GROWTH HORMONE DEFICIENCY IN ADULTS

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

AGHD	Adult Growth Hormone Deficiency Syndrome
AO-GHD	Adult-Onset Growth Hormone Deficiency
CADTH	Canadian Agency for Drugs and Technologies in Health
CO-GHD	Childhood Onset Growth Hormone Deficiency
DEXA	Dual-Energy X-Ray Absorptiometry
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GST	Glucagon-Stimulation Test
HAS	Haute Autorité de Santé
IMT	Intima-Media Thickness
IQWIG	Institute for Quality and Efficiency in Healthcare
ITT	Insulin Tolerance Test
MPHD	Multiple Pituitary Hormone Deficiencies
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PHD	Pituitary Hormone Deficiencies
QoL	Quality of Life
QoL-AGHDA	Quality of Life in Adult Growth Hormone Deficiency Assessment
RhGH	Recombinant Human Growth Hormone
SDS	Standard Deviation Score
TBI	Traumatic Brain Injury

Executive Summary

The Adult Growth Hormone Deficiency Syndrome (AGHD) is a clearly defined medical condition associated with an inadequate production or secretion of growth hormone (GH) by the pituitary gland and marked by reduced lean body mass and bone mineral density, heightened visceral fat accumulation, altered lipid profile, weakened muscle strength and exercise capacity, and a decline in overall well-being. GHD is associated with structural pituitary disease or cranial irradiation, and usually occurs in the context of additional features of hypopituitarism. The most prominent causes of adult-onset GHD are pituitary adenomas followed by craniopharyngiomas. Less commonly, adult-onset GHD is associated with irradiation, head injury, vascular, infiltrative, infectious, and autoimmune diseases[1,2].

The AGHD prevalence amounts to 2–3 per 10,000 population. Similarly, AGHD incidence is not well documented, but has been estimated at approximately 2 per 100,000 population, when cases with childhood-onset GHD persisting into adulthood are included[3].

Adult GH deficiency is associated with an extensive array of non-specific symptoms and physical signs involving body composition, metabolism, cardiac and bone manifestations which are nevertheless recognized by experienced endocrinologists[1].

If left untreated, Adult Growth Hormone Deficiency may increase the risk for heart disease, stroke, and bone fractures as a result of the alteration in body fat, cholesterol levels and circulation. Therefore, early detection and treatment for GHD can help prevent or reverse some of the adverse effects associated with the deficiency. It can also help restore hormone levels thereby preventing or reducing the severity of potential complications[4].

This report compiles all clinical and economic evidence related to Adult Growth Hormone Deficiency according to the relevant sources. The ultimate objective of issuing AGHD 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 AGHD patients in Saudi Arabia**. The main focus of the review was on North American and joint European and other international guidelines issued within the last five years. To elaborate, North American guidelines detailed the management of growth hormone deficiency in both adults and patients transitioning from pediatric to adult care. It also discusses rhGH replacement therapy in pregnancy and rhGH abuse. Furthermore, joint European and International guidelines elaborated on the use of the newly approved and SFDA registered drug; Somapacitan for the management of Adult GH deficiency. The guidelines also emphasize on safety considerations and potential hormonal interactions when a patient is subjected to hormone replacement therapy. In addition, a recent systematic review and meta-analysis was

tackled; thereby providing an in-depth understanding of the different AGHD drug therapies and their placement in pharmacological management.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in AGHD 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 AGHD involves a **multidisciplinary approach**. **Drug therapy is an integral component for the management of Adult Growth Hormone Deficiency.** The major goal for the AGHD pharmacological approach is to correct the wide spectrum of associated clinical alterations. The standard pharmacological interventions for AGHD include growth hormone therapy. Growth hormone is administered subcutaneously once a day, titrated to clinical symptoms, signs and IGF-1 (Insulin Like Growth Factor-1). It is generally well tolerated at the low doses used in adults. Newer agents for the treatment of AGHD include the Human Growth Hormone Analog – Somapacitan and the Growth Hormone Secretagogue Receptor Agonist – Macimorelin as a diagnostic agent. In 2020 and 2017, the two new drugs (Somapacitan and Macimorelin) were approved by the FDA for the treatment of Adult Growth Hormone Deficiency and for the diagnosis of AGHD respectively. Somapacitan is registered by the SFDA; however, Macimorelin is not.

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 AGHD.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 1. SFDA-Registered Drugs for the Management of Adult Growth Hormone Deficiency

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Somatropin	**Transition Patients with CO-GHD** **Patients With AO-GHD**	**1st**	Grade A[5]	Positive Recommendation from NICE[6], CADTH[7], HAS[8], and PBAC[9].
Somapacitan	**Patients With AO-GHD**	**1st**	No Grade	Positive Recommendation from PBAC[10].

Table 2. Non-SFDA-Registered Drugs for the Management of Adult Growth Hormone Deficiency

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Macimorelin	**Diagnostic Aid for Adult Growth Hormone Deficiency**	**1st**	Strong Recommendation[11,12]

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

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, there are no available clinical guidelines issued by Saudi bodies for the management of adult growth hormone deficiency.

1.2 North American Guidelines

1.2.1 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care [2019]

The AACE has opted for the following Grades of Recommendation/Level of Evidence to support its claims[13]:

Table 3. AACE Strengths of Recommendation/Levels of Evidence (Adapted from GRADE System)

Recommendation Type	Definition	Certainty of the Evidence	
Strong AACE recommends for/against…	High confidence is the estimate of effect across outcomes. Most informed patients would choose the recommended option.	High	⨁⨁⨁⨁
		Moderate	⨁⨁⨁
Conditional AACE suggest…	Lower confidence in the estimate of effect across outcomes. Patient choices may vary based on values and preferences.	Moderate	⨁⨁⨁
		Low	⨁⨁
Good Practice Statement*	Ungraded guidance statements with no direct supporting evidence.	None	

The 2019 AACE Growth Hormone Task Force has issued the following guidelines regarding the management of growth hormone deficiency in adults[14].

Adult GHD Definition

- The possibility of Adult GHD should be considered in every patient with a history of hypothalamic-pituitary disease, as this condition is a well-defined clinical entity that is associated with excess morbidity and mortality.

