CADTH Health Technology Review

Somatropin

Indication: Growth hormone deficiency (in adult and pediatric populations), Turner syndrome (in the pediatric population), short stature secondary to small for gestational age (in the pediatric population), and idiopathic short stature (in the pediatric population)

Drug Implementation Advice

Table of Contents

List of Tables

Implementation Advice

Background

Somatropin, a recombinant human growth hormone, 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 Canadian Drug Expert Committee (CDEC), resulting in recommendations for listing in pediatric GHD, adult GHD, and TS indications. Despite these efforts, a gap remains in providing specific guidance on reimbursement conditions and criteria. As such, public drug programs requested implementation advice to address this gap. The scope of the implementation advice was decided in consultation with public drug programs. Long-acting growth hormone formulations were considered out of scope for this panel.

Objectives

The objective of this project was to convene a panel of clinical expert to establish reimbursement criteria for somatropin for patients with GHDs, TS, short stature due to being SGA, and ISS.

Consultation Process

The clinical expert panel comprised a panel chair and 4 specialists in Canada with expertise in the diagnosis and management of patients with GHD in the adult and pediatric populations, as well as TS, short stature due to being SGA, and ISS in pediatric populations. A consensus-based approach was used, and input was captured using a questionnaire and a panel meeting.

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–approved indications as identified and discussed in the clinical report.

Expert Panel Advice

This section aims to synthesize the deliberations of the expert panel.

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

Criteria	Implementation advice
Initiation	
Initiation of GH therapy should be based on a confirmed diagnosis of GHD.	The panel emphasized the need for a confirmed diagnosis of GHD before initiating treatment. The panel discussed the importance of addressing any underlying conditions before initiating GH therapy, including addressing poor nutrition and optimizing corticosteroid, thyroid, and gonadal steroid treatment. The panel discussed that the diagnosis of GHD involves comprehensive clinical assessment, growth monitoring, endocrine testing, and GH stimulation testing. For GH stimulation testing, an inadequate response to at least 2 different GH stimulation tests is required to diagnose deficiency.
Diagnosis of GHD should be undertaken in a centre that routinely performs GH stimulation testing.	—
GH therapy should be initiated in the presence of unfused epiphyses.	The panel discussed the importance of timely treatment initiation to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates the 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 upon the occurrence of any of the following: • height velocity slows to less than 2 cm per year and/or bone age is more than 16 years in boys and 14 years in girls • closure of the epiphyseal growth plates.	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 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. The fusion of the growth plates (epiphyses), which can be seen in radiographic evaluations, signifies the end of longitudinal bone growth. The panel emphasized the importance of obtaining radiographic evidence of this epiphyseal fusion to confirm that a child has reached their maximum growth potential. This assessment typically involves checking the bone age, which is usually less than 14 years for girls and 16 years for boys, and evaluating the status of the 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

Criteria	Implementation advice
	delayed or precocious puberty, the timing of epiphyseal fusion and final height achievement may differ from typical patterns.
Prescribing	
GH therapy for GHD in pediatric patients should be initiated by a pediatric endocrinologist; then, 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 to 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.

GH = growth hormone; GHD = growth hormone deficiency.

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

Criteria	Implementation advice
Initiation	
Treatment should be initiated in adults with childhood-onset GHD upon re-testing to confirm the presence of a treatable GHD.	The panel discussed that for adults with childhood-onset GHD who are transitioning to adulthood, re-testing to confirm the presence of a treatable GHD is recommended. The panel also noted that in some circumstances, the permanent nature of certain conditions that lead to GHD makes re-testing impractical and unnecessary. These conditions include, but are not limited to, genetic defects affecting hypothalamic-pituitary axes, hypothalamic-pituitary structural brain defects, and a history of tumour, surgery, and/or radiation therapy.
Treatment should be initiated in adults with confirmed acquired GHD as documented through structural defects, irradiation, tumour, surgery, or through testing of low baseline IGF-1, presence of more than 2 pituitary axes deficiencies, or GH deficit on a GH stimulation test.	—
Patients older than aged 18 with unfused epiphyses may be considered for treatment based on clinical judgment.	The panel discussed that adults with unfused epiphyses have the potential for continued growth and the opportunity to impact their final adult height positively. The panel noted that GH therapy dosing for adults with unfused epiphyses requires distinct considerations (e.g., these patients may benefit from higher doses of GH therapy than adults with GHD and fused epiphyses).
Renewal	
Treatment should be renewed 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 that outweigh benefits, contraindications, or lack of continued clinical benefit.

Criteria	Implementation advice
Patients with GHD etiologies in which changes in the underlying reasons for the disease are not expected should be exempt from annual reassessments for renewal eligibility.	Reassessment of funding for these patients may be considered at less frequent intervals at the discretion of public drug plans to ensure continued appropriateness and benefit of treatment. These patients include, but are not limited to, those with structural, traumatic, neoplastic, surgical, or congenital basis for GHD (e.g., organic hypothalamic-pituitary disease, multiple pituitary hormone deficiencies together with low-serum IGF-1 levels, genetic defects or structural brain defects that affect the hypothalamic-pituitary axes). The panel noted that renewal in such cases can lead to impracticality and unnecessary burden.
Prescribing	
GH therapy for GHD in adults should be initiated by an endocrinologist; then, 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.

GH = growth hormone; GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1.

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

Criteria	Implementation advice
Initiation	
Initiation of GH therapy should be based on a diagnosis of TS confirmed via genetic testing.	—
GH therapy should be initiated in the presence of unfused epiphyses.	The panel discussed the importance of timely treatment initiation 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 the patient's growth potential.
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.

Criteria	Implementation advice
Discontinuation	
Treatment should be discontinued upon the occurrence of any of the following: • height velocity slows to less than 2 cm per year and/or bone age is more than 14 years • closure of the epiphyseal growth plates.	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	
GH therapy for TS should be provided as part of the care offered by a multidisciplinary team and a clinic with expertise in TS. GH therapy for TS should be initiated by a pediatric endocrinologist; then, 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, hearing, and among. 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. Furthermore, a shared care model facilitates continuous care by ensuring that all aspects of the child's health are considered.

GH = growth hormone; TS = Turner syndrome.

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

Criteria	Implementation advice
Initiation	
GH therapy in pediatric patients with short stature secondary to SGA should not be initiated before the age of 2 to 4 years, where patient height has been monitored for a period of more than 6 months by at least 2 measurements and catch-up growth has not been observed (i.e., height velocity is not increasing).	The panel discussed the importance of addressing any underlying conditions before initiating GH therapy, including considering and addressing poor nutrition and other chronic medical conditions (e.g., celiac disease, irritable bowel syndrome, anemia, chronic renal failure). The panel discussed that initiation of treatment varies across different countries, ranging from age 2 to 4.
GH therapy should be initiated in the presence of unfused epiphyses.	The panel discussed the importance of timely initiation of treatment to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates the 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.

Criteria	Implementation advice
Discontinuation	
Treatment should be discontinued upon the occurrence of any of the following: • height velocity slows to less than 2 cm per year and/or bone age is more than 16 years in boys and 14 years in girls • closure of the epiphyseal growth plates.	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	
GH therapy for short stature secondary to SGA in pediatric patients should be initiated by a pediatric endocrinologist; then, 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. Furthermore, a shared care model facilitates continuous care by ensuring that all aspects of the child's health are considered.

GH = growth hormone; SGA = small for gestational age.

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

Criteria	Implementation advice
Initiation	
GH 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 GH therapy, including considering and addressing poor nutrition and other chronic medical conditions (e.g., celiac disease, irritable bowel syndrome, anemia, chronic renal failure).
GH therapy should be initiated in the presence of unfused epiphyses.	The panel discussed the importance of timely initiation of treatment to maximize height outcomes before the natural closure of growth plates. The presence of open epiphyses indicates the 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 upon the occurrence of any of the following: • height velocity slows to less than 2 cm per year and/or bone	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

Criteria	Implementation advice
age is more than 16 years in boys and 14 years in girls • closure of the epiphyseal growth plates.	that this discontinuation criterion is in line with the guidelines discussed in the clinical report.
Prescribing	
GH therapy should be initiated by a pediatric endocrinologist; then, 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 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. Furthermore, a shared care model facilitates continuous care by ensuring that all aspects of the child's health are considered.

GH = growth hormone; ISS = idiopathic short stature; SDS = standard deviation score.

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 final height within an acceptable range that is close to average 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 GHD, including improving body composition, bone density, and metabolic function.

For specific conditions such as TS, short stature due to being 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 well-being of the patients.

Unmet Need

Unmet needs in the management of GHD 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 the affected individuals.

Proposed Conditions and Criteria

GHD 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 rigour of clinical guidelines and regulatory mandates, ensuring somatropin's benefits are

reserved for those with established clinical indications. Furthermore, a 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.

The discontinuation criteria for the pediatric population is based on achieving near-final height when the potential for further growth is minimal and on mitigating unnecessary prolonged exposure to medication. The classic criteria are that height velocity slows to less than 2 cm per year, and/or bone age is more than 16 years in boys and 14 years in girls, or closure of the epiphyseal growth plates.

TS 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 SGA 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.

ISS 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. Growth hormone therapy is not routinely recommended in pediatric patients with ISS, and careful assessment on a case-by-case basis is required before initiation of growth hormone. The decision to initiate growth hormone 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 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 the accurate diagnosis and safe initiation of growth hormone 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 using the broader perspective provided by pediatricians who often manage other aspects of a child’s health.

Clinical Background Summary

Context and Policy Issues

Somatropin, a recombinant human growth hormone (rhGH), has been a cornerstone in the management of GHDs and other growth-related disorders since its introduction in the 1980s.[1] Before its introduction, the treatment for GHD involved the extraction of growth hormone from human donors' pituitary glands, a process that was both complex and limited in its capacity to meet patient needs.[1] The advent of recombinant DNA technology allowed for the production of somatropin, which is structurally identical to the naturally occurring human growth hormone secreted by the pituitary gland.[1] The primary mechanism of action of somatropin involves the stimulation of linear growth in children and the regulation of metabolic functions in both children and adults.[2] It exerts its effects by binding to growth hormone receptors on various cell types, leading to the activation of intracellular signalling pathways that promote growth and metabolism.[2]

In the market in Canada, several somatropin products have been approved by Health Canada; these products reflect a diverse range of formulations and delivery systems designed to meet the needs of patients with varying clinical indications. Of these, the following somatropin products are currently marketed: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin.[3-8]

Currently, access to somatropin through the public drug plans can fall under a number of reimbursement programs, including the Exceptional Access Program (EAP). Under the EAP there are no criteria for initiation or discontinuation of somatotropin for patients with GHD, TS, short stature secondary to SGA, or ISS. Representatives of participating public drug plans have expressed to CADTH their desire to enhance the efficiency of the reimbursement process for somatropin and to reduce the turnaround time for decision-making. As such, there is a need for an evidence review to inform the process of developing reimbursement criteria for somatropin in the following indications: GHD, TS, short stature secondary to SGA, and ISS.

