CADTH Reimbursement Review

Implementation Advice Report

SOMATROPIN

Indication: Growth Hormone Deficiency (in Adult and Pediatric Populations), Turner Syndrome (in Pediatric Population), Short Stature Secondary to Small for Gestational Age (in Pediatric Population), and Idiopathic Short Stature (in Pediatric Population)

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1. BACKGROUND

Somatropin, a recombinant human growth hormone (rhGH), has significantly improved the management of growth hormone deficiencies (GHD) and other growth-related disorders. Its introduction in the 1980s marked a pivotal shift from the complex and limited capacity of extracting growth hormone from human donors. With a mechanism of action that stimulates linear growth in children and regulates metabolic functions in both children and adults, somatropin represents a key therapeutic intervention for a variety of conditions characterized by inadequate growth or hormone deficiencies.

In Canada, several somatropin products have received approval, reflecting a diversity in formulations and delivery systems to meet the clinical needs of patients with GHD, Turner Syndrome (TS), short stature due to being small for gestational age (SGA), and idiopathic short stature (ISS), among others.

Somatropin products have previously been reviewed by the Common Drug Expert Committee (CDEC), resulting in recommendations for listing in TS, pediatric GHD, and adult GHD indications. Despite these efforts, a gap remains in providing specific guidance on reimbursement conditions and criteria.

To address this gap, stakeholders from public drug programs have expressed a desire to convene a panel of clinical experts to discuss and establish criteria for somatropin reimbursement for the specified indications. During consultations with the public drug programs, long-acting growth hormone formulations were considered out of scope for this panel.

2. CONSULTATION PROCESS AND OBJECTIVES

The clinical expert panel was comprised of a panel chair and 4 Canadian specialists with expertise in the diagnosis and management of patients with GHD in the adult and pediatric populations, TS in the pediatric population, SGA in the pediatric population and ISS in the pediatric population. The objective of the panel was to provide advice with respect to criteria for reimbursement to the participating drug programs. A consensus-based approach was used, and input sought using a questionnaire and a panel meeting. In addition to the clinical panelists and CADTH staff, representatives from public drug programs were invited to participate in the discussion and provide input in advance of the meeting on the topics up for discussion.

The advice in this report is based on the experience and expertise of the implementation advice panel members, the patient population in the pivotal trials, and the Health Canada (HC) indication requirements as identified and discussed in the clinical report.

3. IMPLEMENTATION ADVICE

This section aims to synthesize the deliberations of the expert panel The panel sought to provide advice on appropriate criteria and conditions for somatropin's reimbursement across the highlighted indications.

Table 1: Summary of Initiation, Renewal, Discontinuation, and Prescribing Criteria for Growth Hormone Deficiency in the Pediatric Population

Proposed Condition/Criteria	Implementation Advice
Initiation	
Initiation of growth hormone therapy should be based on a confirmed diagnosis GHD.	The panel emphasized the need for a confirmed diagnosis of GHD prior to initiating treatment. The panel discussed the importance of addressing any underlying conditions before initiating growth hormone therapy, including addressing poor nutrition and optimizing corticosteroid, thyroid, and gonadal steroid assessment.
Diagnosis of GHD should be undertaken in a centre that routinely performs GH stimulation testing.	Diagnosis of GHD involves clinical assessment, growth monitoring, and endocrine testing, including GH stimulation tests, to confirm the deficiency.
Growth hormone therapy should be initiated in the presence of unfused epiphyses	The panel discussed the importance for timely initiation of treatment to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates potential for growth.
Renewal	
Patients should be followed up annually to ensure none of the discontinuation criteria have been met.	The panel discussed the importance of continuous follow-up and assessment to ensure the appropriateness of treatment continuation.
Discontinuation	
Treatment with somatropin should be discontinued when the patient has achieved their near-final height. The decision on when a patient has reached their final height may involve considerations such as growth rate slowing to less than 2–2.5 cm per year, which indicates that growth potential has been maximized.	Once a child has achieved their final height, the potential for further linear growth is minimal. Monitoring growth velocity is essential for determining the effectiveness of somatropin treatment and timing its discontinuation. A consistent growth rate below the threshold of 2–2.5 cm per year suggests that the child may not benefit from continued therapy. The panel emphasized that there can be individual variations in the timing of growth completion. Therefore, decisions on discontinuing somatropin should consider the child's growth pattern, bone age, and overall health status.

