Canadian Journal of Health Technologies

CADTH

February 2022 Volume 2 Issue 2

CADTH Reimbursement Recommendation

Mecasermin (Increlex)

Indication: For the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency

Sponsor: Ipsen Biopharmaceuticals Canada, Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Increlex?

CADTH recommends that Increlex should be reimbursed by public drug plans for the treatment of treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (SPIGFD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Increlex should only be covered to treat patients who are at least 2 years of age with confirmed diagnosis of SPIGFD and in whom epiphyseal growth plates have not yet closed.

What Are the Conditions for Reimbursement?

Increlex should only be reimbursed if prescribed by a pediatric endocrinologist, if it is not prescribed in combination with recombinant growth hormone treatment, and the price of Increlex is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Increlex increases height velocity in children with open epiphyses and diagnosed with growth failure due to SPIGFD.
- Increlex may address some of the needs that are important to patients as it improves growth outcomes.
- Based on CADTH's assessment of the health economic evidence, Increlex does not represent good value to the health care system at the submitted price and requires at least a 92% price reduction.
- Increlex is expected to increase drug costs to the public drug plans by $35,982,122 over 3 years.

Additional Information

What Is SPIGFD?

SPIGFD is a rare genetic disorder and characterized by extreme short stature. In Canada, it is estimated that approximately 5 cases of SPIGFD are diagnosed each year, or 1 case in every 77,000 births

Unmet Needs in SPIGFD

There is a need for a treatment that would improve growth, heart strength, lung capacity, and bone strength.

How Much Does Increlex Cost?

Treatment with Increlex is expected to cost approximately $183,416 per patient per year, assuming an average patient weight of 14.1 kg. The cost of Increlex will vary by each patient's weight.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mecasermin be reimbursed for the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed SPIGFD, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multi-centre, single arm, open-label trial (Study 1419, N = 92) in children with open epiphyses and diagnosed with growth failure due to SPIGFD associated with either growth hormone (GH) receptor defects or GH-deletion defects and anti-GH antibodies, demonstrated that during year 1 of mecasermin treatment, there was an increase in mean (SD) height velocity from 2.6 (1.7) cm per year at baseline to 8.0 (2.3) cm per year ($P < 0.0001$). Height velocities for years 2 through 8 of treatment remained greater than baseline (i.e., 5.9 [1.7] cm per year in year 2 and 4.4 [1.5] cm per year in year 8). Given the totality of the evidence, CDEC concluded that mecasermin met some of the needs identified in a patient group submission by improving growth outcomes. Although the patient group submission identified the need for a treatment that would also improve heart strength, lung capacity, and bone strength, evidence was not available for these outcomes.

The cost-effectiveness of mecasermin is highly uncertain due to the lack of robust clinical and safety data in comparison with best supportive care (BSC), as well as uncertainty in the impact of the predicted gain in height on patient quality of life over their lifetime. As such, a base-case cost-effectiveness estimate was unable to be determined for children and adolescents aged 2 to 18 years with confirmed SPIGFD. CDEC considered exploratory analyses conducted by CADTH and determined the incremental cost-effectiveness ratio (ICER) was likely closer to the estimate of $624,249 per quality-adjusted life-year (QALY) gained and mecasermin is not cost-effective at a $50,000 per QALY willingness-to-pay threshold. A price reduction of at least 92% for mecasermin would be required for mecasermin to achieve an ICER of $50,000 per QALY compared to BSC.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Treatment can be initiated in patients who are at least two years of age and in whom epiphyseal closure has not yet occurred, and with confirmed diagnosis of SPIGFD, defined by: 1.1. The patient has a known genetic mutation recognized as a cause of SPIGFD and/or 1.2. The patient has clinical and biochemical features of SPIGFD.	Patients enrolled in Study 1419 were children who were at least 18 months of age with open epiphyses and growth failure due to SPIGFD associated with either GH receptor defects or GH gene-deletion defects and anti-GH antibodies. The clinical expert noted that identifying patients with SPIGFD who would benefit from mecasermin treatment should include genetic testing, GH antibodies, low GH binding globulin, or clear biochemical diagnostic tests such as poor IGF-1 response to GH. Other causes of short stature (e.g., nutritional causes and chronic diseases) need to be ruled out.

Reimbursement condition	Reason
Discontinuation	
2. Treatment with mecasermin must be discontinued upon the occurrence of any of the following: 2.1. height velocity is less than 1 cm per 6 months or less than 2 cm per year, or 2.2. bone age is more than 16 years in boys and 14 years in girls.	The clinical expert noted that treatment with mecasermin should be discontinued in patients with bone age more than 16 years in boys and 14 years in girls, or height velocity less than 1 cm per 6 months or less than 2 cm per year.
Prescribing	
3. The patient must be under the care of a pediatric endocrinologist.	Carefully considered diagnosis and follow-up of patients with SPIGFD is important to ensure that mecasermin is prescribed to the most appropriate patients.
4. Mecasermin must not be prescribed concomitantly with recombinant GH treatment.	Patients with confirmed SPIGFD are, by definition, not expected to respond adequately to exogenous GH treatment.
Pricing	
5. A reduction in price.	The cost-effectiveness of mecasermin is highly uncertain. Given the lack of robust clinical and safety data in comparison with BSC, as well as uncertainty of the impact of gains in height on health-related quality of life over the lifetime time horizon, a CADTH base-case analysis could not be conducted. Exploratory analyses, which varied key parameters in the model, were conducted instead. These analyses indicated that a reduction in price of at least 92% is required to achieve an ICER of $50,000 per QALY.

GH = growth hormone; IGF-1 = insulin-like growth factor-1; SPIGFD = severe primary insulin-like growth factor-1 deficiency.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance from CDEC

Condition no. in Table 1	Implementation considerations and guidance
1.1	CDEC noted that patients with known genetic abnormalities or GH antibodies are appropriately diagnosed with confirmed SPIGFD; however, genetic testing to confirm SPIGFD diagnosis may not be available in all jurisdictions. Given the limited availability of these tests and the cost burden that their implementation would place on public health care systems, CDEC recommends that the sponsor be required to cover the cost of these tests across Canada and to ensure their availability where needed.

