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CADTH Reimbursement Recommendation

Somapacitan (Sogroya)

Indication: For the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency)

Sponsor: Novo Nordisk Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Sogroya?

CADTH recommends that Sogroya should be reimbursed by public drug plans for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency [GHD]) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Sogroya should only be covered to treat children who are at least 2.5 years of age, have not reached puberty yet, and are diagnosed with GHD.

What Are the Conditions for Reimbursement?

Sogroya should only be reimbursed for a patient who is under the care of a pediatric endocrinologist and whose growth plates have not closed if Sogroya does not cost more than somatropin and somatrogon.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that weekly injections of Sogroya works the same as daily injections of Norditropin (somatropin) in terms of growth outcomes; children who took weekly injections of Sogroya grew at the same rate as children who took daily injections of Norditropin (somatropin).
- Sogroya may meet some of the needs identified by patients and their caregivers, such as comparable growth results as existing treatment, similar quality of life compared with existing treatment, and weekly injections instead of daily injections.
- Based on CADTH's assessment of the health economic evidence, Sogroya does not represent good value to the health care system at the public list price. The committee determined there is not enough evidence to justify a greater cost for Sogroya compared with somatrogon and somatropin.
- Based on public list prices, Sogroya is estimated to cost the public drug plans approximately $458,079 over the next 3 years.

Additional Information

What Is Growth Hormone Deficiency?

GHD occurs when there is not enough growth hormone in the body. Children with GHD are very short with normal body proportions. If untreated, children with GHD will not reach their full adult height. There are approximately 1,600 children who are living with GHD in Canada.

Summary

Unmet Needs in Growth Hormone Deficiency

There are many treatments approved in Canada to treat GHD; however, these predominately need to be injected every day. Some patients might not take the medicine as prescribed due to anxiety and pain of injections, frequency of injections, inconvenience in storing and handling, or simply forgetting. There is a need for a treatment that might improve adherence. A treatment that is taken once a week might address that need.

How Much Does Sogroya Cost?

Treatment with Sogroya is expected to cost approximately $15,454 per patient per year, assuming a patient weight of 31.08 kg.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that somapacitan be reimbursed for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency [GHD]) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized, active-controlled trial (REAL 4) compared somapacitan (0.16 mg/kg once weekly) with Norditropin (somatropin) (0.034 mg/kg once daily) via subcutaneous injections. Results from this study demonstrated that somapacitan was noninferior to Norditropin (somatropin) in terms of height velocity at week 52 in prepubertal children with GHD who had no prior exposure to growth hormone (GH) therapy or insulin-like growth factor I (IGF-I) treatment. The height velocity at week 52 was 11.2 cm/year in the somapacitan arm and 11.7 cm/year in the Norditropin (somatropin) arm, with an estimated treatment difference (ETD) of −0.5 cm/year (95% confidence interval [CI], −1.1 cm/year to 0.2 cm/year). For secondary outcomes such as change from baseline to week 52 in height standard deviation score (SDS) and height velocity SDS, the results of both treatment arms were also comparable, with −0.05 difference (95% CI, −0.18 to 0.08) in height SDS and −0.78 difference (95% CI, −1.63 to 0.08) in height velocity SDS. Somapacitan had a similar safety prolife to Norditropin (somatropin), and no new safety concerns were observed in the somapacitan arm in the long-term extension studies (REAL 4 and REAL 3).

Patients and their caregivers identified a need for treatments that demonstrate improvement in growth, improvement in quality of life, and lessen burden of treatment (e.g., frequency of administration, improvement in adherence, easier to administer [oral or powder form], and longer lasting). CDEC concluded that somapacitan may meet some of the needs identified by patients and their caregivers, including comparable growth results to existing treatment, comparable quality of life compared with existing treatment, and weekly injections instead of daily injections.

Using the sponsor-submitted price for somapacitan and publicly listed prices for somatrogon and somatropin, somapacitan was determined to be more costly than somatropin. Because there is insufficient evidence to suggest somapacitan is more effective than somatrogon and somatropin, the total drug cost of somapacitan should not exceed the total drug cost of the lowest cost somatropin.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Prepubertal children who have growth failure due to an inadequate secretion of endogenous growth hormone:	REAL 4 enrolled boys aged ≥ 2.5 years and < 11 years and girls aged ≥ 2.5 years and < 10 years with growth failure due to an	Based on patient and clinician input, as well as evidence from the REAL 4 long-term extension study, somapacitan would be appropriate for treatment-naive

Reimbursement condition	Reason	Implementation guidance
1.1. diagnosed with GHD: 1.1.1. for patients aged ≥ 2.5 years.	inadequate secretion of endogenous growth hormone (GHD).	and treatment-experienced children. Boys between the ages of 2.5 years and < 11 years, and girls between the ages of 2.5 years and < 10 years were enrolled in REAL 4. There is no evidence reviewed for patients older than 11 years of age.
Discontinuation		
2. Treatment with somapacitan must be discontinued upon closure of the epiphyseal growth plates.	Consistent with clinical practice guidelines and aligns with clinical practice. According to the clinical expert, a contraindication that precludes ongoing use of somapacitan (or any other growth hormone therapy) is when the epiphyses are closed.	–
Prescribing		
3. Patient is under the care of a pediatric endocrinologist.	Accurate diagnosis and follow-up of patients with GHD are important to ensure that somapacitan is prescribed to the most appropriate patients.	–
Pricing		
4. Somapacitan should be negotiated so that it does not exceed the drug program cost of treatment with the least costly somatropin reimbursed for the treatment of pediatric patients with GHD.	There is insufficient clinical evidence to justify a cost premium for somapacitan over the least expensive growth hormone reimbursed for pediatric patients with GHD.	–
Feasibility of adoption		
5. The feasibility of adoption of somapacitan must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption given the difference between the sponsor's estimate and CADTH's estimate(s).	–

GHD = growth hormone deficiency.