- Adult-Onset GHD (AO-GHD) is most commonly caused by isolated idiopathic GHD and hypothalamic-pituitary tumors and/or their treatment regimens, respectively.
- Other causes of adult GHD that are not associated with tumors include TBI, subarachnoid hemorrhage, ischemic stroke, and infections in the central nervous system.

Differences Between CO-GHD Versus AO-GHD

- It is recommended that differences be recognized in the etiology of CO-GHD compared to AO-GHD; specifically when tackling phenotypic features.
- The onset of CO-GHD begins during the developmental years and adults with CO-GHD may have had a longer duration of being GH-deficient than their AO-GHD counterparts.

Benefits of Continuing rhGH Replacement in Transition Patients with CO-GHD

- Adults with CO-GHD attributed to structural pituitary or brain tumors are recommended to be followed up meticulously during transition due to their heightened risk of lower bone mineral density, impaired bone microarchitecture, and more adverse body composition abnormalities and cardiovascular risk markers compared to those with AO-GHD.

Testing for Adult GHD

- The accuracy and reliability of GH–stimulation tests for the diagnosis of adult GHD have not been properly established; however, screening may be considered.

Figures 1 and 2 portray algorithms for testing transition and adult patients with clinical suspicion of GHD and were retrieved from the 2019 AACE Growth Hormone Task Force guideline for the management of adults with growth hormone deficiency[14]:

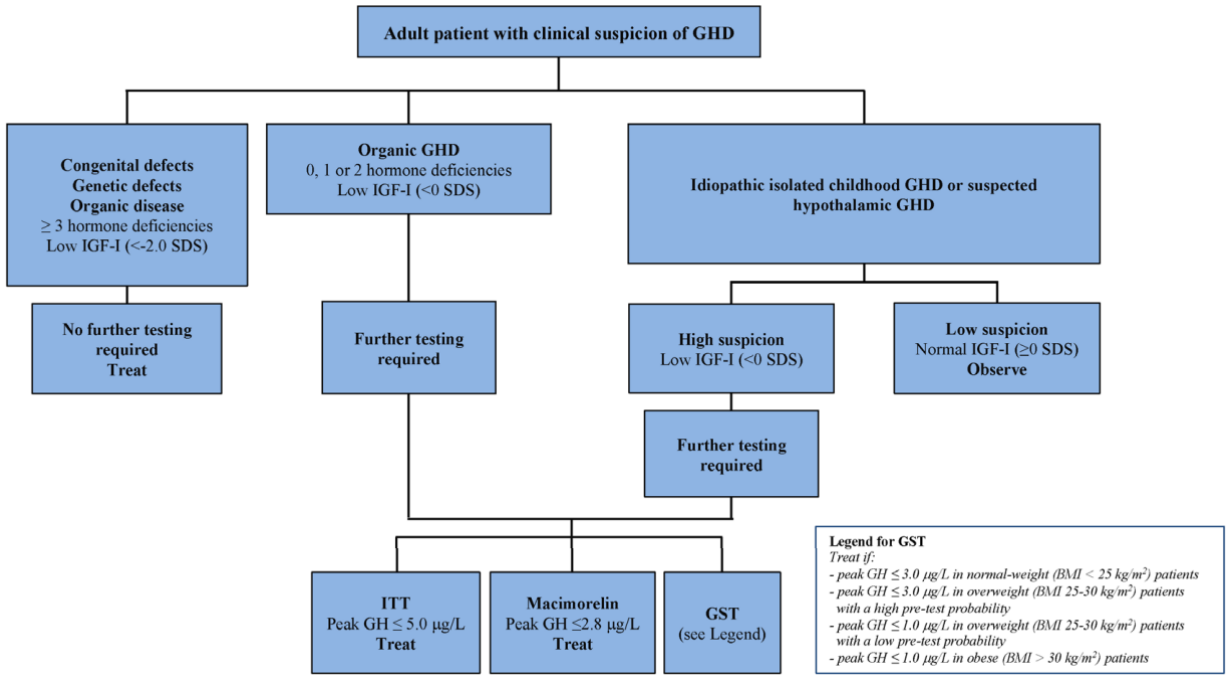

Figure 1. *Algorithm for testing transition patients with clinical suspicion of GHD*

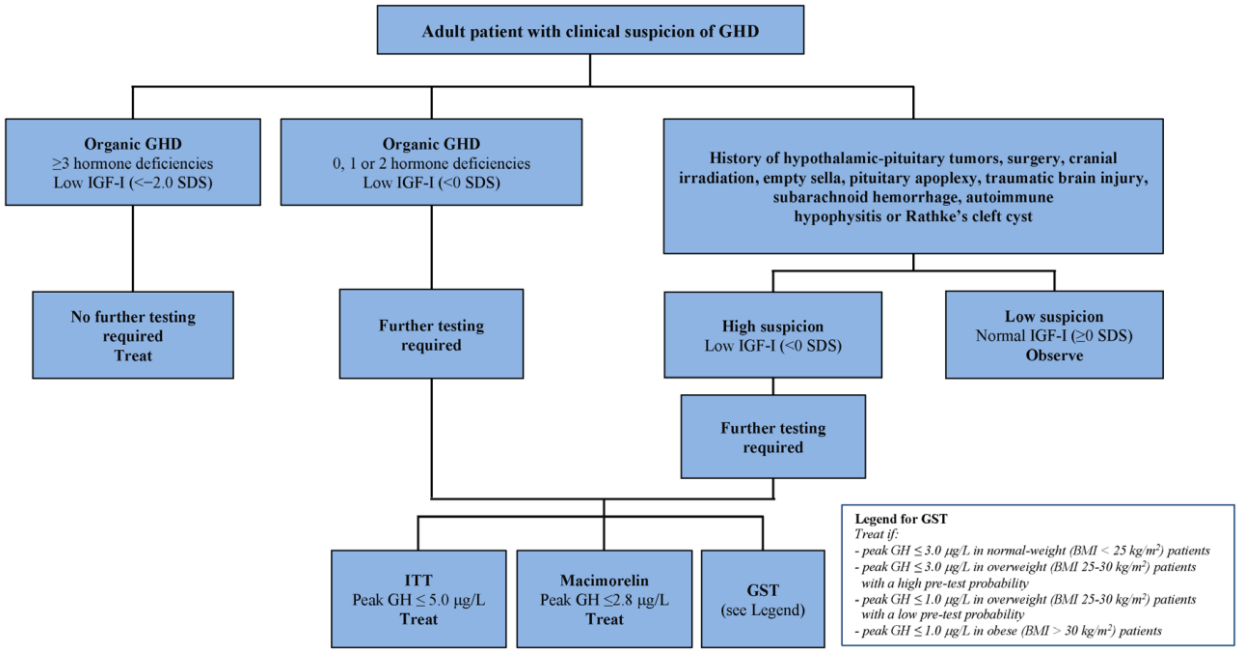

Figure 2. *Algorithm for testing adult patients with clinical suspicion of GHD*

- GH–stimulation test/s should be performed selectively for patients with a history suggestive of a reasonable clinical suspicion of GHD and with the intent of initiating rhGH replacement upon diagnosis confirmation.

