD

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Duncan et al. (2022)[30]	"Sex Steroid Priming for Growth Hormone Stimulation Testing in Children and Adolescents with Short Stature: A Systematic Review"	In this systematic review, the authors addressed the following research questions: Does priming increase GH stimulation test efficacy in peripubertal children? Does priming identify those who would benefit most from treatment in terms of final height?	Effect of sex-steroid priming on outcome of GHST or final adult height.	Sex-steroid priming increases the growth hormone response during GHST, resulting in fewer patients meeting the threshold required for a diagnosis of GHD. Unnecessary GH treatment may be avoided in some patients without a detrimental effect on final height. Numerous sex-steroid priming regimens have been used in clinical practice and the majority appear to be effective, but an optimal regimen has not been determined.

			Is there evidence for an optimal sex-steroid priming regimen?		
2	Mameli et al. (2023)[31]	"Efficacy, Safety, Quality of Life, Adherence and Cost-effectiveness of Long-acting Growth Hormone Replacement Therapy Compared to Daily Growth Hormone in Children with Growth Hormone Deficiency: A Systematic Review and Meta-analysis"	Evaluating the efficacy, safety, adherence, quality of life (QoL) and cost-effectiveness of long-acting growth hormone (LAGH) vs daily growth hormone (GH) preparations in the treatment of growth hormone deficiency (GHD) in children.	Efficacy, safety, adherence, quality of life, cost-effectiveness	Regarding efficacy and safety, all the LAGH formulations were similar to daily GH. Future high-quality studies are needed to confirm these data. Adherence and QoL should be addressed from real-world data studies for both the mid and long term and in a larger population. Cost-effectiveness studies are needed to measure the economic impact of LAGH from the healthcare payer's perspective.

Section 2.0 Drug Therapy

2.1 Human Growth Hormone (hGH) Analogs

2.1.1 Somatropin

Information on Somatropin is detailed in the table below[32,33]:

Table 10. Somatropin Drug Information

SCIENTIFIC NAME SOMATROPIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E23
Drug Class	Anterior Pituitary Lobe Hormones and Analogues
Drug Sub-class	Somatropin and Somatropin Agonists
ATC Code	H01AC01
Pharmacological Class (ASHP)	Growth Hormone Analog
DRUG INFORMATION	
Dosage Form	Solution for injection Suspension for injection in pre-filled pen Powder and solvent for solution for injection Solution for injection in cartridge
Route of Administration	Subcutaneous Use
Dose (pediatrics)	Therapy should be continued until growth velocity decreases to <2 to 2.5 cm/year; the decision to discontinue prior to this must be individualized. 0.16 to 0.24 mg/kg weekly divided into equal doses 6 to 7 days/week
Maximum Daily Dose Pediatrics*	N/A

Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	RhGH is to be prescribed by an endocrinologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Peripheral edema, facial edema, pain, headache. **Most serious**: Upper respiratory tract infections, breast neoplasm, impaired glucose tolerance/prediabetes.
Drug Interactions*	**Category X:** Macimorelin
Special Population	**Pediatric:** Failure to increase growth rate, particularly during the first year of therapy, indicates need for close assessment of adherence and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human growth hormone.
Contraindications	Hypersensitivity to somatropin or any component of the formulation; acute critical illness due to increased complications/mortality following open heart or abdominal surgery, multiple

	accidental traumas, or acute respiratory failure; active malignancy; active proliferative or severe non-proliferative diabetic retinopathy. Patients with Prader-Willi syndrome who have a history of upper airway obstruction or sleep apnea (Genotropin, Norditropin, Omnitrope).
Monitoring Requirements	Monitor growth response; progression of scoliosis in patients with a history of scoliosis; clinical evidence of slipped capital femoral epiphysis, such as a limp or hip or knee pain; thyroid function; glucose in patients with risk factors for glucose intolerance. In addition, guidelines recommend a physical exam at every visit; monitoring serum IGF-1; adrenal and thyroid function in patients with growth hormone deficiency due to multiple pituitary hormone deficiencies; funduscopic exam if symptoms of intracranial hypertension occur.
Precautions	**Glucose tolerance:** Somatropin may decrease insulin sensitivity. Previously undiagnosed impaired glucose tolerance or diabetes mellitus may be detected; new-onset type 2 diabetes mellitus and exacerbation of preexisting diabetes mellitus may occur. Diabetic ketoacidosis and hyperosmolar hyperglycemic state have been reported in some patients. Discontinuing somatropin may improve glucose tolerance in some patients. Adjustment of antidiabetic medications may be necessary. **Hypersensitivity:** Serious systemic hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported.