Condition no. in Table 1	Implementation considerations and guidance
1.2	When there is no genetic test to confirm SPIGFD, diagnosis of severe primary insulin-like growth factor-1 deficiency may not be straightforward and not all causes of SPIGFD have known genetic markers. CDEC recommends that when there is no identified known mutation to confirm SPIGFD, the diagnosis, the need for treatment with mecasermin, and the continuing need for treatment with mecasermin be confirmed by more than one pediatric endocrinologist. CDEC recognizes that because some jurisdictions might not have access to a sufficient number of pediatric endocrinologists to implement this recommendation, public drug plans should consider whether to take advantage of clinical expertise in larger jurisdictions that could confirm the diagnosis of SPIGFD.
1.2	CDEC noted that the key clinical and biochemical features of SPIGFD are defined by the following: • height standard deviation score ≤ –3.0 • basal IGF-1 levels below the 2.5th percentile for age and gender • random or stimulated GH level of > 10 ng/mL and failure to increase IGF-1 by 50 ng/mL in response to exogenous GH during an IGF-1 generation test • exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

GH = growth hormone; IGF-1 = insulin-like growth factor-1; SPIGFD = severe primary insulin-like growth factor-1 deficiency.

Discussion Points

- CDEC discussed that mecasermin is the first Health Canada–approved treatment for SPIGFD, and that mecasermin might addresses an unmet need for patients diagnosed with SPIGFD.
- CDEC discussed that due to the design limitations of Study 1419, it is not possible to determine with certainty the clinical significance of changes in height on treatment, and how the observed changes in height and height velocity would differ from untreated patients. The clinical expert noted to CDEC that a height velocity of at least 2 cm per year (or 1 cm per 6 months) is generally considered sufficient to continue mecasermin treatment, by analogy with the clinical practice in patients treated with GH for GH deficiency.
- Health-related quality of life (HRQoL) was not measured in Study 1419; therefore, CDEC was unable to draw any conclusions pertaining to the potential benefit of mecasermin on HRQoL.
- Clinical outcomes other than height were not assessed in Study 1419; therefore, CDEC was unable to draw any conclusions pertaining to the potential benefit of mecasermin on other clinical outcomes such as heart strength, lung capacity, and bone strength.

Background

Mecasermin has a Health Canada indication for the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed SPIGFD. SPIGFD is defined by: height standard deviation score of at least –3.0, basal IGF-1 levels below the 2.5th percentile for age and sex, GH sufficiency, and exclusion of secondary forms of IGF-1 deficiency, such

as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids. SPIGFD includes patients with mutations in the GH receptor (GHR) gene/Laron syndrome, post-GHR signalling pathway, and IGF-1 gene defects. Patients with SPIGFD are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. Mecasermin contains recombinant human insulin-like growth factor-1 (rhIGF-1), produced by recombinant DNA technology. Mecasermin is supplied in a 5 mL multi-dose vial, with each vial containing 4 mL (40 mg) of solution. The Health-Canada recommended starting dose is 0.04 to 0.08 mg/kg (40 to 80 mcg/kg) subcutaneously (SC) twice daily.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- A review of 1 clinical trial in children who were at least 18 months with open epiphyses, and had to have a confirmed diagnosis of SPIGFD.
- Patients perspectives gathered by 1 patient group, the International Coalition of Organizations Supporting Endocrine Patients (ICOSEP).
- Input from public drug plans that participate in the CADTH review process.
- Input from 1 of clinical specialist with expertise diagnosing and treating patients with SPIGFD.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 1 patient group submission from the International Coalition of Organizations Supporting Endocrine Patients (ICOSEP). The group emphasized the importance of diagnosing and treating children with SPIGFD early to reduce needless medical hardships over their lifetimes. ICOSEP highlighted that although short stature is the most visible symptom of SPIGFD, the consequences of the condition run deeper than just height and affect children's daily lives. For example, everyday activities like getting out of bed, playing with others, and concentrating on tasks can take substantial effort. ICOSEP stressed that the condition of children with SPIGFD who remain untreated will not improve; thus, patients may require a lifetime of specialized care if left untreated.

Input From Clinical Expert Consulted by CADTH

CADTH received input from a clinical specialist with expertise in the diagnosis and management of SPIGFD. The clinical expert indicated that there is no existing treatment for SPIGFD, so mecasermin would be a first-line treatment in cases where there is either a clear diagnosis of SPIGFD or the presence of GH antibodies. The clinical expert felt that when the clinical and biochemical criteria (height standard deviation score of at least −3.0; basal IGF-1 levels below the 2.5th percentile for age and sex; and GH sufficiency) are supported by

a genetic diagnosis or the presence of GH antibodies (after ruling out other causes of short stature such as nutritional causes and chronic diseases), mecasermin is indicated.

The clinical expert reemphasized that a genetic diagnosis would be ideal before the use of mecasermin, however acknowledged that this would cause a shift in the current treatment paradigm at the diagnostic level, because in many Canadian jurisdictions there is limited access to the tests required for a definitive diagnosis of SPIGFD. Further, not all genetic causes of SPIGFD are known, and currently less than half of the cases have an identifiable genetic variant.[13] If the above clinical and biochemical criteria are not supported by a genetic diagnosis (mutations in the GHR gene/Laron syndrome, post-GHR signalling pathway, and IGF-1 gene defects) or by the presence of GH antibodies, the clinical expert suggested that treatment decisions be informed by a panel of clinical experts to avoid misdiagnosis and overtreatment. This may not be feasible since there are few Canadian clinicians with direct experience in the diagnosis and treatment of SPIGFD; however, physicians with expertise in managing pediatric endocrine growth disorders may also be qualified to contribute.