- Resuming rhGH replacement in adulthood requires retesting for GHD with GH–stimulation test/s in most transition patients, especially patients with idiopathic isolated GHD and serum IGF-1 SDS<0, when longitudinal growth is complete, and at least 1 month after discontinuation of pediatric rhGH therapy.
- In transition patients with MPHD (≥3 PHD) and low-serum IGF-1 levels (<–2.0 SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects, retesting is not required and rhGH therapy may be continued in these patients without interruption.

Testing and Diagnosis of GHD

- The diagnosis of adult GHD cannot be based solely on random serum GH and IGF-1 levels; GH–stimulation test/s should be performed to confirm the diagnosis with the exception of specific subpopulations, such as patients with organic hypothalamic pituitary disease who have MPHD (≥3 PHD) and low serum IGF-1 levels (<–2.0 SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic pituitary structural brain defects.
- The gold standard test to be able to diagnose adult GHD is the insulin tolerance test (ITT) with a peak GH cut point of 5 mcg/L.
- If the ITT is contraindicated or in case it is not feasible, the glucagon-stimulation test (GST) and the Macimorelin test could be considered as alternative tests for adults suspected to have GHD.

Pharmacological Management

- There is no evidence that one rhGH product is more advantageous than another; therefore, the use of one commercial rhGH product is not suggested over other rhGH products.
- For the purpose of guiding rhGH dose adjustment, serum IGF-1 is recommended to be used as a biomarker.
- RhGH dosing is recommended to be individualized independent of body weight, initiating with a low dose, and gradually up-titrating the dose to normalize serum IGF-1 levels with the primary aim of minimizing the induction of side effects.
- Serum IGF-1 levels should be targeted within the age-adjusted reference range (IGF-1 SDS between –2 and +2) provided by the laboratory utilized all

while taking into consideration the pretreatment IGF-1 SDS and the circumstances and tolerability of each individual patient.

- The goals of treatment include clinical response, avoidance of side effects, and targeting serum IGF-1 levels to fall within the age-adjusted reference range (IGF-1 SDS between –2 and + 2).
- In GH-deficient patients with concurrent DM, obesity, older age, and previous gestational DM, to avoid impairment of glucose metabolism, initiating rhGH therapy using low GH dosages of 0.1-0.2 mg/day is recommended.
- In non-diabetic young adults less than 30 years of age and women on oral estrogen therapy, higher rhGH starting doses of 0.3 to 0.4 mg/day are advised.

Follow Up

- Follow up is conducted at 1-to-2-month intervals initially, all while increasing the rhGH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations.
- Follow-up can be implemented at approximately 6- to 12-month intervals once maintenance doses are achieved.
- If clinically indicated, the parameters to be assessed include serum IGF-1, fasting glucose, hemoglobin A1c, fasting lipids, BMI, waist circumference, waist-to-hip ratio, serum-free T4, and the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin stimulation test.
- For the elderly and those with other comorbidities as Diabetes Mellitus, shorter follow-up time intervals and smaller dose increments can be implemented.

Transition Patients

- rhGH therapy is to be resumed at 50% of the dose used in childhood when restarting rhGH therapy.
- Modification of the dose is based on several factors including clinical response, side effects, serum IGF-1 levels, serum IGF-1 levels and individual patient considerations.
- The following measurements are recommended for transition patients; annual measurements of height, weight, BMI, and waist and hip circumference, measuring bone mineral density and fasting lipids after discontinuing rhGH therapy as a baseline assessment, subsequently every 2 to 3 years and every year, respectively.

Adult GHD Complications

- Increased risk of cardiovascular morbidity and mortality; clinicians should monitor cardiovascular parameters at 6-to-12-month intervals and include fasting lipids, systolic and diastolic blood pressure, and heart rate.

  If clinically indicated, more detailed examinations such as electrocardiogram, echocardiogram, and carotid echo-Doppler examinations may be performed.

- Increased risk of developing osteopenia and osteoporosis; it is suggested that physicians measure bone mineral content and bone mineral density in GH-deficient patients before starting rhGH therapy. If the initial bone dual-energy X-ray absorptiometry (DEXA) scan is abnormal, clinicians should repeat bone DXA scans at 2- to 3-year intervals to assess the need for additional bone-treatment modalities.

- Glucocorticoid and thyroid hormone requirements may be altered as a result of interactions of GH with other pituitary hormone axes. Close monitoring of the hormones is therefore required especially before initiation of rhGH therapy, as the introduction of these hormones or dose increments may be required while on rhGH therapy.

- Impaired Quality of Life (QoL); before rhGH treatment initiation and at 12-month intervals, clinicians should consider assessing baseline QoL using specific Quality of Life in Adult Growth Hormone Deficiency Assessment (QoL-AGHDA) questionnaires to determine whether there is a change or sustained impact of rhGH therapy on QoL.

Duration of Treatment with rhGH Replacement Therapy

- The optimal duration of rhGH replacement therapy remains unclear.

- rhGH treatment can be continued indefinitely if patients on rhGH replacement experience beneficial effects on QoL and objective improvements in biochemistry, body composition, and bone mineral density.

rhGH During Conception and Pregnancy

- Although the use of rhGH is supported by previous studies, more data is needed to establish its safety.

- Routine use of rhGH for conception or continued use during pregnancy in women with GHD cannot be recommended at this present time.

Safety of rhGH Replacement Therapy

Side Effects Profile of rhGH Replacement Therapy

- Side effects as fluid retention are typically seen at dose initiation and escalation of rhGH and generally subside upon dose reduction or therapy cessation.
- In older and obese patients, lower doses of rhGH are recommended since these patient populations are more susceptible to the side effects of rhGH replacement.
- The use of high rhGH doses is recommended to be avoided to minimize the risk of side effects and aim to maintain target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between –2 and + 2).