Discussion Points

- CDEC deliberated on the unmet therapeutic needs raised by patient and clinician groups. CDEC discussed that GHD is a rare condition in children but, despite its rarity, effective treatment options are available for patients. CDEC noted that these available treatment options are predominately daily injections and acknowledged that a weekly injection treatment option (somatrogon) exists. Although patients believed that these existing therapies met key needs, particularly related to growth, CDEC noted that for patients on daily injections, somapacitan may reduce treatment burden by

allowing weekly injections. CDEC also discussed that for patients with needle phobia or anxiety, somapacitan has the potential to close some of the gaps in adherence. CDEC noted that the therapy adherence rate, measured with a patient e-Diary device for electronic data recording, was higher in the somapacitan arm than in the Norditropin (somatropin) arm (96% versus 88%). However, there remains some uncertainty if this observation will translate to higher adherence for the weekly injections compared with daily injections in the real-world setting. Nonetheless, CDEC acknowledged there is a need for a treatment that might improve adherence, and a treatment that is taken once a week might address that need.

- CDEC discussed patient-reported outcomes results, such as Growth Hormone Deficiency–Child Impact Measure (GHD-CIM), Growth Hormone Deficiency–Child Treatment Burden (GHD-CTB), and Growth Hormone Deficiency–Parent Treatment Burden (GHD-PTB). CDEC noted that the results were suggestive of no difference between somapacitan and Norditropin (somatropin), with the exception of GHD-PTB total score which was suggestive of some benefit in favour of somapacitan; however, CDEC acknowledged these patient-reported outcomes were exploratory. CDEC concluded that overall quality of life while on somapacitan was comparable to existing treatment.
- CADTH noted that there was no direct evidence comparing weekly GH injections (somapacitan versus somatrogon). The sponsor submitted an indirect treatment comparison (ITC) to address this gap. Although there were several limitations to the analysis, there were no differences detected in efficacy outcomes in the sponsor-submitted ITC comparing somapacitan with somatrogon.

Background

GHD is a rare disease caused by impaired secretion of GH by the pituitary gland, which affects patients' growth, body composition, metabolic profile, bone mineral density and quality of life. The physical manifestation of GHD can vary depending on the types of cells affected, the age of onset, and the combination of genetic mutations. Estimates of pediatric GHD suggest a prevalence of 1 in 4,000 to 10,000 children worldwide, suggesting a prevalence of approximately 1,600 children in Canada.

GH stimulation testing is considered standard of care for the diagnostic of GHD. The treatment of GHD is injections of synthetic GH. Somatropin, administered as a daily SC injection, has traditionally been the primary GH used for treatment of GHD. In March 2022, somatrogon (Ngenla), a Health Canada–approved GH, received a CADTH reimbursement recommendation for treatment of pediatric GHD as a weekly SC injection.

Somapacitan (Sogroya) has been approved by Health Canada for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous GH (GHD). It is available in 5 mg/1.5 mL (3.3 mg/mL), 10 mg/1.5 mL (6.7 mg/mL), and 15 mg/1.5 mL (10 mg/mL) as a prefilled pen for subcutaneous injection. The recommended dosage in the product monograph is 0.16 mg/kg body weight once weekly. The maintenance dose can be adjusted based on the patient and their response.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized, open-label, active-controlled, phase III trial in patients aged 2.5 years to younger than 11.0 years (boys), and 2.5 years to younger than 10.0 (girls) with GHD (REAL 4)
- patient perspectives gathered by patient groups: Canadian Organization for Rare Disorders (CORD) and the MAGIC Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with pediatric GHD
- input from 1 clinician group, the Pediatric Endocrinology Nurses group
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of 1 long-term, open-label extension study (REAL 4)
- a review of the indirect evidence from 1 network meta-analysis submitted by the sponsor
- a review of 1 randomized, open-label, active-controlled, multiple-dose, dose-finding phase II trial with open-label extension as well as a long-term safety extension phase (REAL 3).

Stakeholder Perspectives

Patient Input

Two patient groups, CORD and the MAGIC Foundation, provided input for the treatment of GHD. CORD recruited participants through patient membership list and parents attending a European summit, and then conducted interviews. The MAGIC Foundation gathered data from surveys. A total 12 parents (6 from the list and 6 from the summit) participated in the interviews conducted by CORD. Among these 12 participants, 4 were from Ontario, 2 were from the US, and 6 were from Europe. All participants responding to the MAGIC Foundation's surveys were from the US; none of their current members in Canada had experience with long-acting GH. The children represented in the CORD input ranged in age from 4 to 15 years, and those from the MAGIC Foundation input were between 3 and 18 years.