Specifically, representatives from public drug programs have requested that a panel of clinical experts be convened to discuss and provide implementation guidance for somatropin in the treatment of GHD, TS, short stature secondary for SGA, and ISS. The panel was asked to focus their discussion on the following questions:

1. What criteria and conditions are appropriate for the reimbursement of somatropin for the following indications and respective populations:
    - GHD (adult and pediatric population)
    - TS (pediatric population)
    - short stature secondary to SGA (pediatric population)
    - ISS (pediatric population)?
2. How long do patients with the previously noted conditions need to be treated with somatropin?

CADTH has previously conducted reviews on somatropin products, providing recommendations for listing. However, specific guidance on reimbursement conditions and implementation has not been included.

Regulatory Background

In the market in Canada, several somatropin products are used to treat a range of medical conditions, with some overlapping and distinct indications among them.

Pediatric GHD is a common indication for most of these products, including Humatrope, Genotropin, Saizen, Omnitrope, Norditropin, and Nutropin.[3-8] Similarly, TS is another broadly addressed condition, with Humatrope, Genotropin, Saizen, Omnitrope, Norditropin, and Nutropin all being indicated for its treatment.[3-8]

ISS is treated with Humatrope, Genotropin, and Omnitrope, while short stature secondary to SGA is a condition for which Humatrope, Genotropin, Saizen, Omnitrope, and Norditropin provide treatment options.[3-8]

Adult GHD also sees wide coverage, with Humatrope, Genotropin, Saizen, Omnitrope, and Nutropin all indicated for its management. Unique among these, Genotropin is additionally approved for Prader-Willi syndrome (PWS), a genetic condition, and Norditropin is indicated for Noonan syndrome, a genetic disorder that prevents typical development in various parts of the body.[3-8]

Growth failure resulting from chronic renal failure is specifically addressed by Saizen and Nutropin, which distinguishes them in their therapeutic applications compared to the other somatropin products.[3-8]

Table 6 provides an overview of the indications for each product. Table 7 provides further details into each of these products.

Table 6: Description of Formulation and Indication of Each of Currently Marketed Somatropin Products

Characteristic	Product
	Humatrope
Formulation	For subcutaneous or intramuscular administration after lyophilized powder reconstitution with the supplied diluent. Provided with a 5 mg vial or 6 mg, 12 mg, 24 mg cartridges for use with the HumatroPen.
Indication	• **Pediatric growth hormone deficiency**: "for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone and whose epiphyses are not closed."[4] • **Turner syndrome**: "for the treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed."[4] • **Idiopathic short stature**: "for the long-term treatment of idiopathic short stature defined by: normal birth weight, careful diagnostic evaluation that excludes other known causes of short stature that should be either observed or treated by other means, height at least 2.25 standard deviation scores (SDS) below the mean for age and sex, height velocity below the 25th percentile for bone age and sex over 12 months of observation and unlikely to permit attainment of adult height in the expected range."[4] • ***SHOX* gene deficiency**: "for the treatment of short stature or growth failure in children with SHOX (short stature homeobox-containing gene) deficiency whose epiphyses are not closed."[4] • **Small for gestational age**: "for the treatment of growth failure in children born small for gestational age (birth weight and/or length below −2 SD) and who fail to achieve catch-up growth by 2 to 4 years or later."[4] • **Adult growth hormone deficiency**: "for replacement of endogenous growth hormone in adults with growth hormone deficiency, who meet either of the following two criteria: ◦ Adult Onset: Patients must have somatotropin deficiency syndrome, either alone or associated with

Characteristic	Product
	multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or ◦ Childhood Onset: Patients who were growth hormone-deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes."[4]
Genotropin	
Formulation	For subcutaneous injection after lyophilized powder reconstitution. Genotropin is administered through prefilled pens or syringes at the following strengths: GoQuick: 5 mg, 5.3 mg, and 12 mg prefilled pen MiniQuick: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg prefilled syringe
Indication	• **Pediatric growth hormone deficiency:** "the long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency (GHD))".[4] • **Small for gestational age**: "the treatment of growth failure (current height standard deviation score [SDS] < - 2) in short children born SGA (birth weight and/or length below −2 SD) and who fail to achieve catch-up growth (height velocity SDS < 0 during the last year) by 2 to 4 years or later."[4] • **Turner syndrome**: "the treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed."[4] • **Idiopathic short stature**: "the long-term treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature, defined by height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means. Genotropin treatment for ISS should be prescribed only for those patients whose epiphyses are not closed."[4] • **Prader-Willi syndrome**: "the treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS)."[4] • **Adult growth hormone deficiency**: "for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria: ◦ Adult Onset (AO): Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or ◦ Childhood Onset (CO): Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes."[3]
Saizen	
Formulation	For subcutaneous or intramuscular administration after lyophilized powder reconstitution in a 5 mg vial or through 6 mg (5.83 mg/mL), 12 mg (8 mg/mL), 20 mg (8 mg/mL) cartridges for use with the easypod electromechanical autoinjector or the Aluetta pen injector.
Indication	• **Pediatric growth hormone deficiency**: "for the long-term treatment of children with growth failure due to inadequate secretion of normal endogenous growth hormone."[5] • **Turner syndrome**: "for the treatment of short stature in girls with gonadal dysgenesis (Turner syndrome) when epiphyses are not closed."[5] • **Growth failure due to chronic renal failure**: "for the treatment of growth failure in children due to Chronic Renal Failure."[5] • **Small for gestational age**: "for growth disturbance (current height Standard Deviation Score (SDS) <-2) in short children born small for gestational age (SGA) with a birth weight and/or length below −2 standard deviations (SD), who failed to show catch-up growth (Height Velocity SDS < 0 during the last year) by 2 years of age or later."[5]

Characteristic	Product
	• **Adult growth hormone deficiency**: "for the replacement therapy in adult patients with acquired or idiopathic growth hormone deficiency (GHD) as diagnosed by a single dynamic test for growth hormone deficiency (peak GH ≤ 5 µg/L). Patients with a growth hormone deficiency with onset in childhood should be retested before treatment starts."[5]
Omnitrope	
Formulation	For subcutaneous or intramuscular administration after lyophilized powder reconstitution in a 5 mg vial or through 6 mg (5.83 mg/mL), 12 mg (8 mg/mL), 20 mg (8 mg/mL) cartridges for use with the easypod electromechanical autoinjector or the Aluetta pen injector.

Indication	• **Pediatric growth hormone deficiency**: "The long-term treatment of children, who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency [GHD])".[6]
	• **Turner syndrome**: "treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed."[6]
	• **Idiopathic short stature**: "The long-term treatment of idiopathic short stature (ISS), also called non-growth hormone-deficient short stature, defined by height standard deviation score (SDS) <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means. Omnitrope treatment for ISS should be prescribed only for those patients whose epiphyses are not closed."[6]
	• **Small for gestational age**: "for the treatment of growth failure (current height standard deviation score [SDS] < - 2) in short children born SGA (birth weight and/or length below −2 SD) and who fail to achieve catch-up growth (height velocity SDS < 0 during the last year) by 2 to 4 years or later."[6]
	• **Adult growth hormone deficiency**: "for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:
	  ◦ Adult Onset: Patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; Or
	  ◦ Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes."[6]

Norditropin	
Formulation	Subcutaneous administration of somatropin injection prefilled disposable pens at the following strengths: Norditropin FlexPro: 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL Norditropin NordiFlex: 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL
Indication	• **Pediatric growth hormone deficiency**: "The long-term treatment of children with growth failure due to an inadequate secretion of endogenous growth hormone (Growth Hormone Deficiency)."[7] • **Turner syndrome**: "treatment of children with short stature associated with Turner syndrome."[7] • **Small for gestational age**: "treatment of growth disturbance (current height Standard Deviation Score (SDS) < −2) in short children born small for gestational age (SGA) with a birth weight and/or length below −2 standard deviations (SD), who failed to show catch-up growth (Height Velocity SDS < 0 during the last year) by 2 years of age or later."[7] • **Noonan syndrome**: "treatment of children with short stature associated with Noonan syndrome."[7]
Nutropin	
Formulation	Somatropin subcutaneous injection solution; NuSpin injection device prefilled with cartridge at 5 mg/2 mL, 10 mg/ 2mL, or 20 mg/2 mL

Characteristic	Product

Indication	• **Pediatric growth hormone deficiency**: "the long-term treatment of children who have growth failure due to growth hormone inadequacy."[7]
	• **Growth failure due to chronic renal failure**: "the treatment of children who have growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Therapy with NUTROPIN AQ should be used in conjunction with optimal management of chronic renal insufficiency."[7]
	• **Turner syndrome**: "the long-term treatment of short stature associated with Turner syndrome."[7]
	• **Adult growth hormone deficiency**: "the replacement of endogenous growth hormone (GH) in patients with adult GH deficiency (GHD) who meet both of the following criteria:
	  ◦ Biochemical diagnosis of adult GH deficiency by means of a subnormal response to a standard growth hormone stimulation test (peak GH ≤ 5mcg/L), and
	  ◦ Adult-onset: Patients who have adult GH deficiency either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
	  ◦ Childhood-onset: Patients who were GH deficient during childhood, confirmed as an adult before replacement therapy with NUTROPIN AQ is started."[7]

AO = adult onset; CO = childhood onset; GH = growth hormone; GHD = growth hormone deficiency; ISS = idiopathic short stature; SD = standard deviation; SDS = Standard deviation score; SGA = small for gestational age.

Source: Health Canada product monograph.[3-8]

Table 7: Common Indications Across Somatropin Products

Indication	Humatrope	Genotropin	Saizen	Omnitrope	Norditropin	Nutropin
Pediatric growth hormone deficiency	Yes	Yes	Yes	Yes	Yes	Yes
Turner syndrome	Yes	Yes	Yes	Yes	Yes	Yes
Idiopathic short stature	Yes	Yes	No	Yes	No	No
SHOX gene deficiency	Yes	No	No	No	No	No
Small for gestational age	Yes	Yes	Yes	Yes	Yes	No
Adult growth hormone deficiency	Yes	Yes	Yes	Yes	No	Yes
Prader-Willi syndrome	No	Yes	No	No	No	No
Chronic renal failure	No	No	Yes	No	No	Yes
Noonan syndrome	No	No	No	No	Yes	No

Note: *Yes* indicates that Health Canada has approved the stated indication for the corresponding formulation listed in that row's column. *No* indicates that the indication is not approved by Health Canada.