Treatment should be discontinued at the presence of fused epiphyses, which indicates the completion of growth.	The fusion of epiphyses, as seen in radiographic evaluations, signifies the end of longitudinal bone growth. The panel discussed the need for radiographic evidence of epiphyseal fusion to ensure that growth potential has indeed been maximized. This involves assessing bone age (less than 14 years in females and 16 years in males) and the status of growth plates. The panel emphasized that the relationship between somatropin treatment, pubertal development, and hormonal status should be considered. For some pediatric patients, especially those with delayed or precocious puberty, the timing of epiphyseal fusion and final height achievement may differ from typical patterns.
Prescribing	
Growth hormone therapy for GHD in pediatric patients should be initiated by a pediatric endocrinologist and ongoing management can be under the care of a local pediatrician or other prescribers within a shared care model.	The panel discussed that in regions where access to pediatric endocrinologists may be limited, supporting pediatricians or other prescribers may prescribe GH therapy, after diagnosis is made, within a shared care model can improve accessibility to necessary treatments. This ensures that pediatric patients with GHD receive timely treatment initiation and ongoing management, regardless of their geographical location. Furthermore, a shared care model facilitates continuous care by ensuring that all aspects of the child's health are considered in the management of GHD.

Table 2: Summary of Initiation, Renewal, and Prescribing Criteria for Growth Hormone Deficiency in the Adult Population

Proposed Condition/Criteria	Implementation Advice
Initiation	
Treatment should be initiated in adults with childhood-onset GHD upon retesting to confirm the presence of a treatable GHD. Patients with a structural, traumatic, neoplastic, surgical, or congenital basis for GHD whose disease is not expected to change should be exempt from retesting.	The panel noted the permanent nature of certain conditions leading to GHD and the impracticality and unnecessary burden of retesting in these documented cases.

Treatment should be initiated in adults with confirmed acquired GHD as documented through structural defects, irradiation, tumor, surgery, or through testing of low baseline IGF-1, presence of more than 2 pituitary axes deficiencies, or GH deficit on GH stimulation test.	-
Individuals over the age of 18 with unfused epiphyses may be appropriate for treatment with somatropin based on clinical judgement.	The panel discussed that adults with unfused epiphyses have the potential for continued growth and the opportunity to impact final adult height positively. The panel noted that growth hormone therapy dosing for adults with unfused epiphyses requires distinct considerations (eg, these patients may benefit from higher doses of GH therapy than adults with GHD and fused epiphyses).
Renewal	
Renewal of treatment annually upon demonstration of evidence of continued benefit in body composition or function.	The panel discussed the importance of longitudinal follow-up and assessment to ensure the appropriateness of treatment continuation. The panel noted that the clinical report has discussed discontinuation in cases of adverse effects outweighing benefits, contraindications, or lack of continued clinical benefit.
Patients with GHD etiologies where changes in the underlying reasons for the disease are not expected should be exempt from annual reassessments for renewal eligibility. This includes congenital, tumour, trauma, surgical, or structural etiologies.	The panel noted that renewal in such cases can lead to impracticality and unnecessary burden.
Prescribing	
Growth hormone therapy for GHD in adults should be initiated by an endocrinologist and ongoing management can be under the care of a physician or other prescribers within a shared care model.	The panel noted that during the transition from pediatric to adult care, the pediatric and adult health care teams should establish a workflow to support a coordinated transition process. The panel discussed that in regions where access to endocrinologists may be limited, supporting physicians or other prescribers to prescribe GH therapy, after diagnosis is made, within a shared care model can improve accessibility to necessary treatments. This ensures that adults with GHD receive timely treatment initiation and ongoing management, regardless of their geographical location. Furthermore, a shared care model facilitates continuous care by ensuring that all aspects of the patient's health are considered in the management of GHD.