When parents were asked by CORD about the impact of the disease on patients' and caregivers' day-to-day life and quality of life, they expressed going through a variety of emotions, such as denial, blame, sadness, acceptance, and compassion. Parents from both groups reported a variety of psychological and social impacts on the child and the family, particularly due to short stature. In the MAGIC Foundation's input, parents mentioned that their children were shorter than their peers, were fatigued, lacked concentration and appetite, had poor stamina, and were often very sick before beginning GH treatment.

Patients from both groups were reported to have been on GH therapy. All patients in the CORD group were reported to have experience with daily subcutaneous injections of somatropin, and 4 patients were reported to have current experience with long-acting GH therapy (somatrogon, lonapegsomatropin, and somapacitan-

beco) through clinical trials, compassionate access, or reimbursement or insurance. Some patients from the MAGIC Foundation group were reported to have experience with both daily and weekly injections, whereas others were reported to be strictly on daily injections.

Parents from the CORD group described the daily injections every night as the most consistent challenge. These parents also recognized the importance of GH therapy despite the challenges and worries about the future. Parents from the MAGIC Foundation group mentioned the high cost of GH treatment and dependence on insurance companies in getting the treatment for children in the US. When parents were asked by the CORD group about the outcomes to consider when evaluating new therapies, an injection that lasted longer and was easier to administer was a desired change. All 4 respondents with experience with long-acting GH therapy shared positive feedback when describing their experience with the current drug under review, such as the positive impact it had on the child's and the family's quality of life. Some even described this impact as "transformational" and "life-changing."

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert indicated that the current treatment paradigm for children with GHD is to offer recombinant GH. The treatment goals are to optimize (restore height targeting achievement of) the near-final adult height that is close to the patient's midparental target heights by improving height velocity, to restore metabolic health, to address hypoglycemia (especially in the neonatal or infantile periods), and to restore well-being. The clinical expert pointed out that several brands of somatropin are available to treat GHD. Somapacitan can be used in the treatment of pediatric GHD for those who are willing to try or those who are using somatropin and want to switch to once-weekly injections. The clinical expert noted that patients who are most in need of somapacitan would be those who experience significant pain or anxiety from the injections to the extent that there is a threat to optimal adherence to daily somatropin. The clinical expert indicated that treatment responses include change in absolute height and height SDS, change in height velocity and height velocity SDS, and change in IGF-I level (and IGF-I SDS). According to the clinical expert, patients prescribed somapacitan should be under the care of pediatric endocrinologists and pediatric endocrine nurses, in either community settings or academic referral centres.

Clinician Group Input

Clinician group input on the review of somapacitan was received from the Pediatric Endocrinology Nurses group. A total of 5 nurses provided input for this review.

The Pediatric Endocrinology Nurses group mentioned that daily somatropin injections are used as the current treatment paradigm for GHD. These injections are administered to increase growth, stabilize blood sugar levels, increase bone density, and increase muscle development. The Pediatric Endocrinology Nurses group described the treatment gaps or unmet needs of currently available treatments. These unmet needs were poor compliance in patients with daily injections, availability of GH, anxiety with daily injections, treatment with better tolerance, treatment with improved compliance, and formulations with improved

convenience. The Pediatric Endocrinology Nurses group indicated that somapacitan could be used as a first-line treatment for GHD if approved or funded.

When describing the patients who would be best suited for treatment with the drug under review, the Pediatric Endocrinology Nurses group mentioned those who experience needle anxiety, compliance issues, complex social situation, and remote living conditions. The group also added that patients with GHD could be identified by clinician examination, GH stimulation testing, bone age, IGF-1, and so on. The Pediatric Endocrinology Nurses group emphasized that without GH (either daily or weekly), patients will not grow and could have hypoglycemia, decreased bone density, poor muscle development, and altered body composition. The Pediatric Endocrinology Nurses group pointed out that improved growth velocity and normalized glucose in infants would be considered as clinically meaningful response to treatment. They also added that factors such as achieving final adult height, closed epiphyses, and growth rate less than 2 cm/year should be considered when deciding to discontinue treatment with the drug under review. The clinician group noted that the patients must be diagnosed, treated, monitored, and prescribed by a pediatric endocrinologist.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions From the Drug Programs

Implementation Issues	Response
Relevant comparators	
The sponsor submitted a pivotal trial that compared somapacitan and Norditropin (somatropin) which is once-daily GH. There are no comparative head-to-head trials between somapacitan and Ngenla (Somatrogon, reviewed October 2021) which is also once-weekly GH. The sponsor submitted an indirect comparison among somapacitan, somatropin and somatrogon.	Comment from the drug programs to inform CDEC deliberations.
Some provinces and territories (e.g., Ontario) fund GH through alternative pathways, such as the special drug program at the Hospital for Sick Children (SickKids) in Toronto. Typically, NIHB would not cover the pediatric patients who have growth failure due to an inadequate secretion of endogenous GH (GH deficiency) as they would apply for funding through the available provincial or territorial routes.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
It is anticipated that patients who are taking daily injections would want to transition to subcutaneous weekly injections. It does not appear that this would be an issue based on the trial, weekly injections were noninferior to daily injections.	Comment from the drug programs to inform CDEC deliberations.