GHD Adults with Comorbidities and Special Considerations

- If rhGH therapy is considered in patients with concurrent Diabetes Mellitus or in those with newly developed Diabetes Mellitus, the use of low dose rhGH therapy, and addition and/or adjustments in antidiabetic medications are suggested.

  If pre-existing Diabetes Mellitus worsens while on rhGH therapy, it would be appropriate to initiate or increase the doses of antidiabetic therapy or discontinue rhGH therapy and optimize treatment of Diabetes Mellitus first before considering resuming rhGH therapy in these patients.
- Treatment with rhGH is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy and a history of active malignancy excluding basal-cell or squamous-cell skin cancers.
- Clinicians should be cautious when initiating rhGH treatment in patients with a strong family history of cancer.
- In GHD adults with a history of cancer who are willing to start rhGH replacement therapy, low dose rhGH therapy should be initiated at least 5 years after cancer remission is achieved and after discussion with the patient's oncologist.

RhGH Abuse

- Detection of rhGH abuse is challenging; this is attributed to GH being a naturally occurring substance which has a short half-life after subcutaneous and intravenous injection, is released in a pulsatile fashion, and its levels increase after exercise.

- Drug testing: Urine sampling is not recommended as it has not been shown to be accurate and reliable. Repeated blood sampling over 24-hours is neither practical nor feasible in the sports setting.
- Under no circumstances should rhGH be prescribed for sports or for "anti-aging" purposes.

1.2.2 Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline [2011]

In 2011, the Endocrine Society updated its Clinical Practice Guideline on Evaluation and Treatment of Adult Growth Hormone Deficiency (GHD) previously published in 2006[15]. The grading scheme is detailed in tables 4 and 5.

Table 4. Endocrine Society Guidelines Levels of Evidence

Certainty of Evidence	Interpretation
High ⨁⨁⨁⨁	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⨁⨁⨁◯	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⨁⨁◯◯	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very Low ⨁◯◯◯	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Table 5. Endocrine Society Guidelines Strengths of Recommendations

Strength of Recommendation	Criteria	Interpretation by Patients	Interpretation by Healthcare Providers	Interpretation by Policy Makers
1 - Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in	Most individuals in this situation would want the recommended course of action, and only a small	Most individuals should receive the recommended course of action. Adherence to this recommendation	The recommendation can be adopted as policy in most situations. Adherence to this recommendation

	most settings (or vice versa)	proportion would not.	according to the guidelines could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	according to the guideline could be used as a quality criterion or performance indicator.
2 - Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa)	The majority of individuals in this situation would want the suggested course of action, but many would not.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their individual risks, values and preferences.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

The main recommendations are summarized below[16]:

Diagnosis of Adult GHD

- Adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies are recommended to be considered for evaluation for acquired GHD.
- Idiopathic adult GHD is very rare, and stringent criteria are necessary to make this diagnosis. The use of two tests is suggested prior to diagnosing patients with adult GHD. The presence of a low IGF-I also increases the likelihood of a credible diagnosis.
- The insulin tolerance test (ITT) and the GHRH-arginine test are recommended for the diagnosis of GHD as they have sufficient sensitivity and specificity. However, using the GHRH-arginine test in those with clearly established, recent hypothalamic causes – within 10 years – of suspected GHD as irradiation may be misleading.
- The glucagon stimulation test is suggested to be used to diagnose GHD when GHRH is not available and the performance of an ITT is either contraindicated or not practical in a given patient.
- A normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to make the diagnosis of GHD.
- A low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing.

Pharmacological Management with GH Therapy

- It is recommended that GH therapy offers a clinical benefit in body composition and exercise capacity.
- It is suggested that GH therapy offers a clinical benefit in skeletal integrity.
- It is suggested that GH therapy improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid intima-media thickness (IMT), and aspects of myocardial function, but tends to increase insulin resistance.
- Mortality is increased in patients with hypopituitarism and GHD has been implicated in this; however, GH has not been shown to improve mortality.
- It is suggested that GH therapy has improved the QoL of adult GHD patients.

- It is recommended that GH dosing regimens be individualized rather than weight based all while initiating the patient at a low dose and titrating the regimen based on clinical response, side effects and IGF-I levels.
- It is recommended to take into consideration gender, estrogen status and age when dosing GH.
- It is suggested that patients receiving GH therapy be monitored at 1-to-2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-I levels, and other parameters of GH response.

Side Effects and Risks Associated with GH Therapy

- In the presence of an active malignancy, treatment is contraindicated.
- It is recommended that GH therapy in patients with diabetes mellitus may require adjustments in antidiabetic medications.
- Thyroid and adrenal function are to be monitored when treating GHD adults with GH therapy.

1.3 European Guidelines

There are no available separate European Guidelines for the management of Adult Growth Hormone Deficiency; the guidelines are only joint between European and other international entities found in section 1.4 below.

1.4 International Guidelines

1.4.1 Guidance For The Treatment Of Adult Growth Hormone Deficiency with Somapacitan, A Long-Acting Growth Hormone Preparation [2022]

This guidance was established with the contribution of international institutions from Germany, the United States, Denmark, and Japan. The recommendations are detailed below[17]:

Recommendations for initiating GH replacement with Somapacitan in treatment-naïve patients with AGHD

- Patients aged 18 to 59 years and who are treatment naïve should receive a starting dose of 1.5 mg/week.

  Younger patients aged 18–30 years may require higher maintenance doses. Therefore, more frequent dose increases and/or larger dose increments may be needed.

- Patients aged 60 years and older and who are treatment naïve should receive a starting dose of 1.0 mg/week.

  Dose titration in this patient population is to be undertaken with caution specifically since men approaching 60 years of age are prone to experience more adverse effects.
- Women on oral estrogen and who are treatment naïve should receive a starting dose of 2.0 mg/week.
- When initiating treatment with Somapacitan, the treating physician and the patient should agree on the injection day to ensure the feasibility of IGF-I sampling on day 3–4.

Recommendations for Somapacitan therapy in AGHD patients switching from daily GH to Somapacitan

- A starting dose of 1.5 mg/ week should be given to patients aged 18–59 years switching from daily GH to Somapacitan.