According to the clinical expert consulted by CADTH, patients likely to demonstrate a clinically meaningful response to mecasermin include those with SPIGFD due to a genetic defect of the GH-IGF-1 pathway, those who show biochemical evidence of inappropriate GH receptors, and those who have GH antibodies or GH resistance. The clinical expert stated that treatment should begin as early as possible to maximize gain in height. Treatment should be discontinued when the height velocity is less than 1 cm over 6 months or less than 2 cm over 1 year. Another indicator classically used for stopping treatment (in patients treated with GH for GH deficiency) is a bone age that is in the near-adult range (i.e., > 16 years in males and > 14 years in females). The clinical expert stated that the most important outcomes for assessing response to treatment are height velocity and final adult height.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for mecasermin:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
There is a group of GH insensitivity syndromes which could respond to mecasermin, but some may also respond to relatively high doses of GH. • Is molecular testing for GH receptor gene mutations available across the country to definitively diagnose SPIGFD? • Should eligibility criteria for mecasermin include the requirement to trial 3 to 6 months of GH unless SPIGFD is definitively diagnosed (e.g., by molecular testing)?	CDEC agreed with the clinical expert that patients with GH deficiency will likely respond to mecasermin. Conversely, patients with mild primary insulin-like growth factor deficiency may also respond to high doses of GH. The Pediatric Endocrine Society guidelines recommend starting mecasermin directly for patients with hormone signalling defects known to be unresponsive to GH treatment; this includes patients with very low or undetectable levels of GHBP and/or proven GH receptor mutations, GH-neutralizing antibodies, and other known gene mutations associated with SPIGFD (e.g., STAT5b gene mutations and IGF-1 gene deletion or mutation). The clinical expert consulted by CADTH stated that molecular testing for GH receptor gene mutations (or other known mutations associated with SPIGFD) would be ideal; however, while molecular testing is available it is difficult to access in some Canadian jurisdictions and the cost is high. Moreover, molecular testing will always be limited to known genetic causes of SPIGFD. The guidelines note that genetic testing is desirable for patients for whom diagnostic uncertainty is problematic, to better inform the treatment plan. CDEC noted that while there are clinical practice guidelines which state that for patients with unexplained IGF-1 deficiency a trial of GH treatment is reasonable; there is no clear evidence to support the practice and it may lead to use of a dose higher than that recommended by Health Canada.
In Study 1419, 21 patients (out of 92) received leuprolide to delay puberty and prolong the growth period in an attempt to achieve a greater adult height. Will leuprolide be used in clinical practice to delay puberty and prolong the growth period in patients who were treated with mecasermin?	CDEC noted that in Study 1419 while a statistical evaluation of the effect of leuprolide on adult height is not possible because of the small number of patients and the large number of potential influences on adult height, the majority of the patients (18 out of 21 patients) who received leuprolide in combination with mecasermin either had a marginal improvement in their HT-SD score or a decrease, and that leuprolide in combination with mecasermin appeared to have been successful in increasing HT-SD score in only 3 out of the 21 patients. CDEC noted that in clinical practice the use of leuprolide in combination with mecasermin might be considered by the specialist and could occur on a case-by-case basis. The clinical expert noted to CDEC that although not an approved indication, some clinicians may prescribe leuprolide to patients with SPIGFD to increase the length of the growth period (namely in patients near the end of the growth period or for whom bone age is rapidly increasing). The decision to prescribe leuprolide would occur on a case-by-case basis.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
The primary efficacy end points in Study 1419 was height velocity and near-adult height compared to baseline. Once a patient is started on mecasermin, is it appropriate to continue treatment with mecasermin if they do not achieve height velocity outcomes similar to the clinical trial at a yearly exam (e.g., 8 ± 2.3 cm per year during year 1)? Or are growth targets considered patient-specific so once therapy is started, it is essentially continued until the patient is 18 years old?	CDEC agreed with the clinical expert that once a patient has begun treatment with mecasermin, treatment should continue so long as the gain in height is ≥ 1 cm per 6 months or ≥ 2 cm per year or they have reached near-adult height based on bone age criteria (i.e., bone age of > 16 years for males and > 14 years for females). Typically, the best response will be observed in the first year of treatment. Bone age is more informative than chronological age when deciding when to stop treatment.
Considerations for discontinuation of therapy	
In the data submitted, the mean follow-up period of patients was 8 years. If patients are responding to mecasermin, at what point should it be discontinued? After 8-years based on the mean follow-up period from the clinical trials? At 18 years old because mecasermin is not indicated for patients beyond that age? After X-ray confirmed closure of the epiphyseal plates?	CDEC agreed with the clinical expert that treatment should be discontinued when the gain in height is < 1 cm per 6 months or < 2 cm per year, or patients have reached near-adult height based on bone age criteria (i.e., bone age of > 16 years for males and > 14 years for females).
Generalizability	
Laron Syndrome has clinical manifestations outside of lower height – small head circumference, characteristics faces with saddle nose and prominent forehead, delayed skeletal maturation, small genitalia and testes, short limb length compared with trunk length, and abnormal body composition, with osteopenia and obesity. Is there evidence that mecasermin provides benefit for these other manifestations?	CDEC agreed with the clinical expert that the primary aim of mecasermin treatment is to improve height velocity and final adult height in patients with SPIGFD. There is no evidence from the studies for a beneficial effect of mecasermin on other clinical manifestations of Laron syndrome.
Care provision issues	
The product monograph clearly warns that there have been post-marketing reports of both benign and malignant neoplasms in children and adolescents who have received treatment with mecasermin because IGF-1 plays a role in the initiation and progression of tumours. Do the benefits of mecasermin (i.e., increased height) outweigh the potential harms of use?	CDEC agreed with the clinical expert that there are inadequate data to draw strong conclusions about the ratio of benefits to harms for patients treated with mecasermin for SPIGFD. The clinical expert noted to CDEC that in clinical practice, the ratio of benefits to harms needs to be discussed individually with each patient and their parent or caregiver. To make an informed decision, patients and their parents or caregivers should be explained that the risk of benign and malignant tumours in children with SPIGFD is lower than for healthy children without SPIGFD (because IGF-1 plays a role in the initiation and progression of benign and malignant tumours). Treatment with mecasermin may increase the risk of benign and malignant tumours, although the relationship between mecasermin and the risk of benign and malignant tumours is uncertain. Better data are available in patients with GH deficiency and the long-term outcomes in terms of malignancy are reassuring.

GH = growth hormone; GHBP = growth hormone binding protein; HT-SD = height standard deviation; IGF-1 = insulin-like growth factor-1; SPIGFD = severe primary insulin-like growth factor-1 deficiency.