Source: Health Canada product monograph.[3-8]

Clinical Background

Pediatric GHD

Pediatric GHD is a medical condition characterized by the insufficient production of growth hormone by the pituitary gland, which can lead to various health issues, including short stature, delayed skeletal maturation, and sometimes metabolic irregularities. Growth hormone plays a crucial role in promoting linear growth, muscle mass, and bone strength during childhood and adolescence. The etiology of GHD can be congenital

or acquired, resulting from genetic mutations; structural issues with the pituitary gland; or damage due to trauma, radiation, or infection.[9-11] Diagnosis typically involves clinical assessment, growth monitoring, and endocrine testing, including growth hormone stimulation tests to confirm the deficiency.[9-11] The estimated prevalence of GHD is 1 in 4,000 children.[12] The psychological and social impact of GHD on affected children and their families can be significant, as the condition may lead to challenges with self-esteem and peer interactions because of differences in stature and development.[13,14] Current management of pediatric GHD primarily involves the administration of rhGH therapy.[13,14] Treatment is tailored to the individual child's needs, with dosing adjusted according to growth response and serum insulin-like growth factor-1 (IGF-1) levels.[15] Unmet needs remain in terms of optimizing treatment regimens, monitoring long-term safety, and addressing the psychological and quality of life aspects of the condition. Adherence to daily subcutaneous injections can be challenging for patients and families, and access to therapy may be challenging in certain populations.[16]

Turner Syndrome

TS is a chromosomal disorder that is estimated to affects approximately 1 in 2,500 live births; studies based on populations outside Canada have estimated the annual incidence to range between 25 to 210 per 100,000 females.[17-19] This condition is associated with a variety of clinical manifestations, including short stature, ovarian insufficiency, congenital heart defects, and certain physical features such as a webbed neck and low-set ears.[17-19] The severity and combination of symptoms can vary widely among individuals with TS. The management of TS is multidisciplinary and typically involves endocrinologists, cardiologists, and other specialists to address the various health concerns. Growth hormone therapy, specifically somatropin, is commonly prescribed to address short stature, and estrogen replacement therapy is used to initiate and maintain secondary sexual characteristics resulting from ovarian failure.[17-19] Regular monitoring and screening for complications such as cardiovascular anomalies, hearing loss, and autoimmune disorders are also integral components of care for individuals with TS.[17-19]

Idiopathic Short Stature

ISS is a condition characterized by a height that is significantly below the mean for a child's age and sex, without any identifiable medical cause.[20,21] Children with ISS are typically defined as being at or below the third percentile for height within their respective age and sex category.[21] Unlike short stature that can be attributed to specific causes such as hormonal deficiencies, chronic diseases, or genetic syndromes, ISS is a diagnosis of exclusion.[21] This means that it is diagnosed after other potential causes of short stature have been ruled out through comprehensive medical evaluation.[21] The incidence and prevalence of ISS in Canada are not readily available but it is estimated that approximately 3% of children could be classified as having short stature based on the statistical definition, with a subset of these meeting the criteria for ISS.[21] The condition affects both boys and girls, and the psychosocial impact of ISS can be significant, potentially affecting self-esteem, social functioning, and quality of life.[21,22] Current management options for ISS include observation and monitoring of growth patterns, as well as interventions such as growth hormone therapy.[21] Somatropin is 1 of the treatments available for children with ISS. It is administered through daily subcutaneous injections with the goal of accelerating growth velocity and increasing final adult height.[21]

Short Stature Secondary to SGA

SGA refers to infants who are born with a birth weight and/or length below the 10th percentile for their gestational age.[23] This condition can be attributed to various factors, including genetic predispositions, maternal health issues, placental insufficiencies, and environmental influences.[23] Not all infants born SGA will experience growth disturbances postnatally; however, a significant proportion may not achieve catch-up growth within the first 2 years of life, leading to short stature and potential developmental concerns.[24] Approximately 10% of all newborns in Canada are classified as SGA.[25] The prevalence of growth disturbances among children who are SGA is more challenging to ascertain because of the dynamic nature of growth and the potential for catch-up growth.[26] The management of children who are born SGA focuses on monitoring growth patterns and addressing any underlying medical conditions.[27] Nutritional support and optimizing general health are initial strategies.[27] For those who do not exhibit catch-up growth by 2 to 4 years of age, growth hormone therapy, such as somatropin, may be considered.[27]

Adult GHD

Adult GHD is a medical condition characterized by the insufficient production of growth hormone by the pituitary gland in adults.[28] The deficiency of growth hormone in adults can lead to a range of adverse effects, such as decreased muscle mass and strength, increased body fat, particularly around the waist, reduced bone density, and a higher risk of cardiovascular disease.[29-31] Additionally, patients may experience diminished quality of life, including fatigue, depression, and impaired cognitive function.[29-31] The incidence and prevalence of adult GHD in Canada are not precisely defined.[32] A European study estimated the prevalence of hypopituitarism at 29 to 45 per 100,000 people.[32] The condition can be a continuation of childhood-onset GHD or can be acquired in adulthood because of various causes, such as pituitary tumours, radiation therapy, traumatic brain injury, or other hormonal dysfunctions.[32] Current management options for adult GHD primarily involve the administration of somatropin.[31,32] This treatment is designed to replace the deficient hormone and alleviate the symptoms associated with adult GHD.[31,32] The dosage and duration of treatment are individualized based on the patient's needs, growth hormone levels, and response to therapy.[31,32]

SHOX Gene Deficiency

SHOX gene deficiency is a genetic disorder that affects bone growth and results in short stature. The *SHOX* gene plays a critical role in the growth and development of the skeletal system, and its deficiency can lead to a range of clinical manifestations, including disproportionately short arms and legs, a short trunk, and other skeletal irregularities.[33-36] *SHOX* deficiency may arise from deletions or mutations within the *SHOX* gene located on the pseudoautosomal region of the X chromosome.[33-36] This condition can occur in isolation or as part of a syndrome, such as TS, where 1 copy of the X chromosome is missing or partially missing.[33-36] The exact incidence and prevalence of *SHOX* deficiency in Canada are not well documented.[37,38] However, international data estimated that 1 per 1,000 people live with the condition.[37,38] Management of *SHOX* deficiency typically involves growth hormone therapy. Somatropin is 1 of the primary treatments used to promote growth in children with this condition. In addition to growth hormone therapy, supportive care, including orthopedic interventions and physical therapy, may be necessary to address skeletal irregularities and improve the quality of life.[39,40]

Prader–Willi Syndrome

PWS is a complex genetic disorder characterized by a spectrum of phenotypic manifestations that result from the loss of function of specific genes in the region of chromosome 15 known as 15q11-q13. This region is subject to genomic imprinting, a process by which certain genes are expressed in a parent-of-origin–specific manner. PWS typically arises from the absence of paternally expressed genes in this region, which can occur through several genetic mechanisms, including paternal deletion, maternal uniparental disomy, or imprinting defects.[41] Clinically, PWS is associated with a distinctive phenotype. Affected individuals often present with neonatal hypotonia; feeding difficulties in infancy, followed by hyperphagia leading to obesity if not carefully managed; developmental delays; cognitive impairment; and behavioural problems.[41] Endocrine dysfunctions such as GHD, hypogonadism, and hypothyroidism are also common, contributing to the physical characteristics such as short stature and incomplete sexual development.[41] The incidence of PWS is estimated to be approximately 1 in 22,000 live births globally.[42] Specific data on the incidence and prevalence of PWS in Canada are limited. Current management of PWS is multidisciplinary and supportive, focusing on the management of symptoms and prevention of complications. Growth hormone therapy, such as somatropin, is commonly used to address growth failure.[43] As PWS was not included in the list of indications for somatropin requested by the representative of the drug plan, it will not be discussed further in this report.

Growth Failure Associated With Chronic Renal Insufficiency or Failure

Growth failure associated with chronic renal insufficiency or chronic renal failure is a significant and detrimental condition that affects pediatric patients.[44,45] Chronic renal insufficiency is characterized by a gradual and irreversible decline in kidney function, typically defined by a glomerular filtration rate of less than 75 mL/min per 1.73 m^2 of body surface area.[44] This condition can progress to chronic kidney disease, a term that encompasses various stages of kidney damage and function.[46] The incidence and prevalence of growth failure due to chronic renal insufficiency or chronic renal failure in pediatric populations is not clear. The etiology of growth failure in these patients is multifactorial, involving irregularities in the growth hormone IGF-1 axis, as well as nutritional and metabolic disturbances that are secondary to impaired renal function.[47] The current management of growth failure in pediatric patients with chronic renal insufficiency or chronic renal failure includes optimizing nutrition, correcting acidosis, and managing bone mineral metabolism. The use of rhGH (e.g., somatropin) is an option for patients who do not improve on conservative treatment.[48] As growth failure associated with chronic renal insufficiency was not included in the list of indications for somatropin requested by the representative of the drug plan, it will not be discussed further in this report.

Noonan Syndrome

Noonan syndrome is a genetic disorder characterized by distinctive facial features, short stature, congenital heart defects, developmental delays, and a range of other physical irregularities.[49] The condition is caused by mutations in several genes involved in the RAS-MAPK signalling pathway, which plays a crucial role in cell growth and differentiation.[49] The most commonly affected gene is *PTPN11*, but mutations in *SOS1*, *RAF1*, *RIT1*, and others have also been associated with the syndrome.[49] The incidence of Noonan syndrome is estimated to be approximately 1 in 1,000 to 1 in 2,500 live births globally.[49,50] In Canada, specific incidence rates are not available. The current management of Noonan syndrome is multidisciplinary and focuses on the specific symptoms present in each individual.[50] Growth hormone therapy, such as somatropin, may

be prescribed to address short stature, which is a common feature of the syndrome.[49,50] Congenital heart defects, which can range from mild to life-threatening, often require medical or surgical intervention.[49-51] Other medical issues, such as bleeding disorders, lymphatic dysplasias, and skeletal malformations are managed symptomatically.[49-51] As Noonan syndrome was not included in the list of indications for somatropin requested by the representative of the drug plan, it will not be discussed further in this report.