  As per the European Union, the starting dose for this group could be 2mg/ week.

  Younger patients aged 18–30 years may require higher maintenance doses. Therefore, more frequent dose increases and/or larger dose increments may be needed.
- A starting dose of 1.0 mg/week is to be given to patients aged 60 years and older switching from daily GH to Somapacitan.

  As per the European Union, the starting dose for this group could be 1.5 mg/week.

  Dose titration in this patient population is to be undertaken with caution specifically since men approaching 60 years of age are prone to experience more adverse effects.
- A starting dose of 2mg/week is to be given to women on estrogen switching from daily GH to Somapacitan.

  As per the European Union the starting dose for this group could be 4mg/week.
- The first dose of Somapacitan can be administered the day after the last dose of daily GH.

  In clinical trials, a one-day washout period between the last dose of daily GH and first dose of Somapacitan was used.

- When patients are switched from daily GH to Somapacitan, the physician and the patient should agree together on the injection day to ensure the feasibility of IGF-I sampling on day 3–4.

Recommendations for IGF-I-guided dose titration and monitoring of AGHD patients treated with Somapacitan

- At 2-to-4-week intervals, the Somapacitan dose should be individually adjusted for each patient and increased gradually.

  Dose titration intervals should be spaced at least 2 weeks apart to allow the IGF-I response pattern to reach a steady state.

- The dose should be titrated up or down at each step by 0.5 mg to 1.5 mg until the desired response is achieved.
- Upon dose titration, the clinical response, experience of adverse reactions and serum IGF-I concentrations should be taken into consideration. Clinical response biomarkers as body composition and quality of life are also important to be evaluated.
- The mean IGF-I SDS target for the week should aim to achieve the upper normal range (0 to +2 SDS), not exceeding 2 SDS.
- If patients experience adverse reactions or mean IGF-I concentrations for the week were found to be above the normal range, the Somapacitan dose should be decreased or temporarily discontinued.
- 8 mg/week is the maximum recommended dosage.
- The mean IGF-I SDS for the week should be measured using a single sample drawn 3–4 days after the previous Somapacitan dose. (IGF-I levels measured on day 4 after dosing represent the best estimate of the weekly mean.)
- Consider postponement of the measurement for one week and measure mean IGF-I levels 3–4 days after the next dose if measurement of IGF-I levels 3–4 days after the Somapacitan dose is not feasible in a certain week.
- If need be, the dosing day can be changed provided that the interval between two doses is at least 4 days.

  Once-weekly dosing should be continued after adjusting to the new dosing day.

  IGF-I levels are maintained if the Somapacitan dose is delayed by 1–3 days.

Treatment Goals and Evaluation

- Treatment aim: Achieving weekly mean IGF-I levels within the age-adjusted normal range within 12 months of beginning dose titration.

  Treatment compliance should be assessed prior to initiating alternate therapy if the target cannot be achieved, and if the patient does not achieve the desired clinical response.

- Treatment evaluation for efficacy and safety is to be considered at 6-to-12-month intervals during Somapacitan maintenance treatment.

  Monitoring parameters include IGF-I, glucose, and lipid levels, body composition, and body mass index.

Recommendations for Missed Doses

- A missed dose is to be administered at the soonest within the following 3 days.

  The regular once weekly dosing regimen is to be resumed.

- In case more than 3 days have passed, the dose should be skipped, and the next dose is to be administered on the regular dosing day.

Special Populations

- There is limited data available on the use of GH replacement therapy in pregnant patients and in women of childbearing potential not using contraception. Somapacitan should not be administered during pregnancy.
- Limited data is available on the use of Somapacitan during breast-feeding; therefore, its use is not recommended.
- Somapacitan is contraindicated in patients with severe hepatic impairment (Child-Pugh score C).

  Patients with moderate hepatic impairment (Child-Pugh score B) should be treated with a starting dose of 1 mg/week.

  Dose titration should be individualized, with a maximum dose of 4 mg/week.

- A lower starting dose of 1 mg/week is required in patients with renal impairment. Dose titration should be individualized.
- It is important to monitor glucose levels, especially for those with risk factors for diabetes mellitus.

  Patients with type 1 or type 2 diabetes should be closely monitored and doses of antidiabetic drugs may need to be adjusted when patients initiate Somapacitan.

1.4.2 Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia [2007]

The European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia have collaborated to issue joint guidelines for the management of Adult GHD[18]:

The recommendations are found below:

Testing for Adult GHD

The three groups of patients to be tested include:

1) Those with signs and symptoms of hypothalamic–pituitary disease (endocrine, structural, and/or genetic causes).

2) Those who have received cranial irradiation or tumor treatment.

3) Those with traumatic brain injury (TBI) or subarachnoid hemorrhage.

Treatment in GHD in Adult

- Goal of treatment: Correct the metabolic, functional, psychological abnormalities associated with adult GHD, as well as to maximize benefit and minimize side effects.
- It is recommended to initiate GH in young men and women at a dose of 0.2 and 0.3 mg/day respectively, and in older individuals at a dose of 0.1 mg/day.
- It is not recommended to determine the dose based on body weight due to large interindividual variation in absorption, in sensitivity to GH and the lack of evidence that a larger replacement dose is required for heavier individuals in adults.
- GH is recommended to be administered in the evening to mimic the greater secretion of GH at night.
- Dose escalation should be individualized, gradual and based on clinical and biochemical response.
- In transition, the doses used in adolescents are intermediate doses between the pediatric doses required during the growth years and the adult dose.

Hormone Interactions

- **Sex Steroid Therapy:** Estrogen administered by the oral route impairs GH action, leading to higher dose requirements. Since GH requirements will be reduced, it is preferable that estrogen be replaced in hypopituitary women physiologically by a non-oral route.
- **Glucocorticoid Replacement Therapy:** Initiation of GH treatment may require an increase in hydrocortisone dose in patients with central adrenal failure. Weight, appetite, and mood are required to assess the need for glucocorticoid dose modification.
- **Thyroid Function:** GH treatment may unmask preexisting central hypothyroidism, which is recognized by a fall of serum T4 into the subnormal range. In thyroxine-replaced patients, GH substitution may necessitate adjustment of the thyroid hormone dose.