	Intracranial hypertension: Intracranial hypertension with headache, nausea, papilledema, visual changes, and/or vomiting has been reported; Funduscopic examination prior to initiation of therapy and periodically thereafter is recommended. **Lipoatrophy:** Lipoatrophy has been reported at injection sites when used at the same site for a prolonged period. Ensure proper injection technique and rotate injection sites. **Neoplasm:** Increased risk of malignancy progression in patients with active malignancy; pediatric patients with short stature (genetic cause) have increased baseline risk of developing malignancies; consider risk/benefits prior to initiation of therapy and monitor these patients carefully. Rule out pituitary tumor (or other brain tumors) prior to initiation of treatment because growth hormone deficiency may be an early sign of the presence of these tumors. **Slipped capital femoral epiphyses:** Patients with endocrine disorders (including growth hormone deficiency) or in patients undergoing rapid growth may develop slipped capital femoral epiphyses more frequently; evaluate any child with new onset of a limp or with complaints of hip or knee pain. **Adrenal insufficiency:** Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) adrenal insufficiency with somatropin therapy; patients with previously diagnosed adrenal insufficiency may

	require increased glucocorticoid doses. Excessive glucocorticoid therapy may inhibit the growth-promoting effects of somatropin in children. **Chronic kidney disease:** Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy. Obtain x-rays of the hip prior to initiating somatropin in chronic kidney disease patients; be alert to the development of a limp or complaints of hip or knee pain. **Hypothyroidism:** Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for central (secondary) hypothyroidism. Untreated/undiagnosed hypothyroidism may decrease response to somatropin therapy, particularly the growth response in children. **Scoliosis:** Progression of scoliosis may occur in children experiencing rapid growth.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Child Growth Hormone Deficiency treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Somatropin.**

Table 11. Somatropin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Somatropin	NICE[11]	**Positive Recommendation** – May 26th 2010 The Committee concluded that within its marketing authorisation somatropin represents a **cost-effective treatment** for children with growth failure associated with all the conditions under consideration; in light of the apparent equivalence of the clinical effectiveness of the different somatropin products, the least costly product that, after discussion between the responsible clinician and the patient and/or their carer, has been agreed to meet the needs of the individual child and to maximize the likelihood of adherence to treatment should be chosen. In the manufacturers' base case the ICERs for somatropin compared with no treatment were below £30,000 per QALY gained. Using the average price for somatropin in the Assessment Group's model resulted in ICERs of £23,196 per QALY gained for growth hormone deficiency.
	CADTH[34]	**Conditional Positive Recommendation** – December 20th, 2013 The Canadian Drug Expert Committee (CDEC) recommends that Genotropin be listed for the treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone with the following condition: **Condition:** • List in a manner similar to other somatropin products for the treatment of children with growth hormone deficiency (GHD).
	HAS[35]	**Positive Recommendation** – September 7th, 2015 Reimbursement of Somatropin was maintained due to the substantial importance of its clinical benefit.
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT- Somatropin

Somatropin is indicated for the treatment of children with growth failure due to growth hormone deficiency (GHD). It is administered subcutaneously as 0.16 to 0.24 mg/kg weekly divided into equal doses 6 to 7 days/week. Somatropin is backed by some HTA bodies such as NICE UK. Its use is limited by the heightened risk of upper respiratory tract infections, breast neoplasm and impaired glucose tolerance/prediabetes.

2.1.2 Somapacitan

Information on Somapacitan is detailed in the table below[32,33]:

Table 12. Somapacitan Drug Information

SCIENTIFIC NAME SOMAPACITAN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E23
Drug Class	Pituitary and Hypothalamic Hormones and Analogues
Drug Sub-class	Somatropin and Somatropin Agonists
ATC Code	H01AC07
Pharmacological Class (ASHP)	Growth Hormone Analog
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous Use
Dose (pediatrics)	Children ≥ 2.5 years and Adolescents: SUBQ: Initial dose: 0.16 mg/kg/dose once weekly; individualize and titrate dose based on patient response. If epiphyses are closed, reevaluate patient before continuing therapy.

	Converting from daily growth hormone products: Begin therapy 1 day after last daily injection of other product.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling; drug exposure increases with decreasing eGFR. **Hepatic Impairment:** Children ≥2.5 years and Adolescents: Mild impairment: There are no dosage adjustments necessary. Moderate to severe impairment: Use is not recommended (has not been studied).
Prescribing edits*	PA, AGE, MD
AGE (Age Edit)	The safety and effectiveness of Somapacitan have not been established in pediatric patients less than 2.5 years of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	The medicine can only be obtained with a prescription and treatment should be started and monitored by doctors who are qualified and experienced in the diagnosis and management of patients with growth hormone deficiency (such as endocrinologists).
PA (Prior Authorization)	Somapacitan is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency. It is given as 0.16 mg/kg/dose once weekly. Fundoscopic exam should be performed prior to initiation. Use actual body weight for dosing. + Check other Prescribing Edits (AGE, MD)

QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Increased serum phosphate, dyspepsia, back pain, arthralgia. **Most serious**: Slipped capital femoral epiphyses, glucose tolerance, intracranial hypertension, neoplasm.
Drug Interactions*	**Category X:** Macimorelin
Special Population	**Pediatric Patients:** Failure to increase growth rate, particularly during the first year of therapy, indicates need for close assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human growth hormone.
Contraindications	Hypersensitivity to somapacitan or any component of the formulation; acute critical illness after open heart surgery, abdominal surgery, or multiple accidental trauma; acute respiratory failure; active malignancy; active proliferative or severe non-proliferative diabetic retinopathy; Prader-Willi syndrome in pediatric patients who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment.
Monitoring Requirements	Monitor clinical response, serum insulin-like growth factor 1 (IGF-1), and adverse reactions every 2 to 4 weeks during dose titration; check IGF-1 levels 3 to 4 days after the prior dose. Once at maintenance dose, monitor serum IGF-

