



CADTH Reimbursement Recommendation

Metreleptin (Myalepta)

Indication: As an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

- with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above
- with confirmed familial partial LD (PL) or acquired PL (Barraquer-Simons syndrome), in adults and children 12 years of age and above with persistent significant metabolic disease for whom standard treatments have failed to achieve adequate metabolic control

Sponsor: Medison Pharma Canada Inc.

Final recommendation: Reimburse with conditions



Summary

What Is the Reimbursement Recommendation for Myalepta?

We recommend that Myalepta should be reimbursed by public drug plans as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in patients with lipodystrophy (LD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Myalepta should be covered to treat patients with confirmed congenital generalized LD (GL) (Berardinelli-Seip syndrome) or acquired GL (Lawrence syndrome) in both adults and children who are at least 2 years old and have at least 1 metabolic abnormality of diabetes, insulin resistance, or high levels of triglycerides (TGs). Myalepta should also be covered to treat patients who have confirmed familial partial LD (PL) or acquired PL in adults and children who are at least 12 years old and have persistent significant metabolic abnormalities, even after trying other treatments for at least 12 months.

What Are the Conditions for Reimbursement?

Myalepta should only be reimbursed if prescribed by an endocrinologist or pediatric endocrinologist with expertise in treating LD and if the cost of Myalepta is reduced. When first prescribed, Myalepta should only be reimbursed for 12 months. Reimbursement may be renewed on a yearly basis for patients who show improvement in their blood sugar and/or triglyceride levels.

Why Did We Make This Recommendation?

- In 1 clinical trial, treatment with Myalepta improved hemoglobin A1C and fasting TG levels in patients with GL. For patients with PL the best results were seen in patients with severe PL who had high levels of hemoglobin A1C and fasting TGs at the start of the study.
- Myalepta may help control metabolic parameters, but there is no evidence that it can improve health-related quality of life (HRQoL) or alleviate feelings of hunger and fatigue.
- Based on our assessment of the health economic evidence, Myalepta does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Myalepta is estimated to cost the public drug plans approximately \$136 million over the next 3 years.



Summary

Additional Information

What Is Lipodystrophy?

LD is a progressive and chronic condition that affects how the body stores fat. It can cause damage to organs such as the liver, kidneys, and pancreas. This condition can significantly impact a person's health, HRQoL, and life expectancy. People who have LD often feel hungry and may need help with everyday tasks. LD is a rare condition, with an estimated prevalence of 0.23 people per million to 0.96 people per million for GL and 1.67 people per million to 2.84 people per million for PL.

Unmet Needs in Lipodystrophy

There is an unmet need for effective therapies that control metabolic parameters for patients with GL and PL whose metabolic parameters are not controlled with current standard-of-care therapies.

How Much Does Myalepta Cost?

Annual treatment with Myalepta is expected to cost approximately \$1,139,730 for patients using the 11.3 mg vial, \$586,066 for patients using the 5.8 mg vial, and \$293,179 for patients using the 3 mg vial.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that metreleptin be reimbursed as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD)

- in adults and children aged 2 years and older with confirmed congenital generalized LD (GL) (Berardinelli-Seip syndrome) or acquired GL (Lawrence syndrome)
- in adults and children aged 12 years and older with confirmed familial partial LD (PL) or acquired PL (Barraquer-Simons syndrome) who have persistent significant metabolic disease and standard treatments have failed to achieve adequate metabolic control

only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

LD is a rare, progressive, chronic, and life-threatening disease characterized by selective absence of adipose tissue. Complications of LD frequently includes multiorgan damage that may become irreversible, affecting organs such as the liver, kidneys, and pancreas. CDEC emphasized that there is an unmet need for effective therapies that control metabolic parameters for patients with GL and PL that are unable to achieve metabolic control with current standard-of-care therapies.