Clinical Evidence

Pivotal Study

Description of Study

One pivotal trial (Study 1419) was included. Study 1419 was a phase III open-label, multi-centre, single-arm, investigator-sponsored trial with linked data from 4 predecessor studies (F0206S, F0375G, F0632G, F0671G). Of the predecessor studies, 3 were open-label single-arm trials (F0206S, F0632G, F0671G), 1 was investigator sponsored (F0206S), and 1 was multi-centre (F0671G). Study F0375G (n = 8) was a 27-month double-blind, placebo-controlled crossover trial including 6 months of mecasermin or placebo treatment, followed by a 3-month washout period, a 6-month crossover period, and a 12-month open-label extension study. Simple randomization was used to assign patients to the initial treatment group in Study F0375G. Since height velocity was an objective end point and the long-term height velocities in the other 4 studies were expected to be substantially greater than baseline and historical results in untreated children with SPIGFD, a randomized controlled group was deemed unnecessary in subsequent studies.

The purpose of this series of studies was to determine the safety and efficacy of long-term IGF-1 replacement therapy with mecasermin SC for the treatment of growth failure in children with SPIGFD. The linking of data from patients who participated in earlier trials allowed for each patient's data to be analyzed both individually and in aggregate with the rest of the treatment population. Many of the patients enrolled in Study 1419 had been continuously treated with mecasermin for many years and had transferred from 1 protocol to another when 1 study ended. All patients enrolled in studies F0206S, F0375G, and F0632G were later enrolled in Study F0671G. All patients (except 1) enrolled in F0671G were later enrolled in Study 1419. The integrated study report includes results for patients enrolled in the 5 studies at 2 investigative sites in the US in conjunction with sites in 23 other countries worldwide. Two patients from Canada were enrolled.

Eligible patients in Study 1419 were those who had a height SD score of less than −2 for age and sex; had a growth rate of less than 50th percentile for age and sex for more than 6 months before study start; had an IGF-1 SD score of less than −2 for age and sex; were older than 18 months (no upper age limit reported); and had open epiphyses. For those with growth hormone insensitivity syndrome (GHIS) and Laron syndrome, eligible patients needed a random or stimulated GH level of > 10 ng/mL and failure to increase IGF-1 by 50 ng/mL in response to exogenous GH during an IGF-1 generation test. For those with GHIS and GH gene-deletion, eligible patients needed the presence of GH antibodies to exogenous GH with a binding capacity of > 10 mcg/mL. Ineligible patients were those with active malignancy or any history of malignancy, growth failure due to other reasons, treatment with any corticosteroids or other medications that influence growth, and a clinically significant electrocardiogram abnormality or a history of a clinically significant cardiac arrhythmia.

Ninety-two patients were enrolled. The mean (SD) chronological age at baseline was 7.6 (4.3) years. The mean (SD) bone age was 3.8 (2.8) years. More than half of the patients were male (n = 53, 58%) and the etiology of GHIS for most patients was Laron syndrome (n = 82, 89%). Most patients began treatment at pubertal stage 1 (n = 79, 86%). Few (n = 9, 10%) had received prior IGF-1 therapy. Most (84%) patients were white. All patients had severe short stature, with a mean (SD) height and height SD score of 88.5 (20.7) cm and −6.7 (1.9), respectively. The mean (SD) pre-treatment height velocity and height velocity SD score were

2.6 (1.8) cm per year and −3.2 (1.8), respectively. All but 1 patient (n = 91/92, 99%) had a pre-treatment height velocity SD score of at least −3. Patients started treatment at a mean (SD) body weight of 14.1 (8.8) kg. The mean (SD) body mass index (BMI) and BMI SD score at baseline were 16.6 (2.8) kg/m^2 and −0.2 (1.2), respectively.

Patients received mecasermin 60 mcg/kg to 120 mcg/kg SC twice daily within 30 minutes of a meal. Naïve-to-mecasermin patients generally started mecasermin at 60 mcg/kg to 80 mcg/kg SC twice daily for 1 to 2 weeks and then increased to 120 mcg/kg SC twice daily as tolerated. The primary efficacy outcomes were height velocity, near-adult height, and estimated improvement in near-adult height. Secondary efficacy outcomes were height velocity SD score, height SD score, change in bone age relative to change in chronological age, and BMI SD score. Data on harms throughout treatment were also collected. The only comparator for efficacy outcomes was within-patient change from baseline, with the exception of estimated improvement in near-adult height, for which a historical cohort of patients with untreated Laron syndrome was used. The longest follow-up was 19 years.

Efficacy Results

All patients included in the primary efficacy analysis were naive-to-mecasermin and had been receiving treatment for at least 1 year (n = 75). Most commonly, patients received 120 mcg/kg mecasermin SC twice daily (356 patient years or 69% of a total 516 patient years). Most of the rest of the exposure was at 80 mcg/kg SC twice daily (50 patient years or 10% of a total 516 patient years).

Height Velocity

During year 1 of treatment, there was an increase in mean (SD) height velocity from 2.6 (1.7) cm per year to 8.0 (2.3) cm per year. Height velocities for years 2 through 8 of treatment remained greater than baseline (i.e., 5.9 [1.7] cm per year in year 2 and 4.4 [1.5] cm per year in year 8). There was no correlation between age at the start of treatment and height velocity during the first year of treatment. The mean (SD) difference in year 1 height velocity was not statistically different in patients with GH gene deletion (7.4 [3.6] cm per year) (n = 7) and patients with Laron syndrome phenotype (6.6 [3.8] cm per year) (n = 72). There was no statistically significant difference in mean (SD) height velocity during the first year of treatment for those with antibodies (7.9 [2.1] cm per year) compared to those without antibodies (7.1 [3.0] cm per year). There was an observed association of dose on height velocity during the first year of treatment. The mean (95% CI) year 1 height velocity at a dose of at least 60 mcg/kg SC twice daily was 6.0 (5.1, 6.9) cm per year compared with 8.5 (7.8, 9.1) cm per year at a dose of 120 mcg/kg SC twice daily.

Height Velocity SD Score

During year 1 of treatment, there was an increase in mean (SD) height velocity SD score from −3.4 (1.6) to 1.7 (2.8). The mean height velocity SD score for years 2 through 10 of treatment remained greater than baseline (i.e., −0.0 [1.7] during year 2 and 0.1 [0.6] during year 10). Results for patients who were naïve-to-mecasermin treatment when they were enrolled in Study 1419 (i.e., excluding patients who had enrolled in any of the other 4 studies or were previously treated with Pharmacia mecasermin) were similar compared with those in the primary efficacy analysis (which included those who were naïve-to-mecasermin at enrolment in any of the studies, including the predecessor studies and Study 1419, but excluded those previously treated with Pharmacia mecasermin).