CADTH Background

CADTH Reimbursement Reviews

In 2013, CADTH, through its reimbursement recommendation services, issued recommendations for 1 somatropin product, Genotropin, for 3 indications: pediatric GHD, adult GHD, and TS.[52] In addition, in 2009, CADTH issued reimbursement advice for Omnitrope for pediatric and adult GHD.[3,53]

A common thread across these recommendations is the recognition of the clinical efficacy of somatropin in improving height-related outcomes in patients with conditions that lead to growth failure. Omnitrope have been recommended for listing based on evidence from randomized controlled trials that demonstrate its similarity to Genotropin in promoting linear growth in children with GHD, with Genotropin also being recommended for the treatment of short stature in patients with TS.[52,53]

The recommendations consistently highlight the similarity in the pharmacokinetic and pharmacodynamic properties of Genotropin and other somatropin products, such as Omnitrope. This similarity supports the rationale for listing Genotropin in a manner similar to other somatropin products as there is no evidence to suggest significant differences in clinical outcomes among these products.[52,53]

Cost considerations were noted in these recommendations, with Genotropin being observed as less costly than other somatropin products like Humatrope, Nutropin, and Saizen, based on the submitted price. Omnitrope, as a subsequent entry biologic, is also recognized for its cost-effectiveness, particularly in children and at starting doses in adults.[52,53]

Despite the positive listing recommendations, the expert committee identified several gaps in the evidence base, including the lack of randomized controlled trials directly comparing Genotropin with other somatropin products, particularly concerning final height, health-related quality of life, and long-latency adverse events. There is also a noted absence of patient input in the review process for Genotropin and insufficient data on the impact of somatropin on health-related quality of life in adults with GHD. Another gap is the lack of evidence on the clinical impact of switching between different somatropin products, including Omnitrope and the other growth hormone therapies available in Canada. This is an important consideration given the potential for patient-specific factors to influence therapy choice. The committees have emphasized the importance of further research to address these gaps and to ensure that reimbursement policies are informed by robust and comprehensive evidence.

Table 8: Summary of CADTH Reimbursement Recommendation for Somatropin

Indication	Product	Date	CDEC recommendation or advice
Turner syndrome	Genotropin	December 20, 2013	List with the following condition: • "List in a manner similar to other somatropin products for the treatment of TS."[52]
Pediatric growth hormone deficiency	Genotropin	December 20, 2013	List with the following condition: • "List in a manner similar to other somatropin products for the treatment of children with growth hormone deficiency (GHD)."[52]
Adult growth hormone deficiency	Genotropin	November 20, 2013	List with the following condition: • "List in a manner similar to other somatropin products for the treatment of adults with GHD."[52]
Growth hormone deficiency in adults and children	Omnitrope	December 16, 2009	"The Canadian Expert Drug Advisory Committee's (CEDAC's) advice on Omnitrope is that drug plans consider a similar reimbursement policy for Omnitrope as for other growth hormone products."[53]

CEDAC = Canadian Expert Drug Advisory Committee; GHD = growth hormone deficiency; TS = Turner syndrome.

Source: CADTH reimbursement reviews.[52,53]

CADTH Health Technology Reviews

CADTH has conducted a number of Health Technology Reviews related to the clinical use of somatropin in various indications. The September 2023 Health Technology Review *Somatropin for Short Stature* addresses the use of growth hormone therapy in children with short stature due to being SGA and ISS.[39] It identified 1 position statement, Allen et al. (2016), and 1 guideline, Grimberg et al. (2016).[54,55] The August 2023 Health Technology Reviews, *Somatropin for Turner Syndrome* and *Somatropin for Growth Hormone Deficiency,* identified guidelines for growth hormone therapy in children with TS and managing children and adults with GHD.[56,57] The 2 reviews identified a total of 3 guidelines, 1 for TS (Gravholt et al. [2017])[58] and 2 for GHD (Yuen et al. [2019] and Grimberg et al. [2016]).[55,59] The June 2023 Reference List *Somatropin for Short Stature Secondary to Small for Gestational Age* identified 1 guideline to inform on the condition, Hokken-Koelega et al. (2023).[27,60] All reviews share a common methodology that involves literature searches on key resources such as MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and various health technology databases, supplemented by focused internet searches. These searches aimed to gather the most relevant and up-to-date evidence to inform the recommendations presented in the reports.[39,56,57,60]

Allen et al. is a consensus or majority position statement on the safety of growth hormone therapy in children and adults.[54] The guideline emphasizes that initiation of somatropin therapy should be based on approved indications with a clear understanding of the underlying condition prompting treatment. Baseline clinical evaluations are recommended, including full pituitary function testing, a detailed medical history, physical examination, and MRI of the brain. The primary objective of growth hormone therapy in children is to achieve satisfactory growth without incurring adverse events. In adults, the goal is to achieve normal age-adjusted serum IGF-1 values. Monitoring should include assessments of bone age, thyroid function, and potentially adrenal function, with adjustments made based on these parameters and growth outcomes. Furthermore,

Allen et al. suggests that if the treatment response is unsatisfactory, the human growth hormone dose may be increased, with the goal of maintaining normal IGF-1 levels.[54]

Grimberg et al. is an updated guideline on the use of GH for GHD, ISS, and primary IGF-I deficiency. For GHD in children and adolescents, the guideline strongly recommends growth hormone therapy to achieve normal adult height, with initial dosing of 0.16 mg/kg to 0.24 mg/kg per week based on weight or body surface area, with individual adjustments as needed. Routine cardiac tests, dual-energy X-ray absorptiometry (DXA) scanning, and lipid profiles are not advised for children treated with growth hormone, while monitoring serum IGF-1 levels is suggested to track treatment adherence and response. The report advises against a blanket increase in growth hormone dose during puberty and recommends discontinuing pediatric growth hormone dosing when growth slows significantly. Regarding growth hormone treatment safety, it highlights the need for guidance on potential adverse effects, such as intracranial hypertension and skeletal complications, with regular monitoring at clinic visits. It also suggests reassessing adrenal and thyroid functions after starting growth hormone therapy, especially in patients with multiple pituitary hormone deficiencies (MPHDs). For transitional care after childhood growth hormone treatment, patients with MPHDs or specific pituitary and/or hypothalamic defects are advised to be assessed for persistent GHD, with growth hormone treatment suggested during the transition period for those with confirmed GHD. For children with ISS, the guideline recommends against routine use of growth hormone therapy for every child with a height standard deviation score (SDS) of −2.25 or less. Instead, it suggests a case-by-case approach, with shared decision-making that considers the physical and psychological burdens, as well as discussions of risks and benefits. A starting growth hormone dose of 0.24 mg/kg per week is recommended, with some children requiring up to 0.47 mg/kg per week. After 12 months of growth hormone therapy, an assessment is suggested to optimize the dosage by evaluating height SDS and psychosocial impact.[55]

Gravholt et al. was an interdisciplinary consensus meeting to develop guidelines for TS based on evidence. The guidelines emphasize that somatropin therapy should be considered early, at around ages 4 to 6 years, and preferably before 12 to 13 years, in children with TS who exhibit growth failure or are predicted to have short stature based on parental heights or pubertal status at diagnosis. Based on the recommendations in the guidelines, initiation of therapy should be contingent on a confirmed diagnosis of TS, evidence of growth failure (e.g., height velocity below the 50th percentile over 6 months), and the absence of other treatable causes of poor growth. It is also recommended that somatropin therapy be considered for children who are already short or have a strong likelihood of short stature. The guidelines suggest that treatment should be monitored closely, with height measurements every 4 to 6 months during the first year and at least every 6 months thereafter. The goal of therapy is to achieve a final adult height within the normal range for age and sex, taking into consideration the genetic potential of the individual. Adjustments to the treatment regimen should be made based on growth velocity and serum IGF-I levels, aiming to maintain IGF-I levels within 2 standard deviations (SD) above the mean for age. The guidelines do not offer recommendations on discontinuation of somatropin therapy; however, the guidelines recommend that if IGF-I levels rise above +3 SD, a decrease in GH dose is warranted, and clinical judgment should guide further dose adjustments for IGF-I levels between +2 and +3 SD. Safety monitoring is an integral part of somatropin therapy. IGF-I levels should be measured at least annually to monitor the efficacy and safety of the treatment. The

recommendations also suggest the use of concomitant treatment with oxandrolone starting from aged 10 years if the diagnosis of TS is delayed or if the adult height outcome is likely to be unsatisfactory with standard growth hormone doses alone.[58]

Yuen et al. is an update of guidelines concerning GHD in adults.[59] The guidelines emphasize that the initiation of somatropin therapy should be based on a confirmed diagnosis of adult GHD, which can be childhood-onset GHD or adult-onset GHD. The diagnosis is typically confirmed through growth hormone stimulation tests, except in certain subtypes of patients with organic hypothalamic-pituitary disease and MPHDs, where low-serum IGF-1 levels (< −2.0 SDS) may suffice. For patients with idiopathic isolated GHD and a serum IGF-1 level SDS of lower than 0 who are transitioning into adult care, re-testing for GHD is recommended at least 1 month after discontinuation of pediatric rhGH therapy. The guidelines do not explicitly define an optimal duration of treatment; however, they outline that the goals of therapy include improvement in body composition, bone health, quality of life, and lipid metabolism. The guidelines recommend individualized treatment, starting with a low dose and titrating up based on clinical response and serum IGF-1 levels, aiming to maintain IGF-1 levels within the age-adjusted reference range (i.e., an IGF-1 level SDS between −2 and + 2). Discontinuation of somatropin was discussed in the guidelines in the scenarios where adverse effects outweigh the benefits, if the patient develops contraindications such as active malignancy or proliferative diabetic retinopathy, or if there is no evidence of clinical benefit despite adequate dosing. Additionally, re-testing for GHD may be warranted in certain circumstances, such as after radiation therapy, to rule out delayed GHD. The guidelines recommend monitoring through regular assessments of serum IGF-1 levels, fasting glucose levels, hemoglobin A1c levels, fasting lipids levels, body mass index, waist circumference, and bone mineral density. Dose adjustments should be made based on these assessments, clinical response, and side effects. For patients transitioning into adult care, a starting dose of 50% of the pediatric dose may be considered, with adjustments based on serum IGF-1 levels and clinical response. The guidelines suggest that patients with concurrent conditions such as diabetes mellitus, obesity, or older age may require lower starting doses to avoid exacerbation of glucose metabolism. In patients with a history of cancer, rhGH therapy should be approached with caution and initiated only after careful consideration and oncologist consultation.[59]