Implementation Issues	Response
If possible, consider aligning with Ngenla (Somatrogon)	Comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
Consider aligning with Ngenla (Somatrogon)	Comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
Consider aligning with Ngenla (Somatrogon) **Question for the clinical expert:** Study populations included girls who were 2.5 years to 10 years of age and boys who were 2.5 years to 11 years of age. Requests are often received to continue funding therapy once the patient has reached adulthood. Should the somapacitan therapy be discontinued when the patient has reached adulthood?	The clinical expert noted that the indication changes when the patient becomes 18 years and older as it changes to adult GHD, and an adult endocrinologist is involved. The individual together with the adult endocrinologist would decide whether to continue growth hormone therapy. CDEC acknowledged the clinical expert's response and noted that the evidence reviewed does not include the adult population.
Considerations for prescribing of therapy	
Consider aligning with Ngenla (Somatrogon)	Comment from the drug programs to inform CDEC deliberations.
Generalizability	
Population outside the indication or reimbursement request but of interest to jurisdictions: patients who are post puberty or adults with GH deficiency.	CDEC noted that the evidence submitted does not include these populations.
System and economic issues	
Annual cost per the submitted budget impact analysis: $15,423.11	Comment from the drug programs to inform CDEC deliberations.
Ngenla completed confidential drug pricing negotiations.	Comment from the drug programs to inform CDEC deliberations.

CDEC = CADTH Canadian Drug Expert Committee; GH = growth hormone; NIHB = Non-Insured Health Benefits.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal phase III, open-label, randomized controlled trial (RCT) was identified that compared somapacitan (0.16 mg/kg once weekly) with Norditropin (somatropin) (0.034 mg/kg once daily) via subcutaneous infusion in children with GHD who were prepubertal and had no prior exposure to GH therapy or IGF-1 treatment (N = 200). Patients were randomized to either somapacitan or Norditropin (somatropin) in a 2:1 ratio for a 52-week randomized controlled period. The primary end point was estimated mean height velocity (centimetres per year) at week 52. The key secondary end points were change from baseline in height SDS and height velocity SDS at week 52. The key exploratory end points were GHD-CIM as well as estimated mean scores in GHD-CTB and GHD-PTB at week 52. Height velocity reflects change rate in height

over time and was converted to be expressed in centimetres per year in the current review. Height SDS and height velocity SDS are end points that reflect whether the auxologic parameters are within a normal range (usually, −2 to 2) considering age and gender; standards of these measurements have been developed and used in clinical settings. The GHD-CIM, GHD-CTB, and GHD-PTB are disease-specific questionnaires that measure the impact or burden of GH treatment on children with GHD and their caregivers in terms of symptoms, physical functioning, social well-being, emotional well-being, and interference in daily life activities. Each of these 3 questionnaires have subdomain and total scores that are presented on a normalized scale ranging from 0 to 100, with a lower score indicating a better health state.

At baseline, the mean age of participants was 6.38 years (SD = 2.23 years) in the somapacitan arm and 6.43 years (SD = 2.42 years) in the Norditropin (somatropin) arm. There were more male patients (74.5%) enrolled than female patients (25.5%). The majority of patients were white (57%) followed by Asian (37%). Most had an idiopathic GHD by cause (88%). Median GH peak level was higher in the somapacitan arm (5.2 mcg/L) than that in the Norditropin (somatropin) arm (3.9 mcg/L). In terms of concomitant medications at baseline, there was a lower proportion of patients who used thyroid hormones in the somapacitan arm (8.3%) than that in the Norditropin (somatropin) arm (14.7%). After initiation of randomization, a higher proportion of patients used any concomitant medications in the somapacitan arm (66.7%) than those in the Norditropin (somatropin) arm (58.8%) based on the detailed documentation of patient records, and the difference potentially did not have an impact on study results.

Efficacy Results

The key efficacy results from the REAL 4 trial are summarized in Table 3. The full analysis set was used for the auxologic response outcomes, and the observations datasets were used for the patient-reported outcomes.

Auxologic Response

The mean height velocity at baseline was 4.3 cm/year (SD = 1.4 cm/year) in the somapacitan arm and 4.1 cm/year (SD = 1.4 cm/year) in the Norditropin (somatropin) arm. The estimated mean height velocity at week 52 in was 11.2 cm/year and 11.7 cm/year in the somapacitan and Norditropin (somatropin) arms, respectively. The ETD was −0.5 cm/year (95% confidence interval [CI], −1.1 cm/year to 0.2 cm/year), which demonstrated noninferiority of somapacitan to Norditropin (somatropin) based on a prespecified noninferiority margin of −1.8 cm/year.