	1, fasting glucose, HbA_{1c}, BMI, waist circumference/waist to hip ratio, thyroid function (free T_4), adrenal function, lipid profile, phosphorus, alkaline phosphatase, parathyroid hormone, BP, heart rate, clinical response, and adverse reactions every 6 to 12 months; fundoscopic examination to evaluate for papilledema (baseline and periodically during therapy); monitor scoliosis progression (in patients with history of scoliosis); monitor limp or hip or knee pain (evaluate for slipped capital femoral epiphyses); lipoatrophy at injection sites; monitor patients with preexisting tumors for recurrence or progression; monitor for malignant transformation of skin lesions; evaluate bone mineral density prior to therapy and dual-energy x-ray absorptiometry scan repeated every 1.5 to 3 years if initial bone scan is abnormal.
Precautions	**Pancreatitis:** Has been rarely reported in pediatric patients receiving somatropin; incidence in children may be greater than adults. Consider pancreatitis diagnosis if abdominal pain occurs. **Acute Critical Illness:** Somapacitan is contraindicated in patients with acute critical illness. Safety of continuing growth hormone products used at lower doses (eg, for replacement therapy) has not been established during critical illness. **Hepatic Impairment:** Use is not recommended in patients with severe hepatic impairment; dosage adjustment is required in patients with moderate hepatic impairment.

	Hypoadrenalism: Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism with somapacitan therapy; patients with previously diagnosed hypoadrenalism may require increased dosages of glucocorticoids due to the effects of somapacitan. **Hypothyroidism:** Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for reduced thyroid function (central hypothyroidism). Untreated/undiagnosed hypothyroidism may decrease response to therapy. **Prader-Willi Syndrome:** Sudden death has been reported in pediatric patients with Prader-Willi syndrome following the use of somatropin. Use of somapacitan is not indicated for the treatment of pediatric patients who have growth failure due to Prader-Willi syndrome. **Scoliosis:** Progression of scoliosis may occur in pediatric patients experiencing rapid growth.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Child Growth Hormone Deficiency treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Somapacitan.**

Table 13. Somapacitan HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Somapacitan	NICE	Review under development. Expected date to be confirmed.
	CADTH	Review under development.
	HAS	Not available
	IQWIG	Not available
	PBAC[13]	**Positive Recommendation** – March 2022 "The PBAC recommended the Section 100 Growth Hormone Program listing somapacitan for the treatment of growth hormone deficiency (AGHD) in patients aged 18 years and above, and those under 18 years of age with a mature skeleton. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of somapacitan would be acceptable if it were cost-minimized to somatropin for the same indication."

CONCLUSION STATEMENT- Somapacitan

Somapacitan is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency. It is given as 0.16 mg/kg/dose once weekly. Fundoscopic exam should be performed prior to initiation. Actual body weight should be used for dosing. Somapacitan is backed by some HTA bodies as PBAC. Its use is limited by the heightened risk of slipped capital femoral epiphyses, glucose tolerance, intracranial hypertension, and neoplasm.

2.1.3 Somatrogon-ghla

Information on Somatrogon-ghla is detailed in the table below[32,33]:

Table 14. Somatrogon Drug Information

SCIENTIFIC NAME SOMATROGON-GHLA	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes

EMA	Yes
MHRA	Yes
PMDA	In process
Indication (ICD-10)	E23
Drug Class	Growth Hormone
Drug Sub-class	Human Growth Hormone Analog
ATC Code	H01AC
Pharmacological Class (ASHP)	Human Growth Hormone Analog
DRUG INFORMATION	
Dosage Form	Solution Pen-injector
Route of Administration	Subcutaneous Use
Dose (pediatrics)	Children 3 to 11 years: SUBQ: 0.66 mg/kg/dose once weekly; individualize dose based on growth velocity, body weight, and insulin-like growth factor-1 (IGF-1); treat with the lowest effective dose. Discontinue treatment if there is evidence of epiphysial growth plate closure. *Converting from daily growth hormone products*: Begin therapy 1 day after last daily injection of other product. *Dosage adjustment for IGF-1*: If IGF-1 is > 2 standard deviation scores higher than mean reference value for age and sex, decrease dose by 15%. More than one dose reduction may be necessary.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling; has not been studied. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; has not been studied.

Prescribing edits*	AGE, PA, MD
AGE (Age Edit)	The safety and effectiveness of Somatrogon-ghla have not been established in pediatric patients less than 3 years of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	The medicine can only be obtained with a prescription and treatment should be started and monitored by doctors who are qualified and experienced in the diagnosis and management of patients with growth hormone deficiency (such as endocrinologists).
PA (Prior Authorization)	Somatrogon-ghla is indicated for the treatment of pediatric patients aged 3 years and older who have growth failure due to an inadequate secretion of endogenous growth hormone. The recommended dosage is 0.66 mg/kg based on actual body weight administered once weekly. + Check other Prescribing Edits (AGE, MD)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Injection site reactions, headache, pyrexia, anemia, cough, vomiting, hypothyroidism, abdominal pain, rash, and oropharyngeal pain. **Most serious:** Eosinophilia, antibody development, nasopharyngitis.
Drug Interactions*	**Category X:** Macimorelin
Special Population	**Pediatrics:** Failure to increase growth rate, particularly during the first year of therapy, indicates need for close