Near-Adult Height and Estimated Improvement in Near-Adult Height

Nineteen naïve-to-mecasermin patients achieved near-adult height based on bone age criteria (at least 16 years for males and 14 years for females). An additional 2 naïve-to-mecasermin patients were considered by the investigators to have completed the intended course of treatment to near-adult height. The mean (SD) difference between the observed and expected increase in height (based on untreated patients with Laron syndrome, who achieve a mean [SD] final adult height of 124 [8.5] cm for males and 119 [8.5] cm for females) was 13 (8) cm (range, −0.5 to +35 cm) after an average 11 years of treatment. The median (range) final adult height was 137.6 cm (112.0 cm to 164.4 cm).

Height SD Score

During the first year of treatment, there was an increase in mean (SD) height SD score from −6.9 (1.8) to −6.1 (1.8). The mean height SD score for years 2 through 14 of treatment remained greater than baseline (i.e., −5.6 [1.7] in year 2 and −4.3 [1.0] in year 14). Results for patients who were naïve-to-mecasermin treatment when they were enrolled in Study 1419 were similar compared with those in the primary efficacy analysis.

HRQoL

HRQoL was not assessed in Study 1419 or its predecessors.

Bone Age Relative to Chronological Age

For patients with bone age measurements after at least 1 year of treatment (n = 56), bone age was delayed at baseline by a mean (SD) 2.8 (1.7) years compared with chronological age (3.9 [2.9] years versus 6.7 [3.8] years, respectively). The change in bone age, for those with measurements after at least 1 year of treatment up to a maximum 17 years of treatment, exceeded the change in chronological age by a mean (SD) 0.9 (1.8) years (+7.4 [3.7] years versus +6.5 [3.7] years, respectively).

BMI SD Score

During the study there was a mean (SD) increase in BMI SD score from −0.3 (1.1) at baseline to 0.3 (1.4) when last evaluated, a difference of 0.6 (1.3).

Harms Results

Seventy-six (83%) patients had at least 1 adverse event (AE). The most reported AEs included metabolism and nutrition disorders (n = 48, 52%); general disorders and administration site conditions (n = 42, 46%); infections and infestations (n = 41, 45%); respiratory, thoracic, and mediastinal disorders (n = 38, 41%); gastrointestinal disorders (n = 33, 36%); nervous system disorders (n = 31, 34%); and musculoskeletal and connective tissue disorders (n = 29, 32%). Eighteen (20%) patients had at least 1 serious adverse event (SAE) that required hospitalization. No patient withdrew from the study due to an AE and no patient died during the study. The most frequently reported notable harms included hypoglycemia (n = 43, 47%); lipohypertrophy at the injection site (n = 32, 35%); tonsillar hypertrophy (n = 19, 21%); and adenoidal hypertrophy (n = 9, 10%).

Critical Appraisal

Study 1419 was a non-randomized, single-arm, open-label trial. Due to the rare and severe nature of SPIGFD, a randomized control group may not have been feasible or ethical. Due to the lack of randomized control group, the findings are at high risk of confounding and establishing a causal link between the treatment and the growth outcomes and harms is

not possible. It is unclear how patients were selected for enrolment, so there is a potential for selection bias. The study may have been underpowered to detect statistically significant changes in outcomes, especially at later time points when fewer patients remained in the study (e.g., after 8 years of treatment when less than 15 patients had measurements available for change in height velocity). There is an increased risk of type I error (i.e., false-positive conclusions) because there were no adjustments for multiple comparisons. For the estimated improvement in adult height, a historical control group of patients with untreated Laron syndrome was used. It is uncertain whether the final adult height in the historical cohort is representative of contemporary patients with SPIGFD. There is a risk that the estimated improvement in adult height could be biased due to differences in baseline characteristics of patients in Study 1419 compared to those studied by Laron et al. (1993) (most notably, in Study 1419 the etiology of SPIGFD was not Laron syndrome in all patients and the patient population was multinational). Further, there are no data to determine whether the final adult height in untreated patients has changed since the time of data collection by Laron et al. nearly 30 years ago. Since the trial was open-label, there is some risk that common subjective harms known to be associated with mecasermin could have been over-reported. A large proportion of patients (62%) discontinued treatment early, many (33%) of whom were lost to follow-up before attaining near-adult height. There is a high risk that the long-term efficacy and harms data could be biased due to missing outcomes for these patients.

Study 1419 included an international group of patients with SPIGFD, with eligibility criteria that allowed for patients with less severe short stature than that described in the product monograph. Since only 1 patient had a baseline height SD score greater than −3, based on height alone the patient population is closely reflective of eligible Canadian patients. Based on the eligibility criteria, some patients without a genetic cause of SPIGFD may have been excluded and it is uncertain whether the results could be extrapolated to this group of patients. Although the condition affects males and females equally, there was an imbalance in the proportion of males and females enrolled in the study (58% male). This is unlikely to severely affect the generalizability of the findings because the treatment is expected to have an equivalent effect in males and females. The exposure to mecasermin is likely reflective of typical exposures for patients who would be treated in the Canadian context. Twenty-one patients were treated with leuprolide to prolong the growth period in Study 1419. Although leuprolide is not approved for this indication in Canada, some physicians may choose to use leuprolide in conjunction with mecasermin treatment, particularly among patients who are near adult height or for whom bone age is rapidly increasing.

Other Relevant Evidence: The European Increlex Growth Forum Database Registry

Description of Study

The European Increlex Growth Forum Database (EU-IGFD) Registry is a descriptive, multi-centre, observational, prospective, open-ended, noninterventional, post-authorization safety surveillance study of mecasermin. The primary objective was to collect long-term safety data on the use of mecasermin for the treatment of children with growth failure. Patients were eligible if they were beginning therapy with mecasermin for growth retardation or were previously treated with mecasermin prescribed by a participating qualified practitioner.