The improvements were comparable between the 2 treatment arms in height SDS and height velocity SDS (secondary end points measured as change from baseline scores at week 52). The baseline mean height SDS was −2.99 (SD = 1.02) in the somapacitan arm and −3.47 (SD = 1.52) in the Norditropin (somatropin) arm. The ETD for height SDS was −0.05 (95% CI, −0.18 to 0.08). The estimated mean change from baseline scores was 1.25 and 1.30 in somapacitan and Norditropin (somatropin) arms, respectively. The baseline mean height velocity SDS was −2.35 (SD = 1.51) in the somapacitan arm and −2.52 (SD = 1.55) in the Norditropin (somatropin) arm. The ETD for height velocity SDS was −0.78 (95% CI, −1.63 to 0.08). The estimated mean change from baseline scores was 8.05 and 8.82 in somapacitan and Norditropin (somatropin) arms, respectively.

Patient-Reported Outcomes

The improvements were comparable between the treatment arms at week 52 in total scores of GHD-CIM (ETD = 1.8 points; 95% CI, −2.9 to 6.6 points) and GHD-CTB (ETD = −2.4 points; 95% CI, −5.7 to 0.9 points). The result of GHD-PTB total score was in favour of somapacitan compared to Norditropin (somatropin) at week 52 with an ETD of −6.0 points (95% CI, −10.0 to −2.1 points).

Harms Results

The full analysis set was used for all the key harm results from the randomized controlled period of the REAL 4 trial.

During the 52-week treatment period, adverse events (AEs) were reported by 71.2% of patients who received somapacitan compared with 60.3% of patients who received Norditropin (somatropin). The most frequently reported AEs were headache (12.1%), nasopharyngitis (11.4%), and pain in extremity (9.1%) in the somapacitan arm; nasopharyngitis (10.3%), pyrexia (10.3%), and headache (8.8%) were the most frequently reported in the Norditropin (somatropin) arm.

No withdrawal from treatment due to treatment-emergent AEs or deaths were reported by patients from either arm.

The occurrence of the 2 notable harms were comparable between the treatment arms at week 52 with relative risk of [redacted] for injection site reactions (5.3% versus 5.9% in somapacitan and Norditropin [somatropin] arms, respectively) and [redacted] for injection site pain (1.5% in both arms). The relative risk and 95% CI for injection site reactions and injection site pain were not part of the statistical analysis plan and were requested by CADTH to assess the imprecision of the findings.

Other Results

Treatment discontinuation (or adherence to therapy) was identified as another relevant and important outcome. One patient discontinued treatment with somapacitan due to a violation of the inclusion and/or exclusion criteria. No patients discontinued treatment in the Norditropin (somatropin) arm. Therapy adherence rate, measured with a patient e-Diary device for electronic data recording, was higher in the somapacitan arm than in the Norditropin (somatropin) arm (96% versus 88%, respectively).

Critical Appraisal

Appropriate methods of randomization were used. The proportion of patients who used thyroid hormones was lower in the somapacitan arm than in the Norditropin (somatropin) arm (8.3% versus 14.7%, respectively),.Whether this difference might impact the study results was uncertain according to the clinical expert consulted by CADTH. The efficacy and harms outcomes were analyzed using the full analysis set; all patient-reported outcomes were analyzed for the observation datasets in countries where available and the impact of the missing data in 4 countries was unknown. The open-label study design could potentially increase the risk of bias for subjective assessment of patient-reported outcomes, such as health-related quality of life, AEs like injection site reactions (including pain, bruising, hematoma, and swelling), and injection site pain. Ethnicity and race are significant predictors of height velocity; however, the REAL 4 trial did not stratify this factor (only Japan was separated from the rest of the world possibly because of different

peak GH levels used in GHD diagnosis). Whether the lack of adjustment by different regions in the analysis might affect the results was uncertain. The study sample size calculation in the REAL 4 trial was based on an assumption of a height velocity SD of 3.5 cm/year and a noninferiority margin of −1.8 cm/year. Most patients in the REAL 4 trial were enrolled from the US (), Japan (), Russia (), India (), Korea (), and Ukraine (), among others. [redacted] ([redacted] of overall study population) [redacted] allocated to the somapacitan group was from Canada; whether [redacted] identified as Indigenous is unknown. A total of 57.0% of the patients were white and 37.0% were Asian. Ages of patients at baseline ranged between 2.5 years and 11 years for boys and 2.5 years and 10 years for girls. Overall, there was a higher proportion of boys (74.5%) than girls (25.5%) in the REAL 4 trial than in the GeNeSIS study (63% male versus 37% female in the Canadian GHD cohort). For context, the GeNeSIS study is a phase IV prospective observational study that evaluated outcomes of GH treatment in pediatric patients in Canada compared with findings from pediatric patients from the US and the overall global population. The REAL 4 trial only enrolled patients who had no prior exposure to GH or IGF-1 treatment. The clinical expert commented that these differences between patients in the REAL 4 trial and those encountered in Canadian clinical practice are less likely to affect the trial results. The majority of the patients in the REAL 4 trial had idiopathic GHD (88.0%) identified as the GHD cause (organic = 12%), which was different from the GHD patient cohort in the GeNeSIS study (28% were idiopathic and 72% were organic). The clinical expert indicated that patients with idiopathic GHD may also have other conditions that might influence GHD; thus, it was uncertain whether the results would be impacted if this patient characteristic is different from that in the REAL 4 trial. The clinical expert expressed that although it may appear that patients whose conditions preclude them from a height evaluation (e.g., they have cerebral palsy and cannot stand) or cancer patients with brain tumours who were excluded from the trial, these are also patients who clinicians would want to treat with GH therapy, if needed, in clinical practice. According to the clinical expert consulted by CADTH, the concomitant medications, the comparator used, and the administration of the study treatments in the REAL 4 trial were reflective of those encountered in Canadian clinical practice.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized with expert committee members: height velocity (centimetres per year, measured as estimated mean at follow-up), height SDS, height velocity SDS, and GHD-CIM (measured as change from baseline in these values), GHD-CTB and GHD-PTB (measured as estimated

mean at follow-up), injection site reactions and injection site pain (measured as occurrence of these AEs), and treatment discontinuation (measured as the proportion of patients who discontinued the treatment).

If possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of an important effect based on thresholds informed by the clinical expert consulted for this review for height velocity, height SDS, and height velocity SDS. The target of the certainty of evidence assessment was the presence of absence of any (non-null) effect for GHD-CIM, GHD-CTB, GHD-PTB, injection site reactions, injection site pain, and treatment discontinuation due to the lack of a formal minimally important difference estimate.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for somapacitan versus Norditropin (somatropin) in prepubertal children with GHD.

Table 3: Summary of Findings for Somapacitan Versus Norditropin (Somatropin) for Pediatric Patients With Growth Hormone Deficiency

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Norditropin (somatropin)	Somapacitan	Difference		
Auxologic response							
Height velocity, estimated mean at follow-up, cm/year Follow-up: 52 weeks	200 (1 RCT)	NA	11.7	11.2 (NR)	−0.5 (−1.1 to 0.2)	High[a,b,c]	Somapacitan results in little to no difference (i.e., a noninferior effect) in height velocity when compared with Norditropin (somatropin).
Height SDS (range, −10 to 10, with 0 representing a height equivalent to the population mean), change from baseline Follow-up: 52 weeks	200 (1 RCT)	NA	1.30	1.25 (NR)	−0.05 (−0.18 to 0.08)	High[a,b,c]	Somapacitan results in little to no difference in the change from baseline in height SDS when compared with Norditropin (somatropin).
Height velocity SDS (range −10 to 10, with 0 representing a height velocity equivalent to the population mean), change from baseline Follow-up: 52 weeks	200 (1 RCT)	NA	8.82	8.05 (NR)	−0.78 (−1.63 to 0.08)	Moderate[a,b,d]	Somapacitan likely results in a smaller increase from baseline in height velocity SDS when compared with Norditropin (somatropin).
Patient-reported outcomes assessed with questionnaires for functioning or disease burden							
Disease-specific functioning as measured with GHD-CIM (TRIM-CGHD-O, 0 [best] to 100 [worst]), change from baseline,	138 (1 RCT)	NA	−10.9	−9.0 (NR)	1.8 (−2.9, 6.6)	Low[b,e,f]	Somapacitan may result in little to no difference in disease-specific functioning when compared with Norditropin (somatropin).

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Norditropin (somatropin)	Somapacitan	Difference		
points Follow-up: 52 weeks							
Child treatment burden as measured with GHD-CTB (TB-CGHD-O, 0 [best] to 100 [worst]), estimated mean at follow-up, points Follow-up: 52 weeks	169 (1 RCT)	NA	13.1	10.7 (NR)	−2.4 (−5.7, 0.9)	Low[b,g,h]	Somapacitan may reduce child treatment burden when compared with Norditropin (somatropin). The clinical importance of the reduction is uncertain.
Caregiver treatment burden as measured with GHD-PTB (TB-CGHD-P, 0 [best] to 100 [worst]), estimated mean at follow-up, points Follow-up: 52 weeks	176 (1 RCT)	NA	14.7	8.7 (NR)	−6.0 (−10.0, −2.1)	Moderate[b,i,j]	Somapacitan probably reduces caregiver treatment burden when compared with Norditropin (somatropin). The clinical importance of the reduction is uncertain.
Notable harms							
Injection site reactions (including pain, bruising, hematoma, and swelling) Follow-up: 52 weeks	200 (1 RCT)	RR = 0.90 (0.27 to 2.97)[o]	59 per 1,000	53 per 1,000 (NR)	6 fewer per 1,000 (from 74 fewer to 62 more per 1,000)	Moderate[b,k,l]	Somapacitan likely results in little to no difference in injection site reactions when compared with Norditropin (somatropin). There is some uncertainty about the clinical importance of the estimates.
Injection site pain Follow-up: 52 weeks	200 (1 RCT)	RR = 1.03 (0.10 to 11.16)[o]	15 per 1,000	15 per 1,000 (NR)	No difference per 1,000 (from 35 fewer to 36 more per 1,000)	Moderate[b,k,l]	Somapacitan likely results in little to no difference in injection site pain when compared with Norditropin (somatropin). There is some uncertainty about the clinical importance of the estimates.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Norditropin (somatropin)	Somapacitan	Difference		
Treatment discontinuation							
Treatment discontinuation Follow-up: 52 weeks	200 (1 RCT)	RR = 1.56 (0.06 to 37.70)	0 per 1,000[m]	8 per 1,000 (NR)[m]	8 more per 1,000 (from 7 fewer to 22 more per 1,000)	High[b,l,n]	Somapacitan results in little to no difference in treatment discontinuation when compared with Norditropin (somatropin). There is some uncertainty about the clinical importance of the estimates.