	assessment of compliance and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human growth hormone.
Contraindications	Hypersensitivity to Somatrogon or any component of the formulation; acute critical illness after open heart surgery, abdominal surgery, multiple accidental traumas, or acute respiratory failure; closed epiphyses; active malignancy; diabetic retinopathy (active proliferative or severe nonproliferative); patients with Prader-Willi syndrome who have severe obesity, severe respiratory impairment, history of upper airway obstruction, or history of sleep apnea, active tumors.
Monitoring Requirements	Growth response; progression of scoliosis in patients with a history of scoliosis; clinical evidence of slipped capital femoral epiphysis, such as a limp or hip or knee pain; thyroid function; glucose in patients with risk factors for glucose intolerance or diabetes; serum IGF-1 (draw 4 days after prior dose); adrenal and thyroid function in patients with growth hormone deficiency due to multiple pituitary hormone deficiencies; funduscopic exam prior to starting therapy, periodically, and if symptoms of intracranial hypertension occur; malignant transformation of skin lesions.
Precautions	**Fluid retention:** Fluid retention may occur; manifestations of fluid retention (eg, edema, nerve compression including carpal tunnel syndrome/paresthesia) are generally transient and dose dependent.

	Glucose intolerance: Growth hormone may decrease insulin sensitivity especially at higher doses. New onset type 2 diabetes mellitus has been reported. Adjustment of antidiabetic medications may be necessary. **Hypersensitivity:** Serious systemic hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported with growth hormones; institute immediate medical attention if hypersensitivity occurs. **Intracranial hypertension:** Intracranial hypertension with headache, nausea, papilledema, visual changes, and/or vomiting has been reported in patients receiving growth hormone treatment; symptoms usually occur within the first 8 weeks of therapy and signs and symptoms of intracranial hypertension may rapidly resolve after discontinuation or reduction of dose. **Lipoatrophy:** Lipoatrophy has been reported at injection sites when used at the same site for a prolonged period. Ensure proper injection technique and rotate injection sites. **Neoplasm:** Increased risk of malignancy progression in patients with active malignancy; any preexisting malignancy should be inactive and treatment complete prior to initiating therapy. An increased risk of second neoplasm has been reported in childhood cancer survivors treated with somatropin; the most common second neoplasms were meningiomas in patients treated with radiation to the head for their first neoplasm. Patients with short stature (genetic cause) have

	increased baseline risk of developing malignancies; consider risk/benefits prior to initiation of therapy and monitor these patients carefully. **Pancreatitis:** Pancreatitis has been reported in patients receiving growth hormone. **Slipped capital femoral epiphyses:** Patients with endocrine disorders (including growth hormone deficiency and Turner syndrome) or patients undergoing rapid growth may develop slipped capital femoral epiphyses more frequently; evaluate any child with new onset of a limp or with complaints of hip or knee pain. **Acute critical illness:** Initiation of somatrogon is contraindicated with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental traumas, or acute respiratory failure; mortality may be increased. Safety of continuing growth hormone products used at lower doses (eg, for replacement therapy) has not been established during critical illness. **Hypoadrenalism:** Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism with growth hormone therapy; patients with previously diagnosed hypoadrenalism may require increased dosages of glucocorticoids due to the effects of growth hormone. **Hypothyroidism:** Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for unmasking of central hypothyroidism

	with growth hormone therapy. Untreated/undiagnosed hypothyroidism may decrease response to therapy, particularly the growth response in children. **Scoliosis:** Progression of scoliosis may occur in children experiencing rapid growth.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Child Growth Hormone Deficiency treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Somatrogon-ghla.**

Table 15. Somatrogon-ghla HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Somatrogon-ghla	NICE[15]	**Positive Recommendation** – February 1st 2023 "Somatrogon is recommended, within its marketing authorisation, as an option for treating growth disturbance caused by growth hormone deficiency in children and young people aged 3 years and over. If people with the condition and their clinicians consider somatrogon to be 1 of a range of suitable treatments (including any preparation of somatropin) discuss the advantages and disadvantages of the available treatments. After that discussion, if more than 1 treatment is suitable, choose the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements."
	CADTH[16]	**Positive Recommendation** – March 2022 "CADTH recommends that Somatrogon should be reimbursed by public drug plans for the treatment

		of growth hormone deficiency if certain conditions are met. Somatrogon should only be covered to treat children who are at least 3 years of age, who did not reach puberty yet, and who are diagnosed with growth hormone deficiency. It should only be reimbursed if prescribed by a pediatric endocrinologist and if it does not cost more than the least costly somatropin."
	HAS[17]	**Positive Recommendation** – October 25th 2022 "Favorable opinion for reimbursement in the treatment of children and adolescents aged 3 years and over with a growth disorder due to insufficient secretion of growth hormone."
	IQWIG[18]	**Positive Recommendation** – June 29th 2022 "The additional benefit of the Orphan Drug is considered proven through its approval. The extent of this additional benefit is assessed by the G-BA."
	PBAC[19]	**Positive Recommendation** – March 2022 "The PBAC recommended the Section 100 Growth Hormone Program listing of somatrogon for the treatment of SSABGHD and SSSG in patients who do not have a mature skeleton (i.e. a bone age of less than 13.5 years in females or less than 15.5 years in males). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of somatrogon would be acceptable if it were cost-minimized to somatropin for the same indications."