As of May 13, 2019, 281 patients from 10 European countries were enrolled. Of these, 275 who had taken mecasermin at least once and completed at least 1 follow-up visit were included in the efficacy analysis. The mean (SD) chronological age at baseline was 9.5 (4.1)

years. Mean (SD) bone age was 8.6 (3.5) years. More than half of patients were male (n = 177, 63%) and most did not have Laron syndrome (n = 238, 85%). Most patients began treatment at pubertal stage 1 (n = 225, 80%). Few (n = 24, 9%) had received prior IGF-1 therapy. About 1 quarter (n = 73, 26%) had received prior therapy with GH. All patients had severe short stature, with mean (SD) height and height SD score of 114.3 (21.4) cm and −3.8 (1.3), respectively. Mean (SD) pre-treatment height velocity was 4.7 (1.7) cm per year. The mean (SD) body weight and body weight SD score at baseline were 22.0 (9.8) kg and −3.3 (1.4), respectively. The mean (SD) BMI and BMI SD score at baseline were 16.1 (2.9) kg/m^2 and −0.7 (1.4), respectively.

All patients received mecasermin at a recommended starting dose of 0.04 mg/kg SC twice daily and maximum dose of 0.12 mg/kg SC twice daily. The recommended dose was individualized for each patient based on treatment response and tolerance.

Efficacy Results

Efficacy outcomes were evaluated for the whole registry population (n = 275), as well as for pre-pubertal patients naive-to-mecasermin (n = 162) and for pubertal or previously treated patients (n = 109).

Height

The mean (SD) height at baseline among pre-pubertal/naïve-to-mecasermin patients was 107.2 (20.4) cm. The mean (SD) change from baseline after 1 year of treatment was +7.2 (2.2) cm. The mean (SD) change in height from baseline in years 2 through 5 of treatment were +13.8 (3.2) cm, +19.5 (4.0) cm, +25.0 (4.2) cm, and +30.9 (4.7) cm, respectively.

The mean (SD) height SD score at baseline among pre-pubertal/naïve-to-mecasermin patients was −3.8 (1.4). The mean (SD) change from baseline after 1 year of treatment was +0.4 (0.4). There was an association between age and height SD score during the first year of treatment (P = 0.024). The mean (SD) changes in height SD score in years 2 through 5 of treatment were +0.7 (0.6), +0.9 (0.6), +1.1 (0.6), and +1.2 (0.8), respectively. Among patients with Laron syndrome, mean (SD) height SD score at baseline was −5.0 (1.75). The mean (SD) change from baseline after 1 year of treatment was +0.9 (0.8). Among patients without Laron syndrome, mean (SD) height SD score at baseline was −3.6 (1.1). The mean (SD) change from baseline after 1 year of treatment was +0.3 (0.4).

The mean (SD) height velocity at baseline among pre-pubertal/naïve-to-mecasermin patients was 4.8 (1.8) cm per year. The mean (SD) change from baseline after 1 year of treatment was +2.5 (2.5) cm per year. The mean (SD) changes in height velocity in years 2 through 5 of treatment were +1.8 (2.3) cm per year, +1.1 (2.6) cm per year, +0.8 (2.2) cm per year, and +0.8 (1.8) cm per year, respectively. In patients concomitantly treated with GH, mean (SD) height velocity at baseline was 4.6 (1.8) cm per year. The mean (SD) changes from baseline after 1 and 2 years of treatment were +1.2 (3.0) cm per year and +0.7 (2.9) cm per year, respectively. For patients with Laron syndrome, mean (SD) height velocity at baseline was 4.8 (1.3) cm per year. The mean (SD) change from baseline after 1 year of treatment was +1.3 (2.5) cm per year. The mean (SD) changes in height velocity from baseline in years 2 through 4 of treatment were +0.7 (2.5) cm per year, −1.9 (3.0) cm per year, and −0.3 (2.7) cm per year, respectively. In patients without Laron syndrome, mean (SD) height velocity at baseline was 4.7 (1.8) cm per year. The mean (SD) change from baseline after 1 year of treatment was +2.2 (2.6) cm per year. The mean (SD) changes in height SD score from baseline in years 2 through

5 of treatment were +1.5 (2.3) cm per year, +1.3 (2.5) cm per year, +0.7 (2.2) cm per year, and +0.2 (1.8) cm per year, respectively.

The mean (SD) final adult height and final adult height SD score among pre-pubertal/naïve-to-mecasermin patients were 158.6 (12.6) cm and −2.3 (1.2), respectively. There was an association between age at baseline (P < 0.001), predicted adult (P < 0.001), and height SD score at baseline (P = 0.003) and final adult height (i.e., those who begin treatment at a younger age and higher height SD score may achieve a higher final adult height). There was an association between predicted adult height (P < 0.001) and actual height SD score at baseline (P = 0.016) and final adult height SD score.

HRQoL

HRQoL was measured in 47 patients from France and/or their parents; however, baseline and follow-up data were only available for 2 patients and could not be summarized in this report.

Bone Age

The mean (SD) bone age at baseline among pre-pubertal/naïve-to-mecasermin patients was 7.3 (3.1) years. The mean (SD) change from baseline after 1 year of treatment was +1.1 (0.5) years. The mean (SD) change in bone age in years 2 and 3 of treatment were +2.3 (0.6) years and +3.3 (0.6) years, respectively. The difference between bone age and chronological age at baseline was −1.9 (1.0) years. The mean (SD) change from baseline after 1 year of treatment was +0.1 (0.6) years. The mean (SD) changes in the difference between bone age and chronological age in years 2 and 3 of treatment were +0.2 (0.6) years and +0.2 (0.6) years, respectively.

Weight and Weight SD Score

The mean (SD) weight at baseline among pre-pubertal/naïve-to-mecasermin patients was 18.4 (7.3) kg and changed by a mean (SD) +3.3 (1.8) kg during the first year of treatment. The mean (SD) changes in weight in years 2 through 5 of treatment were +6.6 (3.6) kg, +9.9 (5.0) kg, +12.0 (5.4) kg, and +15.6 (6.1) kg, respectively. The mean (SD) weight SD score at baseline was −3.4 (1.4) and changed by a mean (SD) +0.5 (0.7) during the first year of treatment. The mean (SD) changes in weight SD score in years 2 through 5 of treatment were +0.8 (1.0), +1.0 (1.1), +1.3 (1.3), and +1.6 (1.4), respectively.