Safety Considerations

- GH replacement therapy is not associated with an increased incidence of either type 1 or type 2 diabetes mellitus. However, it is associated with an increase in insulin resistance and may worsen glucose tolerance. If type 2 diabetes is diagnosed, it should be managed similarly to any other patient with this disease, and GH replacement therapy is to be continued.
- There is no evidence that GH Replacement Therapy is associated with hypothalamic or pituitary tumor recurrence.
- There is no evidence that GH replacement in adults is associated with de novo malignancy or recurrence. GH therapy should be halted in any patient with active malignancy until the underlying condition is controlled.

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in **2022** for Adult Growth Hormone Deficiency.

Table 6. Systematic Review and Meta-Analysis for Adult GHD

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Dutta et al. (2022)[19]	"Efficacy and Safety of Long-Acting Growth	To analyze the efficacy and safety of long-acting	**Primary Outcome:** Evaluate changes in	• Over 24-34 weeks clinical use, patients receiving long-acting GH had comparable change in lean mass [MD-

		Hormone in Adult Growth Hormone Deficiency: A Systematic Review and Meta-Analysis"	growth hormone (GH) therapy in adult GH deficiency.	body composition parameters. **Secondary Outcomes:** Evaluate alterations in glycaemia and adverse events.	0.28 kg (95% CI: 0.94 – 0.38); P = 0.41; I^2 = 29% (low heterogeneity)] and fat mass [MD-0.10 kg (95% CI: 1.97 – 1.78); P = 0.92; I^2 = 77% (considerable heterogeneity)] as compared to daily GH injections. • Long-acting GH use was associated with significantly lower visceral adipose tissue [MD-1.75 cm^2 (95% CI: 2.14 – 1.35); P < 0.01; I^2 = 0% (low heterogeneity)] and higher gynoid fat-mass [MD 0.14 kg (95% CI: 0.02 – 0.26); P = 0.03] compared to daily GH injections. • Total adverse events [Risk ratio (RR) 1.65 (95% CI: 0.83 – 3.29); P = 0.15; I^2 = 68%] and severe adverse events [RR 0.60 (95% CI: 0.30 – 1.19); P = 0.14; I^2 = 0%] were not significantly different in long-acting GH group compared to controls. • Occurrence of headache, arthralgia, nasopharyngitis, new onset diabetes, anti-GH antibodies were comparable among groups. • Long-acting GH users had significantly higher treatment adherence compared to controls [OR 4.80 (95% CI: 3.58 – 6.02); P < 0.01; I^2 = 0%].

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[11,20]:

Table 7. 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 (Adult) [DDD]*	**Non-Weight Based Dosing:** Patients ≤ 60 years of age without diabetes mellitus, glucose intolerance, or obesity: 0.2 to 0.4 mg/day; in patients transitioning from pediatric treatment, higher doses (eg, 50% of the dose used in childhood) may be needed.

	Patients > 60 years of age, or with diabetes mellitus, glucose intolerance, or obesity: SUBQ: 0.1 to 0.2 mg/day. **Weight-based dosing:** Initiating somatropin with weight-based dosing is generally not recommended due to greater risk of dose-dependent adverse effects (eg, edema), particularly in patients with obesity. **Genotropin, Omnitrope:** Weekly dosage: ≤0.04 mg/kg/week divided into equal doses administered 6 or 7 days per week. **Saizen:** ≤0.005 mg/kg/day **Norditropin:** 0.004 mg/kg/day
Maximum Daily Dose Adults*	Saizen: 0.01 mg/kg/day Norditropin: 0.016 mg/kg/day
Dose (pediatrics)	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. **Adjustment for Toxicity:** **Fluid retention:** Consider a dose reduction or discontinuation if clinical manifestations of fluid retention occur. **Intracranial hypertension:** Discontinue therapy if papilledema occurs; may resume somatropin at a lower dose once intracranial hypertension–associated signs and symptoms have resolved.
Prescribing edits*	MD, QL
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)	Genotropin, Omnitrope: 0.08 mg/kg/week
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	**Older Adults:** Older adult patients may be more sensitive to the actions of somatropin; consider lower starting doses and smaller dose increments. **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.
Pregnancy	Data with somatropin use during pregnancy in females with hypopituitarism is limited; however, adequate replacement prior to conception may improve fertility. The Endocrine Society guidelines for hormonal replacement in hypopituitarism suggest

	discontinuation of somatropin during pregnancy.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
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 trauma, 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 clinical response, serum IGF-1, and adverse effects every 1 to 2 months during dose titration. Once at maintenance dose, monitor serum IGF-1, fasting glucose, hemoglobin A1C, BMI, waist circumference/waist to hip ratio, thyroid function (free T_4), adrenal function, lipid profile, BP, heart rate, clinical response, and adverse effects every 6 to 12 months. In patients with a pituitary adenoma lesion, obtain MRI at baseline and periodically thereafter. Evaluate bone mineral density prior to therapy initiation; repeat DXA scan every 1.5 to 3 years if initial bone scan is abnormal.
Precautions	**Fluid retention:** Fluid retention may occur in adults. **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.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Adult 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 8. Somatropin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Somatropin	NICE[6]	August 27, 2003 – **Conditional Positive Recommendation**: The Committee considered – on the basis of all the evidence it had reviewed, the uncertainties surrounding the precise definition of the subgroup that would most benefit from GH treatment, and the extent of any such benefit – that cost-effectiveness should be evident for individual patients. Thus in patients who demonstrate an improvement score lower than 7 points, the Committee concluded that cost effectiveness was not established, and the continued use of GH in these patients after the initial assessment period could not be justified.
	CADTH[7]	December 20, 2013 – **Positive Recommendation**: The Canadian Drug Expert Committee (CDEC) recommends that Genotropin be listed for the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) with the following condition: List in a manner similar to other somatropin products for the treatment of adults with GHD.
	HAS[8]	October 3, 2019 – **Positive Recommendation**: Opinion in favor of maintaining reimbursement in the treatment of growth hormone deficiency in adults.
	IQWIG	N/A
	PBAC[9]	July 2017 – **Positive Recommendation**: The PBAC recommended the listing of somatropin for the treatment of adults with severe GHD, and substantially impaired QoL at baseline, on the basis that it should be available only under special arrangements under Section 100 (Growth Hormone Program). The PBAC was satisfied that somatropin provided, for some patients, a significant improvement in efficacy over standard care.