One open-label, single-arm study (National Institutes of Health [NIH] 991265 pilot study and its long-term extension 20010769) demonstrated that treatment with metreleptin results in added clinical benefit for patients with LD. Patients in the NIH 991265 and 20010769 study (N = 107) received metreleptin for a maximum of 14 years. Actual change from baseline in hemoglobin A1C and percent change from baseline in fasting triglyceride (TG) levels to month 12 were the coprimary efficacy end points. Patients with GL who received metreleptin showed a mean change from baseline in hemoglobin A1C of -2.2% (95% confidence interval [CI], -2.7% to -1.6%) and fasting TG levels of -32.1% (95% CI, -51.0% to -13.2%). Although patients with PL who received metreleptin showed a mean change from baseline in hemoglobin A1C of -0.6% (95% CI, -1.0% to -0.2%) and fasting TG levels of [REDACTED], more favourable outcomes were observed in hemoglobin A1C and fasting TG levels in patients with severe PL (as defined by baseline hemoglobin A1C \geq 6.5% and/or TGs \geq 5.65 mmol/L) who received metreleptin. The mean change from baseline in hemoglobin A1C for this subgroup of patients was -0.9% (95% CI, -1.4% to -0.4%) and fasting TG levels was [REDACTED].

Patients identified a need for an effective treatment that improves metabolic parameters and addresses HRQoL, including hunger, fatigue, and the emotional and/or social impact of physical appearance. Metreleptin may address the unmet need for effective treatment options for controlling metabolic parameters. However, there was no evidence available in study NIH 991265 and 20010769 that shows metreleptin improves HRQoL outcomes, including hunger, fatigue, and the emotional and/or social impact of physical appearance.

Using the sponsor-submitted price for metreleptin and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for metreleptin was \$5,308,188 per quality-adjusted life-year (QALY) compared with supportive care. At this ICER, metreleptin is not cost-effective at a \$50,000 per QALY gained willingness-to-pay (WTP) threshold for patients with GL as well as patients with PL aged 12 years or older with persistent significant metabolic abnormalities and for whom standard treatments have failed to achieve adequate metabolic control. A price reduction is required for metreleptin to be considered cost-effective at a \$50,000 per QALY gained WTP threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
<p>1. In patients with either of the following:</p> <p>1.1. confirmed congenital GL (Berardinelli-Seip syndrome) or acquired GL (Lawrence syndrome) in adults and children aged 2 years and older with at least 1 metabolic abnormality (diabetes mellitus, insulin resistance, or hypertriglyceridemia)</p> <p>1.2. confirmed familial PL or acquired PL in adults and children aged 12 years and older with persistent significant metabolic abnormalities (as defined by baseline hemoglobin A1C \geq 6.5% and/or fasting TGs \geq 5.65 mmol/L), for whom standard treatments have failed to achieve adequate metabolic control after at least 12 months since initiating standard treatments.</p>	<p>In the NIH 991265 and 20010769 trial, treatment with metreleptin demonstrated clinical benefit in patients with GL and PL. Patients with LD were enrolled in NIH 991265 and 20010769 on the basis of having at least 1 of the following 3 metabolic abnormalities:</p> <ul style="list-style-type: none"> • presence of diabetes mellitus as defined by the American Diabetes Association criteria • fasting insulin concentration $>$ 30 μU/mL • fasting TG concentration $>$ 200 mg/dL ($>$ 2.26 mmol/L) or postprandially elevated TG $>$ 500 mg/dL ($>$ 5.65 mmol/L) when fasting was clinically not indicated (e.g., in infants). <p>Patients in the PL subgroup had to have baseline hemoglobin A1C \geq 6.5% and/or fasting TGs \geq 5.65 mmol/L. CDEC noted that 1 year is a reasonable duration to establish if supportive therapies are able to achieve adequate metabolic control. In addition, in NIH 991265 and 20010769, actual change from baseline in hemoglobin A1C and percent change from baseline in fasting TG levels to month 12 were the coprimary efficacy end points.</p>	<p>The physician must provide the baseline hemoglobin A1C and fasting triglycerides when the initial request for reimbursement occurs.</p> <p>The clinical experts noted to CDEC that patients are currently managed using supportive care for comorbid conditions or complications of LD (i.e., diet and exercise, antihyperglycemics, and lipid-lowering medications), and that these standard treatments are aimed at achieving metabolic control to reduce comorbidities.</p>
<p>2. Genetic testing must be conducted.</p> <p>2.1. If genetic testing is positive, then diagnosis is confirmed and treatment with metreleptin can be initiated.</p> <p>2.2. If after conducting genetic testing LD is not confirmed,</p>	<p>In the trial, information on LD genetic mutations was available for [REDACTED] patients with GL and [REDACTED] patients with PL. Because of the challenges in confirming the diagnosis, the price of metreleptin, and to avoid overprescribing, genetic testing is needed to confirm diagnosis.</p> <p>Patients enrolled in NIH 991265 and</p>	<p>CDEC noted that genetic testing can be helpful to confirm a diagnosis of familial LD; however, genetic testing to confirm familial LD 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</p>