CI = confidence interval; GH = growth hormone; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SDS = standard deviation score; TB-CGHD-O = Treatment Burden Measure–Child-Growth Hormone Deficiency–Observer; TB-CGHD-P = Treatment Burden Measure–Child-Growth Hormone Deficiency–Parent; TRIM-CGHD-O = Treatment Related Impact Measure–Child-Growth Hormone Deficiency–Observer.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. For all the outcomes in this table, statistical testing was not adjusted for multiplicity; there is an increased risk of type I error (false-positive results).

[a]Although the CADTH review team identified a potential risk of bias due to several factors, including baseline imbalance in GH peak level at baseline that was higher in the somapacitan group (median = 5.2 mcg/L) than that in the Norditropin (somatropin) group (3.9 mcg/L), imbalance in thyroid hormone use at baseline that was lower in the somapacitan group (8.3%) than that in the Norditropin (somatropin) group (14.7%), and a higher treatment adherence rate in the somapacitan group (96%) than that in the Norditropin (somatropin) group (88%) measured with a patient e-Diary device to record dosing, the certainty of evidence was not rated down because it was uncertain whether these imbalances might raise potential for bias in favour of somapacitan.

[b]Indirectness was not rated down. Differences between the patients in the 1 RCT informing the evidence (prepubertal age, GH therapy-naive, no intracranial tumour, and potential exclusion of patients who could not stand up by some exclusion criteria, such as significant spinal abnormalities and congenital abnormalities) and the patients in clinical practice were noted but their conditions were not considered serious enough to result in important differences in the observed effect according to the clinical expert consulted by CADTH.

[c]Imprecision was not rated down. The point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison indicate trivial or no clinically meaningful difference according to the clinical expert consulted by CADTH; for height velocity, the 95% CI excludes the noninferiority margin (−1.8 cm/year).

[d]Rated down 1 level for serious imprecision. No specific threshold was established, but according to the clinical expert consulted by CADTH, the point estimate (−0.78) and the lower boundary of the 95% CI (−1.63) could be considered a clinical meaningful worse efficacy for somapacitan vs. Norditropin (somatropin), while the upper boundary of the 95% CI (0.08) suggests no clinically meaningful difference between the 2 groups.

[e]Rated down 1 level for serious risk of bias due to potential for bias in favour of somapacitan (once-weekly injections) compared with Norditropin (somatropin) (once-daily injections) arising from the open-label nature of the study and the subjective nature of the outcome. The impact of missing outcome data (31% of the patients) is unclear.

[f]Rated down 1 level for serious imprecision. Based on the minimally important difference identified in the literature (5 points based on within-group data), the point estimate suggested little to no difference, whereas the upper bound of the 95% CI suggested an increase compared to Norditropin (somatropin).

[g]Rated down 1 level for serious risk of bias due to potential for bias in favour of somapacitan (once-weekly injections) compared with Norditropin (somatropin) (once-daily injections) arising from the open-label nature of the study and the subjective nature of the outcome. The impact of missing outcome data (15.5% of the patients) is unclear.

[h]Rated down 1 level for serious imprecision. The CADTH review team was unable to confirm with the clinical expert consulted by CADTH whether the MID identified in the literature (6 points based on within-group data provided by the sponsor) would be suitable to assess a between-group difference; therefore, the null was used to assess certainty. The point estimate suggested a decrease while the upper bound of the 95% CI suggested an increase compared to Norditropin (somatropin).

[i]Rated down 1 level for serious risk of bias due to potential for bias in favour of somapacitan (once-weekly injections) compared with Norditropin (somatropin) (once-daily injections) arising from the open-label nature of the study and the subjective nature of the outcome. The impact of missing outcome data (12% of the patients) is unclear.

[j]Imprecision was not rated down. The CADTH review team was unable to confirm with the clinical expert consulted by CADTH about whether the MID identified in the literature (7 points based on within-group data provided by the sponsor) would be suitable to assess a between-group difference; therefore, the null was used to assess certainty.

[k]Rated down 1 level for serious risk of bias due to potential for bias in favour of somapacitan (once-weekly injections) compared with Norditropin (somatropin) (once-daily injections) arising from the open-label nature of the study and the subjective nature of the outcome.

[l]Imprecision was not rated down. The clinical expert consulted by CADTH could not provide a threshold of important difference; however, the CADTH review team judged that the effect estimate and 95% CI were unlikely to include any important effect.

[m]Treatment discontinuation is for any reason and not limited to adverse events. Treatment discontinuations due to adverse events in both treatment arms in REAL 4 was 0. One patient discontinued somapacitan in the main study due to violation of inclusion or exclusion criteria. In all, 132 somapacitan patients completed main trial period, 131 patients completed main treatment period.

[n]Risk of bias was not rated down. One patient from the somapacitan arm discontinued the treatment due to violation of the study protocol; no patients discontinued the treatment in the Norditropin (somatropin) arm.