Hokken-Koelega et al. is an international consensus guideline developed by experts in the field of SGA. The consensus for initiating growth hormone treatment in children with short stature born SGA includes the absence of spontaneous catch-up growth by aged 2 to 4 years, with a height of more than 2.25 SD below the mean and a height SDS for chronological age that is significantly below the midparental target height SDS.[27] Treatment should generally commence at an age when catch-up growth is unlikely to occur without intervention (typically around aged 3 to 4 years) and continue until the child has reached their genetic height potential or a height within the normal range. According to the consensus guideline, the growth outcomes that should be achieved with rhGH therapy (e.g., somatropin) include an improved growth velocity that is sustained over time and leads to an increase in height SDS that is closer to the midparental target height.[27] The consensus statement suggests that potential discontinuation criteria for rhGH therapy should include the attainment of near-adult height, defined as a growth rate of less than 1 cm over 6 months in conjunction with closed epiphyses. Additionally, if there is a lack of response to therapy, evidenced by an inadequate

growth velocity, despite appropriate dosing and adherence, discontinuation should be considered. There is a strong recommendation to discontinue therapy in the presence of contraindications such as active neoplasia or in conditions where growth hormone therapy is not recommended because of increased risk of adverse outcomes. The consensus guideline recommends regular assessments of growth velocity, IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) levels, thyroid function, and metabolic parameters in those with risk factors. Bone age should be assessed periodically, particularly around the onset of puberty, to inform treatment decisions.[27] It is recommended that the safety profile of rhGH therapy should be continuously evaluated, with attention paid to potential side effects such as insulin resistance, changes in body composition, and intracranial hypertension.[27]

Table 9: CADTH Review Reports and Reference Lists for Somatropin

Title	Date	Report type	Key messages	Methods
Somatropin for Short Stature	September 2023	Health Technology Review	• For children with short stature who were born small for gestational age, 1 guideline suggests increasing the human growth hormone dose when treatment response is unsatisfactory, while aiming for normal insulin-like growth factor-1 levels. • For children with idiopathic short stature, 1 guideline recommends against the routine use of growth hormone. It suggests initiating growth hormone therapy on a case-by-case basis, with a starting dose ranging from 0.24 mg/kg per week to 0.47 mg/kg per week, as well as conducting an assessment 12 months after initiation to optimize dosage. • The development of recommendations from guidelines included in this report was challenged by limited relevant evidence, as well as heterogeneity of the growth hormone dose and frequency and treatment response found in available literature. Future guidelines should also consider patient perspectives, resource implications, and the facilitators of and barriers to therapy within the context	"Limited literature searches were conducted for 2 previous CADTH reports[19,20] by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, and the websites of Canadian and major international health technology agencies, as well as a focused internet search."[39]

Title	Date	Report type	Key messages	Methods
			of health care systems in Canada".[39]	
Somatropin for Turner Syndrome	August 2023	Health Technology Review	• Early initiation of growth hormone therapy is recommended in children with Turner syndrome if the child already has growth failure or has a high chance of short stature (1 guideline). • Growth hormone treatment can be started at 45 mcg/kg per day to 50 mcg/kg per day (1 guideline). • Monitor treatment by regular height measurements and assessment of levels of insulin-like growth factor-1 (1 guideline). • Continue treatment until the desired height is achieved or when no more growth potential remains (1 guideline).[56]	"[L]iterature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, and a focused internet search."[56]
Somatropin for Growth Hormone Deficiency	August 2023	Health Technology Review	• We identified 2 evidence-based guidelines that provide recommendations for the clinical management of children and adults with growth hormone deficiency. • The American Association of Clinical Endocrinologists and American College of Endocrinology guideline provides recommendations on assessment, screening, diagnostic testing, treatment, and monitoring for a range of patients with different causes of adult growth hormone deficiency. The recommendations emphasize accurate diagnosis using appropriate growth hormone cut points for different growth hormone stimulation tests and careful interpretation of serum growth hormone and insulin-like growth factor-1 levels. Treatment with recombinant human growth hormone should be carried out with	"[L]iterature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search."[57]

Title	Date	Report type	Key messages	Methods
			consideration of the benefits and risks specific to each individual patient. • The Pediatric Endocrine Society guideline provides recommendations for the clinical management of children and adolescents with growth failure due to growth hormone deficiency. The guideline lists various conditions for which growth hormone deficiency can be diagnosed by conventional approaches without growth hormone stimulation testing. The treatment dose of the growth hormone should be calculated based on weight and body surface area and not on insulin-like growth factor-1 levels. The guideline highlights that the initial growth hormone dose, subsequent dosing, and discontinuation of pediatric doses should be assessed based on each individual patient. • Both guidelines recognize the uncertainty of long-term safety (i.e., posttreatment effects) of growth hormone treatment, which is a limitation of both guidelines.[57]	

Title	Date	Report type	Key messages	Methods
Somatropin for Short Stature Secondary to Small for Gestational Age	June 2023	Reference List	• One evidence-based guideline about the use of growth hormone therapy for children with short stature secondary to small for gestational age was identified.[60] • The guideline recommends against the 111routine use of growth hormone. It suggests initiating growth hormone therapy on a case-by-case basis, with a starting dose ranging from 0.24 mg/kg/week to 0.47 mg/kg/week, as well as conducting an assessment 12 months after initiation to optimize dosage.[60]	"[A] literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search."[60]

Source: CADTH technology reviews.[39,56,57,60]

Table 10: Identified Guidelines and Position Statements in CADTH Technology Reviews

Indication (authors)	Initiation criteria	Treatment goals	Assessment	Discontinuation criteria
General (Allen et al.)[54]	Approved indications with an understanding of the underlying condition; baseline clinical evaluations, including full pituitary function testing, medical history, physical examination, and brain MRI	Children: Achieve satisfactory growth without adverse events Adults: Achieve normal age-adjusted serum IGF-1 values	Bone age, thyroid function, potentially adrenal function; adjustments based on these parameters and growth outcomes	Not explicitly defined; consider discontinuation when growth outcomes achieved or in the presence of significant adverse effects
GHD in children (Grimberg et al.)[55]	Confirmed diagnosis of GHD; evidence of growth failure without other treatable causes	Achieve normal adult height	Monitoring serum IGF-1 levels; assessing for adverse effects like intracranial hypertension and skeletal complications	Discontinue when growth slows significantly (growth velocity below 2 cm to 2.5 cm per year) or in the presence of contraindications
ISS in children (Grimberg et al.)[55]	Height SDS ≤ −2.25; case-by-case approach considering physical and psychological burdens	Optimize height SDS and assess psychosocial impact	Regular height measurements; adjustments based on height SDS and growth outcomes	Discontinue if unsatisfactory response or significant adverse effects occur
TS (Gravholt et al.)[58]	Confirmed diagnosis of TS; growth failure or predicted short stature based on parental heights and/	Achieve a final adult height within the normal range for age and sex	Height measurements every 4 to 6 months in the first year, then at least every 6 months; monitor serum IGF-I levels	Consider discontinuing when desired growth outcomes achieved, IGF-I levels rise above +3 SDS, if significant adverse

Indication (authors)	Initiation criteria	Treatment goals	Assessment	Discontinuation criteria
	or pubertal status; absence of other treatable causes of poor growth			effects occur, or until little growth potential remains (bone age ≥ 14 years and HV < 2 cm per year). There is no physiological rationale for continuing GH treatment into the transition period after the completion of puberty.
Adult GHD (Yuen et al.)[59]	Confirmed diagnosis of adult GHD through GH stimulation tests or low-serum IGF-1 levels in certain subtypes	Improvement in body composition, bone health, quality of life, and lipid metabolism	Regular assessments of serum IGF-1, fasting glucose, hemoglobin A1C, fasting lipids, BMI, waist circumference, bone mineral density	Discontinue in cases of adverse effects outweighing benefits, contraindications, or lack of clinical benefit

GH = growth hormone; GHD = growth hormone deficiency; HV = height velocity; IGF-1 = insulin-like growth factor-1; ISS = SD = standard deviation; SDS = standard deviation score; TS = Turner syndrome.

Source: Guidelines and position statements identified in CADTH technology reviews.[54,55,58,59]

Pivotal Studies in Product Monographs of Somatropin Formulations

This section is a summary of the clinical trials reported in the product monograph of each somatropin formulation. Data from clinical trials informing the product monograph may not have been published at the time of approval; as such, this section is only able to summarize information presented in the product monograph.

Pediatric GHD

Humatrope efficacy was supported through open-label, multinational clinical trials involving a total of 239 pediatric patients, though the total number of trials is unclear. These patients were categorized into 3 distinct groups: patients from the US and Canada who were naive to treatment, patients from countries outside of North America who were naive to treatment, and patients who had received prior treatment. The core of the study design was a self-comparison approach, where each patient's growth velocity before initiating Humatrope treatment was compared against their growth velocity after starting treatment, with a prescribed dosage of 0.18 mg/kg per week. Improvements in growth rates were observed across all cohorts, with the mean growth rates increasing from 3.51 cm per year to 10.27 cm per year in the US and Canada cohort, from 3.79 cm per year to 9.05 cm per year in the non-North American cohort, and from 3.34 cm per year to 8.74 cm per year in the previously treated cohort. Variability measures such as SD or confidence intervals (CI) were not provided.[4]

Genotropin was evaluated in the Kabi International Growth Study with 388 patients. Over the course of 12 months, patients treated with the 1.3 mg/mL formulation (n = 342) saw an increase in mean height from 123.5 cm ± 19.2 cm to 131.9 cm ± 18.8 cm, and those treated with the 5.3 mg/mL formulation (n = 46) from 125.0 cm ± 20.2 cm to 139.1 cm ± 17.1 cm.[3]

The Saizen studies involved the comparison of pretreatment growth measurements with growth measurements during treatment across 5 pivotal trials in 5 countries. These trials predominantly included a population of children who were diagnosed with GHD and were prepubertal or pubertal, with some having received previous growth hormone treatments. The efficacy of Saizen was assessed based on changes in height velocity. The studies revealed improvements in growth velocities and SDS for chronological age and bone age. For example, over the course of 12 months in Germany (N = 27), height velocity increased from 3.60 cm (SD = 1.22 cm) per year to 9.54 cm ± 2.76 cm per year, in the US (N = 50) from 3.49 cm (SD = 1.10 cm) per year to 8.56 cm (SD = 1.65 cm) per year, and in the UK (N = 12) from 3.77 cm (SD = 1.75 cm) per year to 10.02 cm (SD = 2.08 cm) per year among those who were treatment naive.[5]