Table 3: Summary of Initiation, Renewal, Discontinuation, and Prescribing Criteria for Turner Syndrome in the Pediatric Population

Proposed Condition/Criteria	Implementation Advice
Initiation	
Initiation of growth hormone therapy should be based on a diagnosis of Turner Syndrome confirmed via genetic testing.	-
Growth hormone therapy should be initiated in the presence of unfused epiphyses.	The panel discussed the importance for timely initiation of treatment to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates potential for growth. The panel discussed that GH therapy should be initiated on a case-by-case basis considering height velocity and growth potential of the patient.
Renewal	
Patients should be followed up annually to ensure none of the discontinuation criteria have been met.	The panel discussed the importance of continuous follow-up and assessment to ensure the appropriateness of treatment continuation.
Discontinuation	
Treatment should be discontinued when height velocity is less than 2 cm/year and bone age is greater than or equal to 14 years in females.	The panel discussed the use of height velocity in association with bone age as a measure of the potential for any further benefits from treatment.
Prescribing	
Growth hormone therapy for TS should be provided as part of care offered by a multidisciplinary team and clinic with expertise in TS. Growth hormone therapy for TS should be initiated by a pediatric endocrinologist and ongoing management can be under the care of a local pediatrician or other prescribers within a shared care model.	The panel discussed that TS is a complex condition that affects various body systems, including growth, cardiovascular health, reproductive function, and hearing, among others. Management therefore requires a comprehensive approach that addresses not just the short stature characteristic of TS but also the array of potential comorbidities and health concerns associated with the syndrome. The panel discussed that in regions where access to pediatric endocrinologists may be limited, supporting pediatricians or other prescribers to prescribe GH therapy within a shared care model can improve accessibility to necessary treatments. This ensures that pediatric patients receive timely treatment initiation and ongoing management, regardless of their geographical location.

Table 4: Summary of Initiation, Renewal, Discontinuation, and Prescribing Criteria for Short Stature Secondary to Small for Gestational Age in the Pediatric Population

Proposed Condition/Criteria	Implementation Advice
Initiation	
Initiate growth hormone therapy in pediatric patients with short stature secondary to SGA when there is growth failure, which is characterized by: • a birth weight/length below -2 SDS, and • in whom catch-up growth is not observed by age 2-4 years or later.	The panel discussed the importance of addressing any underlying conditions before initiating growth hormone therapy, including considering and addressing poor nutrition and other chronic medical conditions.
Growth hormone therapy should be initiated in the presence of unfused epiphyses	The panel discussed the importance for timely initiation of treatment to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates potential for growth.
Renewal	
Patients should be followed up annually to ensure none of the discontinuation criteria have been met.	The panel discussed the importance of continuous follow-up and assessment to ensure the appropriateness of treatment continuation.
Discontinuation	
Treatment should be discontinued when height velocity is less than 2 cm/year and bone age is greater than or equal to 14 years in females and 16 years in males.	The panel discussed the use of height velocity in association with bone age as a measure of the potential for any further benefits from treatment.
Prescribing	
Growth hormone therapy for SGA in pediatric patients should be initiated by a pediatric endocrinologist and ongoing management can be under the care of a local pediatrician or other prescriber within a shared care model.	The panel discussed that in regions where access to pediatric endocrinologists may be limited, supporting pediatricians or other prescribers to prescribe GH therapy within a shared care model can improve accessibility to necessary treatments. This ensures that pediatric patients receive timely treatment initiation and ongoing management, regardless of their geographical location.

Table 5: Summary of Initiation, Renewal, Discontinuation, and Prescribing Criteria for Idiopathic Short Stature in the Pediatric Population

Proposed Condition/Criteria	Implementation Advice
Initiation	
Growth hormone therapy for ISS can be considered in patients with short stature (height SDS ≤ -2.25) upon the exclusion of other causes of short stature, optimizing nutrition, and a careful evaluation of the physical and psychological implications for the patient. GH therapy is not routinely recommended in pediatric patients with ISS. The decision to initiate GH therapy should be made on a case-by-case basis, after a careful assessment and discussion of risks and benefits.	The panel discussed the heterogenous etiologies underlying ISS and addressing any underlying conditions before initiating growth hormone therapy, including considering and addressing poor nutrition and other chronic medical conditions.
Growth hormone therapy should be initiated in the presence of unfused epiphyses	The panel discussed the importance for timely initiation of treatment to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates potential for growth.
Renewal	
Patients should be followed up annually to ensure none of the discontinuation criteria have been met.	The panel discussed the importance of continuous follow-up and assessment to ensure the appropriateness of treatment continuation.
Discontinuation	
Treatment should be discontinued when height velocity is less than 2 cm/year and bone age is greater than or equal to 14 years in females and 16 years in males.	The panel discussed the use of height velocity in association with bone age as a measure of the potential for any further benefits from treatment. The panel also discussed and noted that this discontinuation criterion is in line with the guidelines discussed in the clinical report.
Prescribing	
Growth hormone therapy should be initiated by a pediatric endocrinologist and ongoing management can be under the care of a local pediatrician or prescriber within a shared care model.	The panel discussed that in regions where access to pediatric endocrinologists may be limited, supporting pediatricians or prescribers who prescribe GH therapy within a shared care model can improve accessibility to necessary treatments. This ensures that pediatric patients receive timely treatment initiation and ongoing management, regardless of their geographical location. Furthermore, A shared care model facilitates continuous care by ensuring that all aspects of the child's health are considered.