CONCLUSION STATEMENT- Somatropin

There is no evidence that one rhGH product is more advantageous than another; therefore, the use of one commercial rhGH product is not suggested over other rhGH products. It is recommended to initiate GH in young men and women at a dose of 0.2 and 0.3 mg/day respectively, and in older individuals at a dose of 0.1 mg/day. GH is recommended to be administered in the evening to mimic the greater secretion of GH at night. Serum IGF-1 is said to guide rhGH dosage adjustments. Furthermore, it is **recommended** that GH therapy offers a clinical benefit in body composition and exercise capacity and it is **suggested** that GH therapy offers a clinical benefit in skeletal integrity and several cardiovascular surrogate outcomes but tends to increase insulin resistance. Its use is backed by several HTA bodies such as NICE, CADTH, HAS, and PBAC. Limitations to its use include a 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[11,20]:

Table 9. 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 (Adult) [DDD]*	1.5 mg once weekly; may increase dose by 0.5 to 1.5 mg/week every 2 to 4 weeks

	based on clinical response and insulin-like growth factor 1 (IGF-1) levels; reduce dose if needed for adverse reactions or elevated IGF-1 levels.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** Mild impairment: No dosage adjustment is necessary. Moderate impairment: Initial: 1 mg once weekly; adjust dose in smaller increments (maximum dose: 4 mg/week). Severe impairment: Use is not recommended. **Adjustment for Toxicity:** **Malignancy:** Discontinue therapy if evidence of tumor progression/recurrence of preexisting malignancy. **Papilledema:** Discontinue therapy if papilledema occurs; if papilledema is a result of intracranial hypertension, may consider restarting at a lower dose once signs/symptoms of intracranial hypertension resolve.
Prescribing edits*	PA, AGE, QL, MD
AGE (Age Edit)	The safety and effectiveness of Somapacitan have not been established in pediatric patients.
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 adults with growth hormone deficiency (such as endocrinologists).
PA (Prior Authorization)	This drug should be given as replacement of endogenous growth hormone in adults with growth hormone deficiency at a dose of 1.5 mg once weekly; the physician may increase the dose by 0.5 to 1.5 mg/week every 2 to 4 weeks based on clinical response and insulin-like growth factor 1 (IGF-1) levels. This medication is to be prescribed by an endocrinologist. + Check other Prescribing Edits (AGE, QL, MD)
QL (Quantity Limit)	Maximum dose: 8 mg/week.
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**: Fluid retention, glucose tolerance, intracranial hypertension, neoplasm.
Drug Interactions*	**Category X:** Macimorelin
Special Population	**Older adults:** Patients ≥65 years of age may be more sensitive to the actions of somapacitan due to greater drug exposure than patients <65 years of age at the same dose level; lower starting doses and smaller dose increments are required. **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.
Pregnancy	Continued use of short-acting growth hormone replacement early in pregnancy in patients with growth hormone deficiency has not been associated with adverse pregnancy outcomes.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
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, HbA1C, 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. The 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 Adult 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 10. Somapacitan HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Somapacitan	NICE[21]	Not applicable
	CADTH[22]	Still under processing; Not applicable

	HAS	N/A
	IQWIG	N/A
	PBAC[10]	March 2022 – **Positive Recommendation**: The PBAC recommended the Section 100 Growth Hormone Program listing of 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 used as replacement of endogenous growth hormone in adults with growth hormone deficiency. It is given at a dose of 1.5mg once weekly to patients aged 18 to 59 years, and at a dose of 1mg once weekly to patients aged 60 years and older. The physician may increase the dose by 0.5 to 1.5 mg/week every 2 to 4 weeks based on clinical response and insulin-like growth factor 1 (IGF-1) levels; and reduce dose if needed for adverse reactions or elevated IGF-1 levels. The use of Somapacitan is backed by PBAC as an HTA body. Limitations to its use include fluid retention, glucose tolerance, intracranial hypertension and neoplasms.

2.2 Other Drugs

2.2.1 Macimorelin

Macimorelin was approved by the FDA in December 2017 and by the EMA on January 11th of 2019. Macimorelin is used as a diagnostic aid for adult growth hormone deficiency. The dose has not been established for patients whose BMI > 40 kg/m^2. For patients whose BMI ≤ 40 kg/m^2, Macimorelin is to be given as a single dose of 0.5 mg/kg.

Section 3.0 Key Recommendations Synthesis

The guidelines used in this document apply to adult GHD patients defined as patients being aged 18 and above.

- The gold standard test to be able to diagnose adult GHD is the insulin tolerance test (ITT) with a peak GH cut point of 5 mcg/L. (Grade B)
- If the ITT is contraindicated or in case it is not feasible, the glucagon-stimulation test (GST) and the Macimorelin test could be considered as alternative tests for adults suspected to have GHD. (Grade B)
- There is no evidence that one rhGH product is more advantageous than another; therefore, the use of one commercial rhGH product is not suggested over other rhGH products. (Grade D)
- It is recommended to initiate GH in young men and women (With confirmed adult onset GHD or with confirmed persistent CO-GHD) at a dose of 0.2 and 0.3 mg/day respectively, and in older individuals at a dose of 0.1 mg/day. (Grade A)
- GH is recommended to be administered in the evening to mimic the greater secretion of GH at night. (No Grade)
- Serum IGF-1 levels should be targeted within the age-adjusted reference range (IGF-1 SDS between –2 and +2) provided by the laboratory utilized all while taking into consideration the pretreatment IGF-1 SDS and the circumstances and tolerability of each individual patient. (Grade D) When SDS is not available in clinical settings, it is suggested to use GH reference ranges; The normal range for GH level is typically: For adult males: 0.4 to 10 nanograms per milliliter (ng/mL), or 18 to 44 picomoles per liter (pmol/L) For adult females: 1 to 14 ng/mL, or 44 to 616 pmol/L. For children: 10 to 50 ng/mL, or 440 to 2200 pmol/L.
- Serum IGF-1 is said to guide rhGH dosage adjustments. (Grade A)
- Side effects as fluid retention are typically seen at dose initiation and escalation of rhGH and generally subside upon dose reduction or therapy cessation. (Grade A)
- In older and obese patients, lower doses of rhGH are recommended since these patient populations are more susceptible to the side effects of rhGH replacement. (Grade A)
- In the presence of an active malignancy, GH Replacement Therapy is contraindicated. (Grade B)