CONCLUSION STATEMENT- Somatrogon-ghla

Somatrogon-ghla is indicated for the treatment of pediatric patients aged 3 years and older who have growth failure due to an inadequate secretion of endogenous growth hormone. The recommended dosage is 0.66 mg/kg based on actual body weight administered once weekly. It is backed by several HTA bodies such as NICE, CADTH, HAS, IQWIG and PBAC. The use of Somatrogon-ghla is limited by the heightened risk of development of eosinophilia, antibody development and nasopharyngitis.

2.2 Recombinant Human Insulin-Like Growth Factor-1

2.2.1 Mecasermin

Information on Mecasermin is detailed in the table below:[32,33]

Table 16. Mecasermin Drug Information

SCIENTIFIC NAME MECASERMIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E23
Drug Class	Insulin-Like Growth Factor-1, Recombinant
Drug Sub-class	Insulin-Like Growth Factor-1, Recombinant
ATC Code	H01AC03
Pharmacological Class (ASHP)	Insulin-Like Growth Factor-1, Recombinant
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Subcutaneous Use
Dose (pediatrics)	Children ≥2 years and Adolescents: SubQ: Initial: 0.04 to 0.08 mg/kg/dose twice daily; if tolerated for 7 days, may increase by 0.04 mg/kg/dose. Must be administered within 20 minutes of a meal or snack; omit dose if patient is unable to eat. Reduce dose if hypoglycemia occurs despite adequate food intake; dose should not be increased to make up for ≥1 omitted dose.
Maximum Daily Dose Pediatrics*	0.12 mg/kg/dose twice daily

Adjustment	**Altered Kidney Function:** Children ≥2 years and Adolescents: There are no dosage adjustments provided in the manufacturer's labeling; has not been studied. **Altered Hepatic Function:** Children ≥2 years and Adolescents: There are no dosage adjustments provided in the manufacturer's labeling; has not been studied.
Prescribing edits*	AGE, MD, PA
AGE (Age Edit)	Mecasermin has not been studied in children less than 2 years of age or adults with Primary IGFD. The pharmacokinetics of Mecasermin have not been studied in subjects greater than 65 years of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	The medicine can only be obtained with a prescription and treatment should be started and monitored by doctors who are qualified and experienced in the diagnosis and management of patients with growth hormone deficiency (such as endocrinologists).
PA (Prior Authorization)	Mecasermin is used in the treatment of growth failure in pediatric patients ≥ 2 years of age with severe primary insulin-like growth factor-1 (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. It is given as 0.04 to 0.08 mg/kg/dose twice daily. Mecasermin must be administered within 20 minutes of a meal or snack; omit dose if patient is unable to eat. Reduce dose if hypoglycemia occurs despite adequate food intake; dose should not be increased to make up for

	≥1 omitted dose. + Check other Prescribing Edits (AGE, MD)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypoglycemia, local and systemic hypersensitivity, and tonsillar hypertrophy. **Most serious:** Cardiomegaly, heart murmur, intracranial hypertension, and antibody development.
Drug Interactions*	**Category X:** Macimorelin
Special Population	N/A
Contraindications	Hypersensitivity to Mecasermin or any component of the formulation; patients with closed epiphyses; malignant neoplasia; history of malignancy, use in neonates or premature babies (formulation contains benzyl alcohol).
Monitoring Requirements	Pre-prandial glucose during treatment initiation and dose adjustment and as clinically indicated; hypersensitivity reactions; facial features; lymphoid tissue; funduscopic examination (at initiation and periodically thereafter); growth; new onset of a limp or complaints of hip or knee pain; progression of scoliosis. Monitor small children closely due to potentially erratic food intake. Target treatment IGF-1 level: 0 to +2 SD score for age. Decrease dose for adverse events and/or IGF-1 levels ≥3 SD above normal.
Precautions	**Hypersensitivity reactions:** Hypersensitivity reactions (localized skin

	reactions to anaphylaxis) have been reported. If hypersensitivity is suspected; discontinue and instruct patient to seek immediate medical attention. **Hypoglycemia:** May cause hypoglycemic effects, especially in small children (due to inconsistent oral intake); patients should avoid high-risk activities within 2 to 3 hours after dosing, particularly at initiation of treatment, until a tolerated dose is established. Do not administer on days a patient cannot or will not eat. Should be administered with a meal or a snack. **Intracranial hypertension:** Intracranial hypertension with headache, nausea, papilledema, visual changes, and/or vomiting has been reported with growth hormone product; funduscopic examinations are recommended at initiation of therapy and periodically thereafter. **Lymphoid hypertrophy:** Has been reported and may lead to complications such as snoring, sleep apnea, and chronic middle-ear effusions. **Slipped capital femoral epiphyses:** Patients with growth hormone deficiency can develop slipped capital femoral epiphyses more frequently; evaluate any child with new onset of a limp or with complaints of hip or knee pain. **Diabetes:** Use with caution; may suppress hepatic glucose production and stimulate peripheral glucose utilization, thereby increasing the risk of hypoglycemia. **Malignancy:** Malignant neoplasms have been reported; generally observed in

	patients with rare genetic conditions of short stature associated with cancer risk, other cancer predisposing conditions, and use of higher-than-recommended doses and doses that produced elevated age- and sex-matched insulin-like growth factor-1 (IGF-1) levels. Use is contraindicated in patients with malignant neoplasia or history of malignancy. Discontinue use if neoplasia develops. **Scoliosis:** Progression of scoliosis may occur in children experiencing rapid growth. **Benzyl alcohol and derivatives:** Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; avoid or use dosage forms containing benzyl alcohol with caution in neonates. See manufacturer's labeling. **Appropriate use:** Not intended for use in patients with secondary forms of IGF-1 deficiency (GH deficiency, malnutrition, hypothyroidism, chronic anti-inflammatory steroid therapy).
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Child Growth Hormone Deficiency treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Mecasermin.**