BMI SD Score

The mean (SD) BMI SD score at baseline among pre-pubertal/naïve-to-mecasermin patients was −0.8 (1.3). The mean (SD) change from baseline after 1 year of treatment was +0.2 (0.7). The mean (SD) changes in BMI SD score in years 2 through 5 of treatment were +0.3 (0.7), +0.4 (0.8), +0.4 (1.0), and +0.6 (1.1), respectively.

Harms Results

Harms During Treatment

Of these patients, 185 (67%) had at least 1 AE during treatment and 59 (21%) had at least 1 SAE. Fifteen patients withdrew from the study due to AEs and 2 (1%) patients died (1 patient with myelodysplastic syndrome and 1 due to complications of a bone marrow transplant).

The most frequently reported notable harms included hypoglycemia (n = 68, 25%), lipohypertrophy at the injection site (n = 33, 12%) and tonsillar hypertrophy (n = 25, 9%). Myalgia (n = 4, 1%), benign, malignant, and unspecified neoplasms (including cysts and polyps) (n = 2, 1%) and intracranial hypertension (n = 1, 0.4%) were reported less frequently.

Harms Post-Treatment

During the post-treatment period, 39 AEs were reported in 21 (13%) patients. Seventeen SAEs were reported.

During the long-term safety period, 5 (29%) patients experienced 6 AEs (tonsilitis, cyclic vomiting syndrome, hearing loss, tonsillar hypertrophy, decreased thyroxine free, and decreased vitamin D). Two SAEs (tonsillitis and cyclic vomiting syndrome) were reported.

No patient died during the post-treatment or long-term safety periods.

Critical Appraisal

The EU-IGFD Registry provides real-world evidence of growth and safety outcomes among patients treated with mecasermin for SPIGFD. Due to the lack of randomized control group, the findings are at high risk of confounding and establishing a causal link between the treatment and efficacy and harms is not possible. There is an increased risk of type I error because there was no adjustment for multiple comparisons. It is unclear whether patients were consecutively enrolled, so there is a potential for selection bias. It is unclear whether the study was powered to detect statistically significant changes in growth outcomes (although these were not tested statistically). With respect to the analysis of harms, the sample size was not large enough to observe side effects with a true incidence of at least 1 of 100. Only 17 patients were eligible for the long-term safety analysis. It is possible that common subjective harms known to be associated with mecasermin could have been over-reported, since patients and their treating clinicians knew of the treatment received and of their participation in a registry study. A large proportion of enrolled patients discontinued the study early for reasons other than completing the course of treatment or achieving final adult height (n = 76, 27%). No data were collected after withdrawal. Additionally, baseline data were missing for a large proportion of enrolled patients across all outcomes. No imputations or other statistical methods were used to account for missing data and there is a high risk that efficacy and harms data could be biased due to missing data. Sixty-nine patients (25% of those enrolled) were affected by a mecasermin shortage over the course of the study, resulting in a dosage decrease or dose interruption. These dosage decreases and interruptions could have attenuated the growth outcomes and harms observed.

The EU-IGFD Registry included an international group of patients treated with mecasermin. There were no inclusion criteria specific to Health Canada's approved indication for mecasermin (e.g., specifications for height, basal IGF-1 level, GH sufficiency, and exclusion of secondary forms of IGF-1 deficiency); however, the European Medicine Agency's therapeutic indication for mecasermin is identical to Health Canada's. Only 15% of patients were diagnosed with Laron syndrome (in contrast to 89% of those enrolled in Study 1419), the most common cause of SPIGFD. The mean (SD) height SD score was substantially short, on average, at baseline (mean [SD], −3.8 [13]). There was a large range of height SD scores at baseline (−9.4 to −1.3) and not all patients met the height SD score criterion in the product monograph (i.e., height SD score ≤ −3). Height velocity ranged from 0.5 to 10.6 cm per year at baseline. Sixty-three percent of patients were male and the median (range) chronological age at baseline was 9.6 (0.4 to 19.1) years. These patients would be eligible for treatment as per the product monograph based on age but are likely older than the optimal start time of treatment. Although SPIGFD affects males and females equally, the imbalance in the proportion of males and females enrolled is unlikely to affect the generalizability of the findings since the treatment is expected to have an equivalent effect on males and females. The exposure to mecasermin in the EU-IGFD Registry is likely reflective of typical exposures

for patients who would be treated in the Canadian context. Concomitant medications taken by patients during the study were similar to those that would be expected in Canadian clinical practice.

Other Relevant Evidence: The Polish Study on Increlex

Description of Study

The Polish Study on Increlex was a single-arm trial that investigated efficacy and harms for patients with SPIGFD treated with mecasermin during the first 3 years in which it was covered by the therapeutic program in Poland. Patients were eligible if they were diagnosed with SPIGFD according to Polish criteria.

The study enrolled 27 patients, including 22 (81%) males and 5 (19%) females. The mean (range) chronological age at baseline was 10.1 (2.8 to 16.2) years. Nearly all (n = 25, 93%) patients were pre-pubescent. The mean (range) height SD score and height velocity at baseline were −3.5 (−6.5 to −2.3) and 4.6 (0.9 to 7.5) cm per year, respectively. The mean (range) weight SD score at baseline was −3.1 (−5.8 to −1.2). The mean (SD) BMI SD score at baseline was −1.8 (1.3).

All patients received mecasermin. The initial dose was 40 mcg/kg SC twice daily and was increased over time. The maximum dose was 120 mcg/kg SC twice daily. There was no control group and the only comparator was within-patient change from baseline.

Efficacy Results

Growth outcomes were measured every 3 months up to 36 months (3 years) of treatment for 25 patients who completed the study.

Height

The results for height outcomes were consistent with those from the pivotal trial. There was an increase in the mean height SD score and height velocity during the first 3 years of treatment, with the greatest apparent increase in height velocity during the first year of treatment.

HRQoL

HRQoL was not measured in the Polish Study on Increlex.

Skeletal Maturation

Skeletal maturation (e.g., bone age, bone age SD score) was measured in the Polish Study on Increlex, but the findings were not included in the published report.

Body Mass

The results for BMI SD score were consistent with the pivotal trial. BMI SD score increased during the first 3 years of treatment.