- It is recommended that GH therapy in patients with diabetes mellitus may require adjustments in antidiabetic medications. (Grade B)
- Thyroid and adrenal function are to be monitored when treating GHD adults with GH therapy. (Grade B)
- It is **recommended** that GH therapy offers a clinical benefit in body composition and exercise capacity (Strong Recommendation) and it is **suggested** that GH therapy offers a clinical benefit in skeletal integrity (Conditional Recommendation) and several cardiovascular surrogate outcomes but tends to increase insulin resistance. (Conditional Recommendation)
- Follow up is conducted at 1-to-2-month intervals initially, all while increasing the rhGH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations. (Grade A)
- Follow-up can be implemented at approximately 6- to 12-month intervals once maintenance doses are achieved. (Grade A)
- Due to the elevated risk of developing osteopenia and osteoporosis, it is recommended that bone mineral content and bone mineral density be measured in GH-deficient patients before starting rhGH therapy. If the initial bone dual-energy X-ray absorptiometry (DEXA) scan is abnormal, clinicians should repeat bone DXA scans at 2- to 3-year intervals to assess the need for additional bone-treatment modalities. (Grade C)
- rhGH treatment can be continued indefinitely if patients on rhGH replacement experience beneficial effects on QoL and objective improvements in biochemistry, body composition, and bone mineral density. (Grade B)
- Somapacitan is used as replacement of endogenous growth hormone in adults with growth hormone deficiency. (No Grade)
- Somapacitan is given at a dose of 1.5mg once weekly to patients aged 18 to 59 years, and at a dose of 1mg once weekly to patients aged 60 years and older. (No Grade)
- The physician may increase the Somapacitan dose by 0.5 to 1.5 mg/week every 2 to 4 weeks based on clinical response and insulin-like growth factor 1 (IGF-1) levels; and reduce dose if needed for adverse reactions or elevated IGF-1 levels. (No Grade)

Section 4.0 Conclusion

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

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

Section 5.0 References

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21. Somapacitan NICE.

22. Somapacitan CADTH.

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	Sort By	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/Abstr		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	0

act])) OR (Hypophysial Dwarf[Title/Abstract])) OR (Pituitary Dwarf[Title/Abstract])			"purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]) AND ("human growth 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

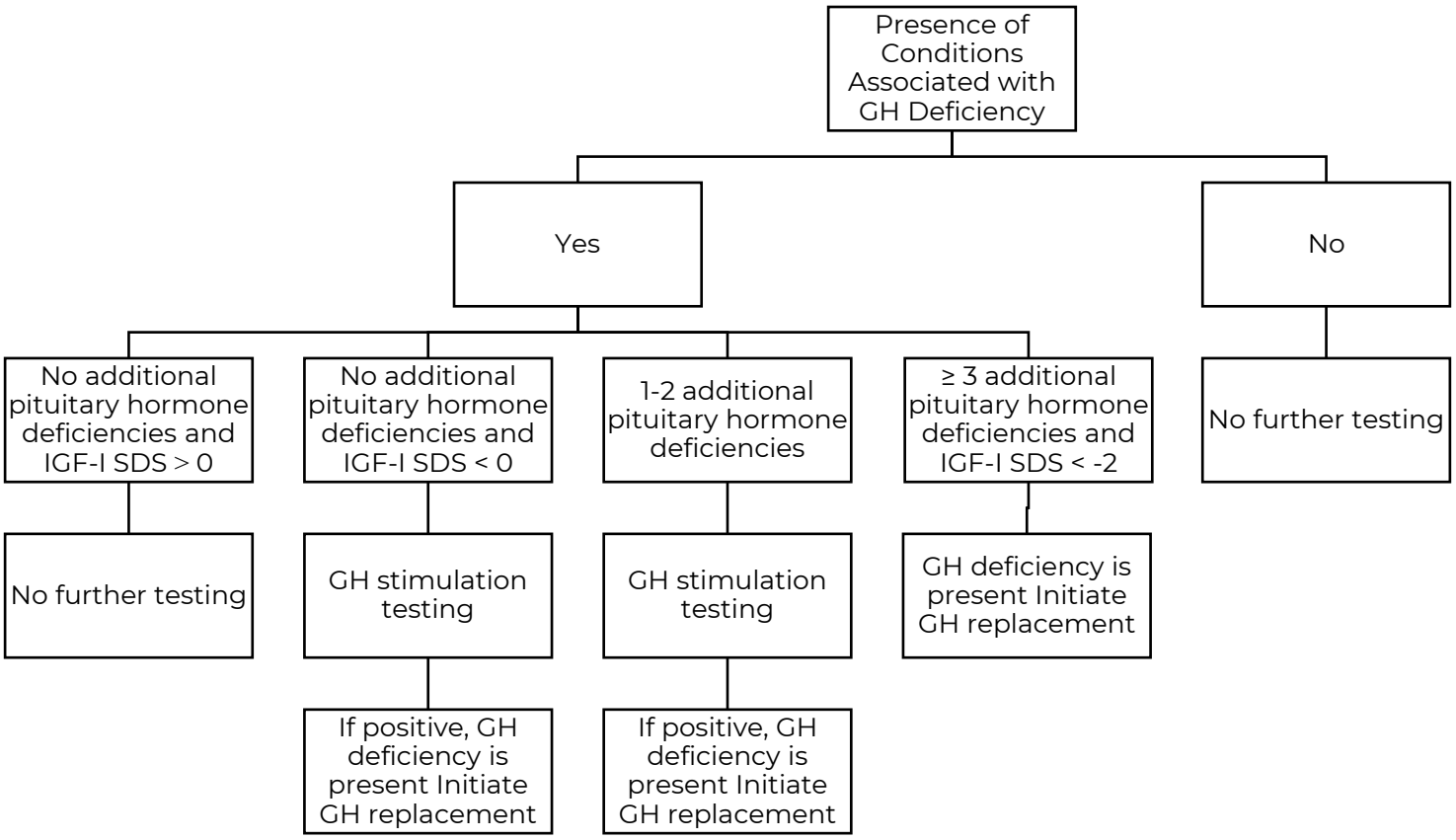

Figure 3. *Treatment Algorithm for the Management of Adult Growth Hormone Deficiency*