Table 17. Mecasermin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Mecasermin	NICE	Not applicable
	CADTH[21]	**Positive Recommendation** – February 2022 "CADTH recommends that Mecasermin should be reimbursed by public drug plans for the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (SPIGFD) if certain conditions are met. Mecasermin should only be covered to treat patients who are at least 2 years of age with confirmed diagnosis of SPIGFD and in whom epiphyseal growth plates have not yet closed. Mecasermin should only be reimbursed if prescribed by a pediatric endocrinologist, if it is not prescribed in combination with recombinant growth hormone treatment, and the price of Mecasermin is reduced."
	HAS[22]	**Positive Recommendation** – July 17th 2020 "Opinion in favor of maintaining reimbursement in the treatment of growth retardation in children and adolescents aged 2 to 18 years with confirmed severe primary IGF-1 deficiency (primary IGFD)."
	IQWIG	Not available
	PBAC[23]	**Positive Recommendation** – March 2022 "The PBAC recommended the listing of Mecasermin on the basis that it be available on a Section 100 Growth Hormone (GH) Program listing for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor 1 deficiency (Primary IGFD)."

CONCLUSION STATEMENT- Mecasermin

Mecasermin is used in the treatment of growth failure in pediatric patients ≥ 2 years of age with severe primary insulin-like growth factor-1 (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. It is given as 0.04 to 0.08 mg/kg/dose twice daily. Mecasermin must be administered within 20 minutes of a meal or snack; and its dose must be omitted if the patient is unable to eat. Its use is backed by several HTA bodies such as CADTH,

HAS and PBAC. The use of Mecasermin is limited by the heightened risk of cardiomegaly, heart murmur, intracranial hypertension, and antibody development.

2.3 Other Drugs

2.3.1 Lonapegsomatropin-tcgd

Lonapegsomatropin-tcgd was approved by the FDA in August of 2021, and by the EMA in January of 2022. It is indicated for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH). Lonapegsomatropin-tcgd should be administered subcutaneously into the abdomen, buttock, or thigh with regular rotation of the injection sites. The recommended dose is 0.24 mg/kg body weight once weekly[36].

2.3.2 Vosoritide

Vosoritide was initially approved by the FDA in November of 2021 and by the EMA in August of 2021. It is indicated to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. The recommended dosage is based on the patient's weight. Vosoritide is to be administered subcutaneously once daily[25]. In September and October 2023 respectively, the EMA and the FDA approved its use in children with achondroplasia that are under the age of 5[37].

Section 3.0 Key Recommendations Synthesis

Height Screening for Short Stature in Primary Care

- To detect children with failure to thrive or growth failure during the first two years of life, the Saudi growth charts established in 2007 would generally be preferable to the WHO charts for use in Saudi Arabia.
- Auxological criteria are required for referral of short stature from primary to secondary care and are found below:

Criteria for Referral of Short Children from Primary to Secondary Care

Infants from birth to three years of age:

- Height SDS ≤ 3 or
- Height SDS ≤ 2 (3rd percentile) on two or more occasions within one year

Children aged three to 10 years:

A combination of:

- Height that is short for parental target height (TH), i.e., height SDS > 1.6 below TH SDS
- Height SDS ≤ 2.5
- Change in height SDS > 1 over an undetermined time interval (minimum four months)

Investigations and Diagnosis

- A low serum IGF-1 for age (≤ 2 SDS) in the presence of auxological abnormalities would indicate a relatively high likelihood of GH deficiency, which should then be confirmed by a GH stimulation test.
- An international consensus has recommended that a cut-off of 6.7 µg/L is appropriate throughout childhood and early adolescence.
- The Growth Hormone Research Society consensus statement recommends two GH stimulation tests to confirm the diagnosis of GH deficiency.
- Many stimulation tests to evaluate GH secretion exist; Clonidine, glucagon, arginine and the insulin tolerance test are the most routinely used.
- The insulin tolerance test is considered the gold standard and is used to assess GH secretion in response to hypoglycemia.
- Most pediatric endocrinologists use sex steroid priming immediately before the GH stimulation tests in boys who are older than 11 years of age and girls who are older than 10 years of age who are not in advanced puberty.

- Choices for priming are a depot testosterone injection 100-125 mg five days before the GH test, ethinylestradiol 100 µg daily for three days, or stilboestrol 1 mg twice daily for the two days before the test.
- An MRI scan of the hypothalamic-pituitary region should be performed in patients diagnosed with GH deficiency.