Omnitrope was evaluated in 5 phase III studies that encompassed a total of 190 pediatric patients. Of these, only 1 employed an external control that served as the control for patients who were randomized to either Omnitrope (n = 44) or Genotropin (n = 45) in an open-label trial. The age of the enrolled patients ranged from 2 to 14 years and females constituted 44.9% of the study population. The key outcomes of the study were measured at 9 months and included height velocity, height velocity SDS, height SDS, IGF-1 levels, and IGFBP-3 levels. At the 9-month mark, both Omnitrope and Genotropin increased height velocity from baseline, with patients receiving Omnitrope achieving a mean change of 6.9 cm (SD = 3.1 cm) per year and patients receiving Genotropin 6.8 cm (SD = 3.2 cm) per year. The treatment effect difference was negligible (−0.1 cm per year; 95% CI, −1.5 to 1.3).[6]

Norditropin was assessed in 2 randomized dose-response studies. Study 1 explored the efficacy of 3 different dose levels of Norditropin (0.025 mg/kg, 0.05 mg/kg, and 0.1 mg/kg per day) administered via subcutaneous injection over a 2-year period. A total of 97 participants were enrolled, with a mean age of 7.5 years, and participants were predominantly male (68%). The study reported significant improvements in height SDS across all dosage levels. Specifically, the estimated mean gains in height SDS over 2 years were 0.81, 1.57, and 1.73 for the 0.025 mg/kg, 0.05 mg/kg, and 0.1 mg/kg per day doses, respectively. Study 2 (N = 53) focused on comparing treatment outcomes using Norditropin by titrating doses to achieve specific serum IGF-1 level SDS targets of either [−0.5 to +0.5] or [+1.5 to +2.5], along with a conventional dosing group at 0.04 mg/kg per day. The results showed that children in all 3 groups experienced increases in height SDS from baseline, with the highest gains observed in the group targeted to achieve the higher IGF-I level SDS range. The estimated mean gains in height SDS over the 2-year period were 1.15, 1.39, and 1.85 for the conventional dose, lower IGF-I level SDS target, and higher IGF-I level SDS target groups, respectively.[7]

Nutropin was assessed in 1 open-label trial where patients (N = 97) were randomized to 2 Nutropin dosing regimens: 0.3 mg/kg per week and 0.7 mg/kg per week, administered subcutaneously. The patients in the trial had a mean age of 13.9 years, comprising both male and female participants. All participants were in puberty (Tanner stage 2) and had bone ages of 14 or fewer years for males and 12 or fewer years for females. The study was designed to continue until the participants reached a bone age of at least 16 years for boys and 14 years for girls, or until their growth rate fell below 2 cm per year for 1 year. Over an average duration of 2.7 years (SD = 1.2 years), males in the 0.7 mg/kg per week cohort experienced an increase in average height that was 3.6 cm (SD = 1.7 cm) greater than their counterparts in the 0.3 mg/kg per week

group. Similarly, females receiving the higher dosage saw an average height increase that was 2.9 cm (SD = 3.4 cm) greater than the lower dose group.[8]

Turner Syndrome

The efficacy of Humatrope in treating patients with short stature due to TS was evaluated in 2 studies: a long-term, randomized, open-label multicenter concurrently controlled study (the GDCT study) and a long-term, randomized, blinded, dose-response study (the GDCI study). These studies aimed to ascertain the benefits of Humatrope therapy in enhancing final adult height in this patient population. In the GDCT study, patients treated with Humatrope were compared to a concurrent control group that did not receive somatropin. Patients in the Humatrope group, treated with a dose of 0.3 mg/kg per week administered 6 times per week from an average starting age of 11.7 years over a mean duration of 4.7 years, achieved a mean near-final height of 146.0 cm (SD = 6.2 cm) (n = 27), which was statistically significantly higher than the 142.1 cm (SD = 4.8 cm) (n = 19) attained by the control group. The analysis of covariance indicated that Humatrope therapy resulted in an average height increase of 5.4 cm more than patients who did not receive somatropin (P = 0.001), showcasing the therapy's efficacy in improving stature. The GDCI study treated patients with an average age of 11.1 years for a mean duration of 5.3 years with weekly Humatrope doses of either 0.27 mg/kg or 0.36 mg/kg, administered 3 or 6 times weekly. The participants across the 2 different regimens in this study reached a mean near-final height of 148.7 cm (SD = 6.5 cm) (n = 31).[4]

The therapeutic efficacy of Genotropin in patients with TS who have short stature was assessed through 2 open-label, randomized clinical trials. Specifically, Study 055 involved 22 patients, while Study 092 included 16 patients, each undergoing a 12-month treatment period with Genotropin dosages ranging from 0.13 mg/kg to 0.33 mg/kg per week. These studies aimed to understand the impact of Genotropin treatment, both as a standalone therapy and in conjunction with adjunctive hormonal therapy (either ethinylestradiol or oxandrolone). The primary outcomes measured were SDS for height velocity and overall height, benchmarked against both the Tanner and Sempé standards for age-matched average children, as well as the Ranke standard for age-matched patients with untreated TS. In Study 055, where patients received a higher dose of Genotropin (0.33 mg/kg per week), the height velocity increased from a baseline of 4.1 cm ± 1.5 cm per year to 7.8 cm ± 1.6 cm per year at month 12, marking a change from baseline of 3.7 cm (95% CI, 3.0 cm to 4.3 cm). The height velocity SDS (Tanner and Sempé standards) saw an increase from −2.3 cm ± 1.4 cm at baseline to 2.2 cm ± 2.3 cm at month 12, with a change of 4.6 cm (95% CI, 3.5 cm to 5.6 cm). Additionally, the height SDS (Ranke standard) improved from −0.2 ± 0.8 at baseline to 0.6 ± 0.9 at month 12, translating to a 0.8 change (95% CI, 0.7 to 0.9). Study 092, which used a lower Genotropin dosage range (0.13 mg/kg to 0.23 mg/kg per week), also demonstrated growth improvements. The height velocity at month 12 was 6.1 cm ± 0.9 cm per year, up from a baseline of 3.9 cm ± 1.0 cm per year, with a change from baseline of 2.2 cm per year (95% CI, 1.5 cm to 2.9 cm). The height velocity SDS (Tanner and Sempé standards) saw an increase from −1.6 ± 0.6 to 0.7 ± 1.3, a change of 2.2 (95% CI, 1.4 to 3.0). The height SDS (Ranke standard) improved modestly from −0.3 ± 0.8 to 0.1 ± 0.8, a change of 0.5 (95% CI, 0.4 to 0.5).[3]

Saizen efficacy in TS was assessed in 1 open-label, comparative, randomized multicenter study involving 91 girls with TS, with an average age of 10.3 ± 2.3 years, who were allocated to either receive Saizen alone

(XO group) or Saizen in combination with oxandrolone (XM group). The treatment regimen for the first year involved administering Saizen at 18 IU/m^2 per week (approximately 0.029 mg/kg per day) to both groups, with the XM group also receiving oxandrolone at 0.1 mg/kg per day. In the second year, the Saizen dosage was increased to 24 IU/m^2 per week (approximately 0.038 mg/kg per day) for the XO group, while the XM group continued at the initial Saizen dosage but with a reduced oxandrolone dose of 0.05 mg/kg per day. Subsequent years saw all groups receiving Saizen at 24 IU/m^2 per week, with adjustments in oxandrolone dosing based on growth velocity responses. Improvements were observed in height velocity across both groups during the first 12 months of treatment, with the XM group demonstrating a more pronounced increase in height velocity of 4.6 cm ± 1.8 cm per year compared to 2.4 cm ± 1.3 cm per year in the XO group, a difference that was statistically significant ($P < 0.0001$). After 2 to 7.5 years of treatment, the majority of patients with TS exceeded the mean height for their age by more than 1 SD and achieved heights greater than 150 cm. Of the original 91 girls with TS, 26 reached their final height, averaging 150.6 cm ± 5.5 cm.[5]

The Omnitrope indication in TS was granted on the basis of established similarity between Omnitrope and its reference product, Genotropin.

Norditropin's efficacy in TS was assessed in 2 studies. Study 1 was a randomized, 3-arm, open-label trial involving 71 girls with TS, with an average onset age of 6.5 years. Participants were allocated to 3 treatment groups, receiving different dosages of Norditropin across a span that could extend up to 13 years, aiming for final height. The study also included estrogen therapy after 4 years of Norditropin treatment for those who had not started puberty spontaneously by age 12. Final height results showed an average of 157 cm (± 6.7 SD) for dose A (0.045 mg/kg per day), 163 cm (± 6.0 SD) for dose B (up to 0.067 mg/kg per day), and 163 cm (± 4.9 SD) for dose C (up to 0.090 mg/kg per day). The second study, Study 2, was considered a supportive study, in which 19 White individuals with euthyroid, all with a bone age of 13.9 years or less, were allocated to receive Norditropin at a dosage of 0.067 mg/kg per day along with ethinyl estradiol. Patients were allocated either to a single-dose group or a split-dose group. The average age of the participants was 13.6 years, with a mean height SDS according to the national standard at −3.5 cm, and the mean height velocity for the previous year at 4.3 cm per year. The treatment period averaged 3.6 years. No statistically significant differences were observed in any of the growth-related outcomes between the 2 treatment modalities. When analyzing the combined data from all participants, the average final height reached was 155 cm among the 17 children who achieved their final height. The mean height SDS improved from −3.5 at the start to −2.4 at the final height according to the national standard, and from 0.7 to 1.3 at the final height, based on the Turner standard.[7]

The efficacy of Nutropin in TS was assessed in 1 pivotal, open-label, historically controlled study (Study 85-044). Patients undergoing Nutropin treatment were also randomized to begin estrogen replacement therapy at either age 12 or 15 years, aiming to mimic the natural onset of puberty. The study involved groups defined by the timing of their growth hormone and estrogen therapy initiation relative to their age, with 1 group starting growth hormone therapy before age 11 and estrogen at age 15 (group A), another starting growth hormone before age 11 with estrogen at age 12 (group B), and a third initiating growth hormone therapy after age 11 with estrogen starting at month 12 (group C). The results demonstrated adult height gains across all groups (estrogen replacement therapy at either age 12 or 15 years). Specifically, group A, which delayed

estrogen therapy until age 15, saw an average adult height gain of 8.3 cm (n = 29), while group B, initiating estrogen at age 12, observed a gain of 5.9 cm (n = 26). Group C, with later growth hormone treatment commencement (mean age 12.7 years) and a shorter mean duration of growth hormone therapy (3.8 years), experienced a mean adult height gain of 5.0 cm (n = 51).[8]