Abbreviations: as necessary.

Rationale and Other Discussion Points

This section synthesizes the panel's rationales and discussion points.

Goals of Treatment

In pediatric patients, the principal goal is the normalization of growth parameters, specifically achieving near-normal adult height. This involves the promotion of linear growth, muscle mass development, and bone strengthening during the key growth years. For adults, treatment aims to mitigate the systemic deficiencies associated with growth hormone deficiency, including improving body composition, bone density, and metabolic function.

For specific conditions such as Turner Syndrome, SGA and ISS, treatment with somatropin addresses not only the physical aspects of growth failure but also aims to enhance the overall quality of life and psychosocial wellbeing of the patients.

Unmet Need

Unmet needs in the management of growth hormone deficiencies and related disorders persist despite available treatment options. Optimization of treatment regimens remains a challenge, with a need for individualized approaches that more precisely adjust somatropin dosing to the individual's response to therapy.
Long-term safety and monitoring of somatropin is another area of concern, requiring better strategies to monitor potential adverse effects such as increased risk of diabetes, orthopedic issues, and intracranial hypertension. Moreover, adequate support systems for the psychosocial issues associated with growth disorders are often lacking, leading to significant emotional and social challenges for affected individuals.

Proposed Conditions & Criteria

Growth Hormone Deficiency in Pediatric and Adult Populations

The panel emphasized the importance of initiating treatment in patients with a confirmed diagnosis of GHD. This aligns with the rigor of clinical guidelines and regulatory mandates, ensuring somatropin's benefits are reserved for those with established clinical indications. Furthermore, the proactive approach to identifying and managing underlying conditions before initiating somatropin therapy underscores a holistic view of patient well-being, ensuring the therapy's efficacy is not compromised by unaddressed health issues.

Discontinuation criteria based on achieving final height or the presence of fused epiphyses ensure the discontinuation of treatment only when the potential for further growth is minimal and mitigates unnecessary prolonged exposure to medication.

Turner Syndrome in the Pediatric Population

For TS, the panel discussions indicated that initiation of growth hormone therapy should be based on a diagnosis of TS confirmed via genetic testing and in the presence of unfused epiphyses. This targeted approach ensures that somatropin therapy is applied cautiously, offering potential height improvements for individuals with TS where short stature significantly impacts quality of life.

Short Stature Secondary to Small for Gestational Age in the Pediatric Population

The panel's criteria for treating pediatric patients with short stature secondary to SGA establishes a clear threshold for growth failure and the absence of catch-up growth ensures that somatropin therapy is reserved for those who are most likely to benefit.

Idiopathic Short Stature in the Pediatric Population

The panel approach to ISS reflects the complexity of this diagnosis, advocating for somatropin therapy only after exhaustive exclusion of other causes of short stature, balancing the potential for benefit against the inherent risks of treatment. GH therapy is not routinely recommended in pediatric patients with ISS, and careful assessment on a case-by-case basis is required prior to

initiation of GH. The decision to initiate GH therapy should be made on a case-by-case basis, after a careful assessment of physical and psychological burdens, and discussion of risks and benefits.

Shared Care Model

The panel's advice to initiate growth hormone (rhGH) therapy under the guidance of a pediatric endocrinologist, with subsequent management potentially transitioning to a local pediatrician or prescriber within a shared care model, is designed to leverage specialized expertise at critical points and enhance overall accessibility to necessary treatments. Pediatric endocrinologists are essential for accurate diagnosis and the safe initiation of GH therapy, while supporting ongoing care by pediatricians via a shared care model addresses the challenges of limited access to specialized care, especially in underserved or rural areas. This model not only facilitates timely adjustments in treatment based on individual growth responses but also integrates care across different health domains by utilizing the broader perspective provided by pediatricians who often manage other aspects of a child's health.