Dosing of GH Treatment for Patients with GHD

- In children with GHD, the use of weight-based or body surface area (BSA)-based GH dosing is recommended. (Strong recommendation, ●●●○)
- An initial GH dose of 0.16–0.24 mg/kg/week (22–35 µg/kg/day) is recommended with individualization of subsequent dosing. (Strong recommendation, ●●○○)
- Measurement of serum IGF-1 levels is suggested as a tool to monitor adherence and IGF-1 production in response to GH dose changes.
- It is suggested that the GH dose be lowered if serum IGF-1 levels rise above the laboratory-defined normal range for the age or pubertal stage of the patient. (Conditional recommendation, ●○○○)
- During puberty, it is not recommended to routinely increase the GH dose to 0.7 mg/kg/week in every child with GHD. (Strong recommendation, ●●○○)
- GH treatment at pediatric doses is not recommended to be continued beyond attainment of a growth velocity below 2–2.5 cm/year. The decision to discontinue pediatric dosing prior to attainment of this growth velocity should be individualized. (Strong recommendation, ●●○○)

Benefits of Growth Hormone Treatment

- GH treatment improves body composition, exercise capacity, and bone mineral density in patients with GH deficiency **(A)**.
- GH treatment lowers the risk of cardiovascular disease in patients with GH deficiency, but there is insufficient evidence regarding its effects on mortality reduction **(B)**.
- GH treatment improves quality of life in patients with GH deficiency **(A)**.

Risks and Side Effects of Growth Hormone Treatment

- GH treatment is contraindicated in patients with an active malignancy (except basal cell or squamous cell skin cancers) **(A)**.

- Changes in blood glucose levels should be observed during the course of GH treatment in patients with diabetes mellitus, who may require their antidiabetic medication to be adjusted **(B)**.
- Thyroid and adrenal gland function should be monitored during GH treatment in patients with hypopituitarism **(B)**.

Transitional Care

- The current guidelines for GH testing during transition all agree on the need for retesting patients with IGHD after stopping rhGH for at least 1 month.
- Patients with idiopathic IGHD and an IGF-1 of ≥ 0 SDS probably do not have persistent GHD, and hence transition therapy might not need to be considered.
- Repeating a GH stimulation test is not necessary in patients with any of the following factors: MPHD (three or more hormonal deficiencies), low serum concentrations of IGF-1 (less than –2.0 SDS), documented genetic defects affecting pituitary function and/or hypothalamic–pituitary structural brain defects. In these patients, rhGH therapy can be continued without interruption, although the dose needs to be reduced to adult age dosing, which is lower than weight-based dosing in children.
- The insulin tolerance test remains the gold standard. An appropriate hypoglycemic stimulus is considered when glucose drops below 2.78 mmol/l (50 mg/dl) and is associated with symptoms.
- This test is contraindicated in patients with a history of seizures, and cardiovascular or cerebrovascular disease.
- Depending on the availability, other tests can be used, such as GHRH in combination with arginine, glucagon, or the Macimorelin stimulation test.
- For glucagon, a GH cut-off of < 3 µg/l is recommended in those with a normal BMI (18.5–24.9kg/m2) and decreases to < 1µg/l in those with a BMI of > 30kg/m2 and low pretest probability.
- For the GHRH and arginine test, the cut-off peak values vary widely between studies from 5.6µg/l to 20.3µg/l.
- For the Macimorelin stimulation test, a GH cut-off of 2.8µg/l was recommended by the FDA.

Treatment with rhGH During Transition

- During transition, patients are treated with daily subcutaneous rhGH similarly to the pediatric population.

- For patients younger than 30 years, most guidelines recommend initiating a dose of 400–500 µg per day, with a mildly increased dose during transition, that is, an increase in daily dosing by 100–200µg per day every 1–2 months based on the individual's response.
- During transition, serum concentrations of IGF-1 should be monitored every 4 to 6 weeks until the optimal maintenance dose of rhGH is achieved.
- A repeat follow-up IGF-1 should be measured every 6 to 12 months.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Child Growth Hormone Deficiency.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