Harms Results

Eight (30%) patients reported AEs during the study. The seriousness of AEs was not reported. Two (7%) patients discontinued the study due to AEs. No patient died during the study. Regarding notable harms, 2 (7%) patients reported hypoglycemia during the sixth month of

treatment. Two (7%) patients had hyperlipodystrophy at the injection site. One (4%) patient developed hypertrophy of the lymphatic tissue of the pharyngeal tonsils.

Critical Appraisal

The Polish Study on Increlex was a single-arm trial that investigated growth outcomes during the first 3 years of treatment. Considering the rare and severe nature of SPIGFD, a randomized control group may not have been feasible or ethical. Due to the lack of randomized control group, the findings are at high risk of confounding and establishing a causal link between the treatment and the growth outcomes and harms is not possible. There is an increased risk of type I error because there was no adjustment for multiple comparisons. It is possible that common subjective harms known to be associated with mecasermin could have been over-reported, since patients and their treating clinicians knew of the treatment received and of their participation in a trial. The study enrolled the first 27 children treated with mecasermin for SPIGFD in Poland and it does not appear that there is a substantial risk of selection bias. The power of the study is unclear; however, all Mann–Whitney U tests to investigate changes from baseline were statistically significant. It is not clear which growth references were used to calculate SD scores. For this reason, the validity of the outcomes based on SD scores is uncertain. There was no published protocol for the Polish Study on Increlex. The risk of bias due to selective reporting is high, namely because some clinically important outcomes were measured but not reported.

The eligibility criteria were aligned with the product monograph and all patients underwent an IGF-1 generation test to assess for insensitivity to GH. The mean age at baseline was 10.1 years (range, 2.8 to 16.2 years) and bone age was not reported. The majority (81%) of patients were male. These patients would be eligible for treatment as per the product monograph based on age but are likely older than the optimal start time of treatment. Although SPIGFD affects males and females equally, the imbalance in the proportion of males and females enrolled is unlikely to affect the generalizability of the findings since the treatment is expected to have an equivalent effect on males and females. The exposure to mecasermin in the Polish Study on Increlex is likely reflective of typical exposures for patients who would be treated in the Canadian context.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (SPIGFD)
Treatment	Mecasermin
Submitted price	40 mg vial, $5,916.64 per vial ($147.92 per mg)

Component	Description
Treatment cost	At a submitted price of $147.92 per mg (or $5,916.64 per 40 mg vial), the annual cost of mecasermin ranges between $65,083 to $183,416, based on the recommended dosage, assuming a patient weight of 14.10 kg, and considering wastage of unused product.
Comparator	No treatment
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (up to a patient's average life expectancy (79.0 years for males and 84.1 years for females))
Key data source	Treatment effectiveness with mecasermin was informed by an investigator-sponsored, single arm, open-label trial. Natural history data for untreated patients was sourced from a study in the literature describing annual height velocities for children with Laron syndrome.
Submitted results	ICER = $391,879 per QALY gained (incremental costs: $2,330,629; incremental QALYs: 5.9). ICER weighted by sex and age of treatment initiation, with starting ages ranging from 2 to 5 years of age.
Key limitations	• The clinical evidence available for mecasermin was from a single-arm trial. As a result, the comparative clinical efficacy and safety of mecasermin in comparison with no treatment is highly uncertain. The sponsor incorporated treatment effects in the model via a naïve comparison of mecasermin and no treatment; as a result, the model predictions of gains in height with mecasermin are uncertain. • The sponsor's model predicts a large QALY gain with mecasermin based on an average gain in height of 12.5 cm in the sponsor's base case. The association between height gain and utility scores in patients with SPIGFD has not been established. There are also concerns with the sponsor's approach to extrapolating utility scores by HSDS in the general adult population in the absence of available data. • The trial informing treatment efficacy with mecasermin in the sponsor's submitted model may have excluded patients without a genetic cause of SPIGFD. The generalizability of the sponsor's economic model results to such patients is uncertain. • A greater proportion of males than females in the modelled population were assumed to have SPIGFD, and as such, the sex distribution of the modelled patient population, used to weight model results, was not truly reflective of patients with SPIGFD. Given ICERs were higher in females, this biased results in favour of mecasermin. • Drug costs may be underestimated due to the exclusion of potential wastage.
CADTH reanalysis results	• Due to the significant uncertainty associated with the comparative clinical efficacy and safety evidence, as well as with the patient utility by HSDS, CADTH produced a best estimate rather than a base case. A base case was considered inappropriate given the considerable uncertainty with the available evidence informing the model. The CADTH best estimate included: revising health state utilities to reflect the sponsor's extrapolation with the least severe decline in utility scores for HSDS less than −3.5 in the absence of more appropriate evidence; assuming an equal proportion of males and females with SPIGFD; and, adjusting drug cost calculations to account for potential wastage. • Based on the CADTH reanalyses, the ICER for mecasermin vs. no treatment was $624,249 per QALY gained (incremental costs: $2,338,189; incremental QALYs: 3.8). A 92% price reduction would be required for mecasermin to be considered cost-effective at a $50,000 per QALY threshold. • The results remain highly uncertain due to limitations with the comparative efficacy of mecasermin vs. no treatment and rely on the assumption that a gain of 11.8 cm (as predicted in the CADTH best estimate) in height would result in approximately 4 additional years in perfect health over a patient's lifetime.

HSDS = height standard deviation score; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SPIGFD = severe primary insulin-like growth factor-1 deficiency.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis. Drug costs may be underestimated due to the exclusion of potential drug wastage, and there is uncertainty around the estimates used to determine the size of the population eligible for treatment with mecasermin (i.e., incidence, prevalence, and diagnosis rate). CADTH undertook a reanalysis to derive the CADTH base case by only adjusting the drug costs of mecasermin based on the cost per vials needed to cover a yearly dose, rather than the exact cost per milligram, which had a limited impact on results. The estimated budget impact with the reimbursement of mecasermin was $11,572,125 in year 1, $12,035,169 in year 2, and $12,374,828 in year 3, for a 3-year budget impact of $35,982,122. However, there remains some uncertainty with the sponsor's estimated budget impact due to uncertainty in the potential population size.

CADTH Drug Expert Committee 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, 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.

Meeting date: November 25, 2021

Regrets: Two expert committee members did not attend

Conflicts of interest: None