Idiopathic Short Stature

Humatrope efficacy in ISS was reported in 2 randomized multicenter trials, including a placebo-controlled study and an open-label, dose-response study. These trials aimed to assess the impact of Humatrope treatment on achieving final adult height in children diagnosed with ISS, after ruling out other causes of short stature and GHD. In the placebo-controlled study, 71 pediatric patients aged between 9 and 15 years, predominantly in the prepubertal or early puberty stages, were enrolled. They were administered Humatrope at a dose of 0.222 mg/kg per week or a placebo through subcutaneous injections 3 times per week until their height velocity decreased to 1.5 cm or less per year. The final height data available for 33 patients indicated that after an average treatment duration of 4.4 years, the Humatrope-treated group achieved a mean final height that was 0.51 SDS higher than that of the placebo group, translating to an approximate height gain of 3.7 cm. The dose-response study included 239 pediatric patients, with a mean baseline height SDS of −3.21, indicating significant short stature. Patients were randomized into 3 groups that received varying doses of Humatrope. The study's primary goal was to observe the increase in height velocity over the first 2 years of therapy, which was expected to be dose-dependent. The results showed that patients receiving the higher dose of 0.37 mg/kg per week experienced a statistically significantly greater increase in mean height velocity than those on the lower dose of 0.24 mg/kg per week after 2 years of treatment.[4]

Genotropin efficacy in ISS was evaluated through a pivotal randomized, open-label clinical trial involving 105 children who were prepubertal, and a supportive smaller open-label trial with 37 randomized children who were prepubertal. Both studies focused on children diagnosed with ISS after ruling out other causes of short stature and GHD. Within the pivotal trial, 105 patients who were prepubertal, with a mean chronological age of 11.4 years and a height SDS of −2.4 cm, were observed for a year before being randomized to receive either Genotropin (at 2 different dosages: 0.033 mg/kg per day [equivalent to 0.23 mg/kg per week; n = 33] and 0.067 mg/kg per day [equivalent to 0.47 mg/kg per week; n = 42]) or observation only, and followed until they reached their final height. After a median treatment duration of 5.7 years, the difference from baseline in height SDS for the untreated group was 0.41 (SD = 0.58), while those treated with 0.033 mg/kg per day of Genotropin showed an improvement to 0.95 (SD = 0.75), and the 0.067 mg/kg per day group improved to 1.36 (SD = 0.64). The difference from baseline in final height SDS compared to patients who were not treated was statistically significant for both treatment groups, with the lower dose showing a mean of + 0.53 (95% CI, 0.20 to 0.87; P = 0.0022) and the higher dose showing a mean of + 0.94 (95% CI, 0.63 to 1.26; P < 0.0001). A direct comparison between the 2 Genotropin doses revealed a statistically significant difference, favouring the higher dose with a mean difference of −0.41 (95% CI, −0.72 to −0.10; P = 0.0105).[3]

The Omnitrope indication in ISS was granted on the basis of established similarity between Omnitrope and its reference product, Genotropin.[6]

Saizen, Norditropin, and Nutropin are not indicated in ISS.[5,7,8]

Short Stature due to SGA

The efficacy of Humatrope in treating growth failure in children born SGA was evaluated through 2 clinical trials: 1 randomized and 1 single-arm study. The primary goal of the randomized Study GDGB (N = 193) was to compare the efficacy of Humatrope administered via an individually adjusted dose (IAD) regimen versus a fixed high dose (FHD) regimen over a period of 1 year. This European study involved 193 children who were prepubertal and not GHD with an average age of 6.8 years (SD = 2.4). These children were selected based on specific criteria, including birth weight below the 10th percentile and/or a significant shortfall in birth length for their gestational age, alongside a height SDS for chronological age of −3.0 or less. The exclusion criteria included having syndromal conditions (e.g., TS), tumour activity, or chronic disease (e.g., diabetes mellitus). At the conclusion of the first year, efficacy evaluations were conducted for 179 participants, comprising 93 from the FHD group and 86 from the IAD group. After 1 year of treatment, the IAD group exhibited a mean height SDS of −3.0 (SD = 0.7) with a change from baseline of + 0.9 (SD = 0.4), while the FHD group showed a mean height SDS of −2.7 (SD = 0.7) with a change from baseline of + 1.1 (SD = 0.4). The results show noninferiority of IAD to FHD within a pre-established noninferiority margin of 0.5 SDS. Study 0908, conducted in France, treated 35 children who were prepubertal with Humatrope at a daily dosage of 0.067 mg/kg (0.47 mg/kg per week) for 2 years. The participants had a mean age of 9.3 years (SD = 0.9) and met similar inclusion criteria focused on gestational age, birth size, and current height SDS (birth length SDS < −2.0 or < third percentile for gestational age and height SDS for chronological age < −2.0). After 2 years of receiving Humatrope treatment in Study 0908, the average height SDS of participants improved from an initial measurement of −2.7 (SD = 0.5) to −1.5 (SD = 0.6).[4]

The efficacy of Genotropin in treating children born SGA who did not exhibit catch-up growth by age 2 was assessed through 4 pivotal, randomized, open-label, controlled, multicenter, multinational clinical trials. These trials involved comparing 2 doses of Genotropin-treated groups to 1 untreated control group across several countries, including Belgium, Denmark, Finland, France, Germany, Norway, and Sweden. The primary metric for assessment was the height velocity SDS, measured over 2 consecutive 12-month periods. Collectively, the studies involved 76 children treated with Genotropin at a dosage of 0.24 mg/kg per week, 93 children treated with a higher dosage of 0.48 mg/kg per week, and 40 children in the untreated control group. At the baseline, the height SDS for these groups were −3.2 (SD = 0.8), −3.4 (SD = 1.0), and −3.1 (SD = 0.9), respectively. After 24 months of treatment, the group receiving 0.24 mg/kg per week of Genotropin experienced an increase in height SDS to −2.0 (SD = 0.8), translating to a change of 1.2 (SD = 0.5) from the baseline. The group treated with the higher dosage of 0.48 mg/kg per week showed height SDS improving to −1.7 (SD = 1.0), a change of 1.7 (SD = 0.6) from the baseline. This contrasted with the change observed in the untreated control group of height SDS improvements of −2.9 (SD = 0.9), a change of 0.1 (SD = 0.3) from the baseline.[3]

Saizen efficacy in the treatment of children born SGA who do not to exhibit catch-up growth by age 2 was assessed in 2 randomized, controlled, phase III clinical trials, GF 4001 (N = 101) and GF 6283 (N = 58). GF 4001 enrolled 101 participants with an average age of 4.5 years (ranging from aged 2 to 8 years), including 51 males and 49 females. The participants were allocated into a treatment group (group T) that began Saizen therapy immediately and a control group (group C) that initiated treatment after the first year. GF

6283 included 58 participants with an average age of 3.3 years (ranging from aged 2 to 5 years), comprising 28 males and 30 females. Participants were allocated to 2 treatment regimens: continuous treatment for 2 years with a subsequent 2-year observation period (group TTOO) and intermittent treatment across 4 years (group TOTO). In the GF 4001 study, group T and group C started with a mean height velocity SDS of −1.42 (SD = 1.23) and −0.40 (SD = 1.11), respectively. After 2 years of treatment, both groups exhibited improvements in height velocity SDS to 4.00 (SD = 1.68) and 4.01 (SD = 2.11), respectively. By the third year, height velocity SDS was 1.97 (SD = 1.56) for group T and 2.05 (SD = 1.68) for group C. In Study GF 6283, the continuous treatment group (group TTOO) noted a height velocity SDS increase to 3.76 (SD = 1.31) by the second year from a baseline of −0.97 (SD = 1.01), with height SDS based on chronological age improving to −1.55 (SD = 0.82) after 2 years from a baseline of −3.55 (SD = 0.60). The discontinuous treatment group (group TOT) saw a height SDS decrease during the observation periods but ultimately achieved a height SDS based on chronological age to −1.68 (SD = 1.05) after 2 years.[5]

The Omnitrope indication in short stature due to SGA was granted on the basis of established similarity between Omnitrope and its reference product, Genotropin.[6]

Norditropin efficacy was assessed in 2 studies. Study 1 focused on a cohort of 53 Dutch children (38 males and 15 females) aged between 3 and 11 years. These children were prepubertal and met specific criteria, including a birth length below the third percentile for gestational age and a height velocity for chronological age below the 50th percentile. The children received Norditropin subcutaneously daily at bedtime, with doses of 0.033 mg/kg per day (dose A; n = 26) or 0.067 mg/kg per day (dose B; n = 27) throughout the treatment period, which lasted up to 13 years. The mean duration of treatment was 9.5 years for boys and 7.9 years for girls. In this study, and across both treatment groups, 38 out of 53 children (72%) reached their final height, with a notable proportion (63%) achieving a height within the average range for their healthy Dutch peers. The actual mean final heights were 171 cm (SD = 6.1 cm) for boys and 159 cm (SD = 4.3 cm) for girls. Study 2 was a randomized controlled trial in which 84 prepubertal Japanese children (aged 3 to 8) were treated with 0.033 mg/kg or 0.067 mg/kg per day of Norditropin subcutaneously or received no treatment for 1 year. For children treated with 0.033 mg/kg per day, the increase in height SDS from baseline to year 1 was 0.6 (95% CI, 0.5 to 0.7; n = 33), the 0.067 mg/kg per day group experienced an increase of 0.9 (95% CI, 0.8 to 1.0; n = 34).[7]

Nutropin is not indicated for the treatment of short stature due to SGA.[8]

Adult GHD

Humatrope efficacy in the treatment of childhood-onset and adult-onset GHD was evaluated through 4 multicenter trials, involving a total of 165 patients. Two of these were for adult-onset GHD (N = 98) and 2 were for childhood-onset GHD (N = 67). All 4 trials included 6 months of a randomized, placebo-controlled phase, followed by an open-label extension of 12 months. Humatrope was given at an initial dose of 0.00625 mg/kg per day, which was then adjusted to a maintenance dose of 0.0125 mg/kg per day. Efficacy measures centred on body composition changes, lipid parameters, and quality of life assessments via the Nottingham Health Profile. Patients with adult-onset GHD treated with Humatrope exhibited increases in lean body mass (+2.59 kg versus +0.22 kg in placebo, P < 0.001) and notable reductions in percent body fat (−3.60% versus