[o]The relative risk and 95% CI were not part of the statistical analysis plan. They were requested by CADTH to allow for an assessment of the imprecision of the findings.

Source: REAL 4 Clinical Study Report (week 52).

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov cohort model
Target population	Pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone
Treatment	Somapacitan (once-weekly injection)
Dose regimen	0.16 mg/kg weekly
Submitted price	Somapacitan, 5 mg/1.5 mL, prefilled pen: $297.20 Somapacitan, 10 mg/1.5 mL, prefilled pen: $594.40 Somapacitan, 15 mg/1.5 mL, prefilled pen: $891.60
Treatment cost	$15,454 annually
Comparators	Somatrogon (once-weekly injection) Somatropin (once-daily injection), consisting of all branded somatropin products weighted by market share
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	11.6 years
Key data sources	REAL 4, a phase III, 52-week, multicentre, multinational, randomized, open-labelled trial comparing somapacitan and Norditropin-branded somatropin in patients aged 2.5 years to 11 years. An additional 52 weeks from a long-term extension of the REAL-4 extension study was also included. REAL 3, a phase II, multicentre, open-label, dose-finding trial that compared somapacitan with Norditropin-branded somatropin in patients aged 2.5 years to 10 years, over 156 weeks of treatment.
Key limitations	• The administered dose for all branded somatropins was likely overestimated and did not reflect the typical dose administered in Canadian clinical practice based on published literature and clinical expert feedback. This would overestimate the drug acquisition costs of somatropin and bias the results in favour of somapacitan. • The incidence of injection site pain, and magnitude of the disutility associated with injection site pain, are associated with uncertainty. • The sponsor incorporated compliance based on information from REAL-4 for weekly and daily treatments (95.8% vs. 88.3%); however, they applied an additional 5% reduction in effectiveness due to noncompliance for daily treatments based on the results of a retrospective study. Reducing efficacy based on suboptimal compliance would double-count the impact of noncompliance because treatment efficacy already accounts for compliance. • The magnitude of the disutility associated with daily somatropin injections compared with weekly injections is uncertain. • Market share distributions used to derive treatment costs of somatropin may not reflect the distribution of these treatments in isolated GHD or GH insufficiency because the various brands of somatropin are indicated for other conditions. • Utility values were applied based on height. These values were obtained from the literature and were further modified by the sponsor. The validity and application of the modified utility values in this population is associated with uncertainty. • Drug costs are likely underestimated due to the exclusion of wastage of partially used doses.

Component	Description
CADTH reanalysis results	• In the CADTH base case, CADTH revised the dose for all somatropin products to align with the dose commonly used in Canadian clinical practice, revised somatrogon's annual rate of injection site pain to be the same as somapacitan and somatropin and removed the pediatric consultation visit cost association with patients who experience an event of injection site pain, included drug wastage, and removed the reduction in effectiveness due to noncompliance. CADTH maintained the sponsor's assumption regarding equal efficacy based on HSDS scores. • CADTH was unable to address limitations regarding the uncertainty of the disutility magnitude associated with daily injections vs. weekly injections, the applicability of utility scores measured by HSDS, and the market share distributions of various branded somatropin treatments. • Over an 11.6-year time horizon, somapacitan is more costly than somatropin and associated with a gain of 0.094 QALYs, resulting in somapacitan having an ICER of $275,250 per QALY gained compared with somatropin. The gain in QALYs is solely due to the disutility associated with patients receiving daily treatments. Somapacitan is less costly than somatrogon and associated with the same or greater benefit (i.e., somapacitan dominates somatrogon). • A price reduction of at least 13% for somapacitan would be required for it to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. A price reduction of at least 41% would be required for somapacitan to be no more costly than the least costly somatropin. • CADTH explored the impact of removing the disutility associated with receiving daily injections. In the scenario where there is no preference between daily and weekly injections, somatropin is dominant (i.e., less costly and associated with no difference in QALYs per the deterministic results).

GH = growth hormone; GHD = growth hormone deficiency; HSDS = height standard deviation score; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs = versus.

Budget Impact

CADTH identified the following key limitations with the sponsors analysis: the estimated treatment costs were likely overestimated as the daily dose for somatropin products was likely overestimated and not aligned with the dose commonly prescribed in Canadian clinical practice, drug costs were likely underestimated due to the exclusion of wastage, uncertainty regarding the anticipated market shares and comparator displacement of somapacitan, uncertainty regarding the market shares of treatments included in the reference scenario, and the proportion of patients covered by public drug plans were likely underestimated.

CADTH reanalysis included aligning the dose of all somatropin treatments with Canadian clinical practice, including drug wastage, incorporating the proportion of patients eligible for public drug plan coverage, correcting the Non-Insured Health Benefits population size, halving somatrogon's estimated market share, assuming somapacitan displaced all comparators proportionate to their market share, and aligning somapacitan's market uptake with the clinical expert input received for this review. CADTH reanalyses suggest that the reimbursement of somapacitan for the requested reimbursement population (pediatric patients with GHD) would be associated with a budgetary increase of $458,079 over the first 3 years (year 1: $52,450; year 2: $128,547; year 3: $277,081).

The estimated budget impact is highly sensitive to the number of patients eligible to receive somapacitan and the price of somapacitan.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

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