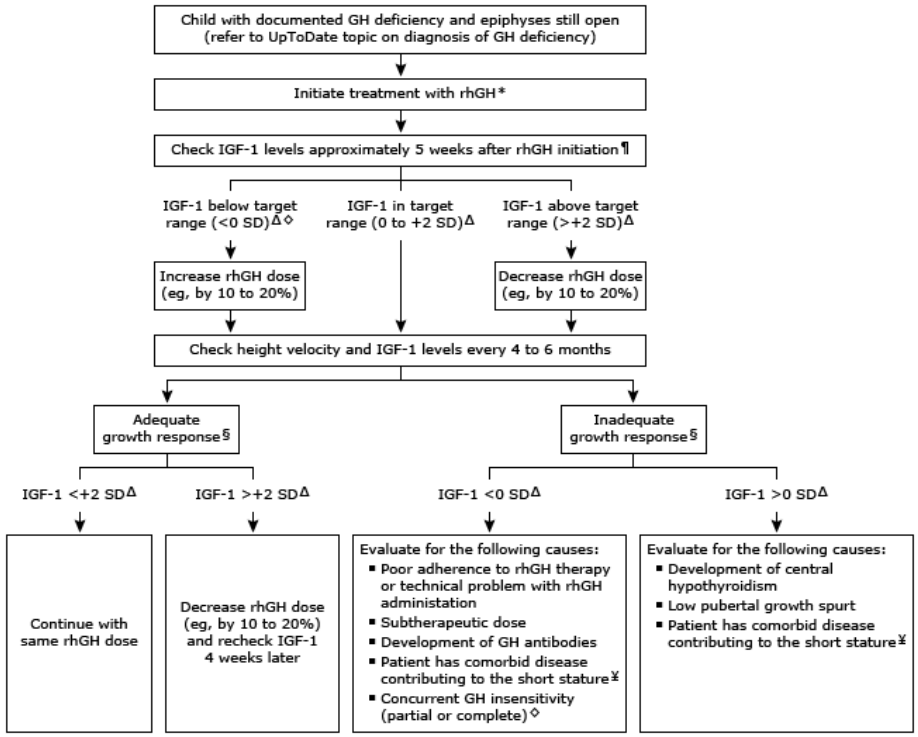
Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Filters	Search Details	Results
((((((((((((Dwarfism, Pituitary[MeSH Terms]) OR (Pituitary Dwarfism[Title/Abstract])) OR (Growth Hormone Deficiency Dwarfism[Title/Abstract])) OR (Hyposomatotrophic Dwarfism[Title/Abstract])) OR (Nanism, Pituitary[Title/Abstract])) OR (Pituitary Nanism[Title/Abstract])) OR (Isolated Growth Hormone Deficiency[Title/Abstract])) OR (Isolated HGH Deficiency[Title/Abstract])) OR (Isolated Human Growth Hormone Deficiency[Title/Abstract])) OR (Isolated Somatotropin Deficiency[Title/Abstract])) OR (Isolated Somatotropin Deficiency Disorder[Title/Abstract])) OR (Dwarfism, Growth Hormone Deficiency[Title/Abstract])) OR (Isolated GH Deficiency[Title/Abstract])) OR (Hypophysial Dwarf[Title/Abstract])) OR (Pituitary Dwarf[Title/Abstract])	Guideline, in the last 5 years	("dwarfism, pituitary"[MeSH Terms] OR "pituitary dwarfism"[Title/Abstract] OR "growth hormone deficiency dwarfism"[Title/Abstract] OR "hyposomatotrophic dwarfism"[Title/Abstract] OR (("Dwarfism"[MeSH Terms] OR "Dwarfism"[All Fields] OR "Nanism"[All Fields]) AND "Pituitary"[Title/Abstract]) OR "pituitary nanism"[Title/Abstract] OR "isolated growth hormone deficiency"[Title/Abstract] OR "isolated hgh deficiency"[Title/Abstract] OR "isolated human growth hormone deficiency"[Title/Abstract] OR "isolated somatotropin deficiency"[Title/Abstract] OR ((("isolate"[All Fields] OR "isolate s"[All Fields] OR "Isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[MeSH Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]) AND ("human growth	0

		hormone"[MeSH Terms] OR ("Human"[All Fields] AND "Growth"[All Fields] AND "Hormone"[All Fields]) OR "human growth hormone"[All Fields] OR "Somatotropin"[All Fields] OR "growth hormone"[MeSH Terms] OR ("Growth"[All Fields] AND "Hormone"[All Fields]) OR "growth hormone"[All Fields] OR "somatotropins"[All Fields])) AND "deficiency disorder"[Title/Abstract]) OR "dwarfism growth hormone deficiency"[Title/Abstract] OR "isolated gh deficiency"[Title/Abstract] OR (("hypophysial"[All Fields] OR "pituitary gland"[MeSH Terms] OR ("Pituitary"[All Fields] AND "gland"[All Fields]) OR "pituitary gland"[All Fields] OR "hypophysis"[All Fields]) AND "Dwarf"[Title/Abstract]) OR "pituitary dwarf"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm



GH: growth hormone; IGF-1: insulin-like growth factor 1; SD: standard deviation; rhGH: recombinant human growth hormone.

* For most patients, we use standard rhGH (somatropin), using a starting dose of approximately 35 micrograms/kg/day (for a total weekly dose of 0.24 mg/kg). For patients with severe GH deficiency, we use a lower starting dose of approximately 20 micrograms/kg/day because these individuals are more sensitive to the drug. For dosing of one of the long-acting rhGH formulations (Lonapegsomatropin-tcgd, somapacitan, or somatrogon), refer to local product information or UpToDate content.

¶ If rhGH is administered daily, then random sampling is sufficient for determining IGF-1 concentration. If a long-acting rhGH preparation is used, interpretation of the IGF-1 result depends on the timing of the sample compared with the preceding dose and the particular long-acting preparation because pharmacokinetics vary among these preparations; refer to UpToDate content.

Δ For monitoring rhGH therapy, target range for IGF-1 is the upper one-half of the normal range (ie, IGF-1 0 to +2 SD). IGF-1 levels below this target range are associated with subnormal growth response to therapy; IGF-1 levels above this target range (ie, >+2 SD) may be associated with possible adverse effects of rhGH. For the long-acting preparations, optimal IGF-1 targets have not been established, but it is reasonable to target mean IGF-1 values in the upper one-half of the normal range, similar to the strategy for standard rhGH preparations.

◊ If the rhGH dose is increased to >0.3 mg/kg/week but IGF-1 levels remain low (<–1 SD) despite good adherence to therapy, the patient may have GH insensitivity. If such patients also fail to have an appropriate growth response to rhGH therapy, the possibility of a GH insensitivity syndrome should be explored; refer to UpToDate content on GH insensitivity.

§ The growth response is typically considered adequate if the height velocity increases to above the 75th percentile for the child's age and gender during the period of "catch-up" growth. Refer to UpToDate topic text for details.

¥ In patients with a comorbid disease that contributes to or causes the short stature, IGF-1 levels vary depending on the nutritional status but are typically below the normal range or in the low end of the normal range.

Figure 1. Treatment Algorithm for the Management of Child Growth Hormone Deficiency[38]