+0.19% in the placebo group, P < 0.001). Quality of life improvements, as measured by the Nottingham Health Profile, revealed statistically significant improvements in the domains of physical mobility and social isolation for patients with adult-onset GHD who were treated with Humatrope, compared to those receiving placebo treatments.[4]

Genotropin was assessed in 6 randomized clinical studies involving 172 adults with GHD (unclear if childhood or adult onset). The effects of Genotropin lyophilized powder were evaluated against a placebo. During these studies, 85 participants were treated with Genotropin, while 87 received a placebo over a 6-month double-blind period, followed by an open-label phase where Genotropin was administered to all participants for up to 24 months. The initial dosage of Genotropin was set at 0.04 mg/kg per week for the first month, increasing to 0.08 mg/kg per week thereafter. At the conclusion of the initial 6-month phase, significant improvements in body composition were noted among those treated with Genotropin compared to those on placebo (data not available in the product monograph). Increases were observed in lean body mass, total body water, and the lean-to-fat ratio, while total body fat and waist circumference saw reductions. These positive changes in body composition persisted with continued Genotropin treatment beyond the initial 6 months. Although bone mineral density decreased at the 6-month mark, it reverted to baseline levels after a year of treatment (data not provided in the product monograph).[3]

Saizen efficacy was assessed in 1 double-blind placebo-controlled randomized trial (N = 115) that was 6 months in duration. The participants were randomized to Saizen (n = 60) at dosages of 0.005 mg/kg per day for the initial month, escalating to 0.01 mg/kg per day for the subsequent 5 months, and to matching placebo (n = 55). All participants then entered a 12- to 30-month open-label treatment phase. After 6 months of Saizen therapy, a statistically significant (P < 0.0001) elevation in lean body mass was observed when compared to the placebo group. For the Saizen group, the lean body mass at baseline averaged 49.1 kg (SD = 11.7 kg; n = 59), which increased to 49.6 kg (SD = 12.0 kg; N = 52) at the 6-month mark. In contrast, the placebo group started with a baseline lean body mass of 53.7 kg (SD = 12.2 kg; n = 54) and saw a change to 53.9 kg (SD = 11.9 kg; n = 52) after 6 months. When centre effects and initial lean body mass were accounted for, the mean difference in treatment outcomes showed an increase of 2.21 kg in the Saizen group over the placebo group, with a 95% CI ranging from 1.27 kg to 3.15 kg.[5]

The Omnitrope indication in adult GHD was granted on the basis of established similarity between Omnitrope and its reference product, Genotropin.[6]

Nutropin efficacy in adult GHD was assessed in 2 randomized, placebo-controlled, double-blind trials, M0431 g (adult onset; N = 166) and M0381 g (childhood onset; N = 64). The adult-onset trial (M0431 g) involved 166 participants (86 males and 80 females) with an average age of 48.3 years, ranging from 20.8 to 70.7 years. They were administered growth hormone at doses of either 0.0125 mg/kg or 0.00625 mg/kg per day via subcutaneous injection for a duration of 12 months. The childhood-onset study (M0381 g) included 64 individuals (39 males and 25 females) with an average age of 23.8 years, spanning from 14.5 to 33.7 years, who were receiving growth hormone doses of 0.025 mg/kg or 0.0125 mg/kg per day over 24 months. For the adult-onset study, M0431 g, the placebo group (n = 62) showed negligible changes in total body percent fat and lean mass, with fat remaining virtually unchanged from a baseline of 36.8% (SD = 11.3) to 36.8% (SD

= 1.5) at month 12, and lean mass from 60.4% (SD = 11.0) to 60.5% (SD = 11.1). In contrast, the Nutropin group (n = 63) experienced reductions in total body fat from 35.0% (SD = 11.2) to 31.5% (SD = 12.5) and increases in lean body mass from 62.2% (SD = 11.0) to 65.7% (SD = 12.3) (P < 0.0001 for both changes). The post-washout measurements further validated these findings, showing a sustained decrease in fat to 32.2% ± 12.5 and an increase in lean mass to 65.0% ± 12.2. In the childhood-onset study, M0381 g, results were available at 12 months that compared Nutropin therapy at 2 dosage levels (0.0125 mg/kg and 0.025 mg/kg per day) against placebo. Baseline total body fat percentage was 35.0% (SD = 7.4) for the placebo group (n = 13) and ranged from 37.1% (SD = 13.2) to 38.4% (SD = 11.8) for the Nutropin groups (n = 15 each). At month 12, the placebo group saw a minor change in fat mass to 35.2% (SD = 8.2), whereas Nutropin groups recorded statistically significant reductions to 31.3% (SD = 13.6) and 32.1% (SD = 13.4), respectively (P values < 0.0001). Concurrently, lean body mass in the Nutropin groups increased from 60.0% (SD = 12.7) and 59.1% (SD = 11.3) at baseline to 66.0% (SD = 13.4) and 65.5% (SD = 12.9) at month 12.[8]

Norditropin is not indicated for adult GHD.[7]

Summary of Evidence

A summary of the collective information in this report is presented in this section. In Canada, multiple somatropin products are authorized by Health Canada, including Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin. These products cater to a spectrum of clinical indications with varying formulations and delivery systems to meet diverse patient needs. The Exceptional Access Program facilitates access to somatropin for conditions like GHD, TS, short stature due to being SGA, and ISS. Somatropin products are broadly indicated for pediatric GHD, TS, ISS, short stature due to being SGA, and adult GHD, with specific products also approved for PWS, Noonan syndrome, and chronic renal failure. These indications are based on clinical trials that support their efficacy in improving growth outcomes and body composition.[3-8]

CADTH's reimbursement reviews and health technology assessments have consistently recognized the clinical benefits of somatropin. However, gaps in the evidence, particularly regarding direct comparisons between somatropin products and their long-term safety, highlight the need for ongoing research to inform robust and comprehensive reimbursement policies.[52,53]

Guidelines and consensus statements identified in CADTH Technology Reports and outlined in this report provide an overview of clinical approach to the initiation and discontinuation of somatropin in various indications.[39,56,57,60] According to Allen et al., treatment initiation across all indications requires a confirmed diagnosis based on approved indications, supplemented by comprehensive baseline clinical evaluations, including but not limited to, full pituitary function testing, medical history review, physical examination, and brain MRI scans. The treatment aims differ by age group; for children, the objective is the achievement of satisfactory growth without adverse outcomes, whereas for adults, the goal is to normalize age-adjusted serum IGF-1 levels. The methodology for ongoing assessment involves monitoring bone age, thyroid, and potentially adrenal function, with treatment adjustments reflective of these findings and growth responses. The guidelines suggest considering treatment cessation when intended growth outcomes are met or if significant adverse reactions occur.[54]

Per Grimberg et al., for pediatric GHD, the criteria for starting treatment include a verified diagnosis of GHD and evidence of growth failure, excluding other treatable causes. The primary objective is reaching a standard adult height, with the approach to assessment centred on serum IGF-1 level monitoring and evaluating potential adverse effects such as intracranial hypertension and skeletal complications. Treatment discontinuation is recommended when there is a notable slowdown in growth or when contraindications are present.[55]

In the context of ISS in children, Grimberg et al. advise a starting criterion based on a height SDS of −2.25 or less, necessitating a tailored approach that weighs physical and psychological considerations. The goal is to enhance height SDS and evaluate its psychosocial impacts, with treatment adjustments guided by systematic height measurements and growth results. Therapy should be halted if responses are unsatisfactory or if significant adverse effects manifest.[55]

For treatment in TS, Gravholt et al. outline initiation criteria that include a confirmed diagnosis, observed growth failure, or a projection of short stature based on parental heights or pubertal status, in the absence of other treatable growth impediments. The treatment ambition is to attain a final adult height within the normal range for the patient's age and sex, with assessment strategies that include regular height measurements and monitoring of serum IGF-I levels. Therapy discontinuation is recommended upon achieving the desired growth outcomes, if IGF-I levels exceed +3 SDS, in the event of significant adverse effects, or when growth potential is minimal.[58]

Yuen et al. specify that, for adult GHD, initiation should be predicated on a confirmed diagnosis via growth hormone stimulation tests or low-serum IGF-1 levels under certain conditions. The treatment aims to ameliorate body composition, enhance bone health, improve quality of life, and optimize lipid metabolism, with assessment protocols that include regular monitoring of serum IGF-1 levels, glucose levels, hemoglobin A1C levels, lipids, body mass index, waist circumference, and bone mineral density. Discontinuation of therapy is advised in instances of adverse effects that outweigh the benefits, the emergence of contraindications, or an absence of clinical benefit.[59]

Health Canada's wording of the various somatropin indications share certain commonalities across the preparations. In pediatric GHD, the language emphasizes ensuring the inadequacy of endogenous growth hormone production. In TS-related indications, a common theme is ensuring patient epiphyses are not closed. Indications for short stature due to being SGA only apply to patients who are born SGA (birth weight and/or length below −2 SD) and who fail to achieve catch-up growth by 2 years or later. ISS-related indications define patients as those with a height SDS of less than −2.25 and are associated with growth rates that are unlikely to permit attainment of adult height within an acceptable range that is close to average. It also emphasizes the exclusion of all other causes and specifies that it should only be prescribed for patients whose epiphyses have not closed. Finally, in adult GHD, the wording of the indication emphasizes the distinction between adult onset and childhood onset. In adult-onset GHD, patients are expected to have a confirmed growth hormone deficiency because of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma. In adult patients with childhood-onset GHD, the indication wording does not necessitate the existence of a diagnosable cause as long as the condition has been diagnosed in childhood. [3-8]

Limitations

This report covered CADTH and Health Canada sources related to somatropin and we did not conduct a literature search or a systematic review for each of the indications. While our report has identified several direct sources of information to inform on the objectives, other sources that may not have been captured in CADTH reports or Health Canada's product monographs may have been missed. Furthermore, evidence of the efficacy of various preparations of somatropin and the characteristics of the patients in the pivotal trials were based on the available data in the associated product monographs. This represents a limitation because of the limited data available in product monographs and the lack of a clear connection between the pivotal studies in the product monographs and the published literature. Furthermore, this report did not aim to critically appraise any identified relevant study.

The identified guidelines included recommendations that are based on various levels of evidence. In this report we provided an overview and did not detail the strength of each recommendation within each guideline. Furthermore, the included guidelines may not have included clear and concise criteria for potential consideration of treatment discontinuation.

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