Reimbursement condition	Reason	Implementation guidance
<p>treatment can be initiated in patients with confirmed clinical diagnosis based on a comprehensive clinician assessment and if fasting leptin levels are < 12.0 ng/mL in females and < 8.0 ng/mL in males older than 5 years of age or < 6 ng/mL in children aged 6 months to 5 years.</p>	<p>20010769 had to have clinically significant LD identified by the study physician during the physical examination as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient. In addition, circulating leptin concentrations had to be \leq 8.0 ng/mL in female patients and \leq 6.0 ng/mL in male patients in NIH 991265. In NIH 20010769, in patients who were at least 5 years of age, the circulating leptin concentrations were < 12.0 ng/mL in females and < 8.0 ng/mL in males as measured by Linco assay on a specimen obtained after an overnight fast. In children aged 6 months to 5 years, a circulating leptin concentration of < 6 ng/mL was used.</p>	<p>Canada and to ensure their availability where needed.</p> <p>Genetic testing can include other proven genetic conditions that are associated with LD.</p> <p>CDEC noted that circulating leptin concentrations can be helpful to confirm a diagnosis of LD; however, measuring circulating leptin levels may not be available in all jurisdictions. Given the limited availability of 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 measuring circulating leptin levels across Canada and to ensure their availability where needed.</p>
<p>3. Patients should not be pregnant or lactating or have HIV-associated LD.</p>	<p>No evidence was identified to support the use of metreleptin in patients that are pregnant or lactating or patients that have HIV-associated LD.</p>	<p>—</p>
<p>4. The maximum duration of initial authorization is 12 months.</p>	<p>In NIH 991265 and 20010769, actual change from baseline in hemoglobin A1C and percent change from baseline in fasting TG levels to month 12 were the coprimary efficacy end points.</p>	<p>—</p>
Renewal		
<p>5. For renewal after initial authorization, the physician must provide proof of beneficial metabolic effect when requesting continuation of reimbursement, defined as 1 or both of the following:</p> <ol style="list-style-type: none"> 5.1. actual hemoglobin A1C reduction of at least 0.5% from baseline 5.2. percent fasting TG reduction of at least 15% from baseline. 	<p>Based on results from NIH 991265 and 20010769 as well as clinical expert opinion, improvements should be expected to be demonstrated by 6 months, with 0.5% change from baseline in hemoglobin A1C and 15% change from baseline in fasting TG levels viewed as a clinically meaningful benefit. In NIH 991265 and 20010769, actual change from baseline in hemoglobin A1C and percent change from baseline in fasting TG levels to month 12 were the coprimary efficacy end points.</p>	<p>—</p>
<p>6. The physician must provide proof of maintenance of reduction in hemoglobin A1C and/or fasting TG from baseline every 12 months for subsequent authorizations.</p>	<p>Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.</p>	<p>—</p>

Reimbursement condition	Reason	Implementation guidance
Prescribing		
7. Prescribing should be limited to endocrinologists or pediatric endocrinologists with expertise in treating LD.	To ensure that metreleptin is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	—
Pricing		
8. A reduction in price.	The ICER for metreleptin is \$5,308,188 per QALY gained when compared with supportive care. A price reduction of 99% would be required for metreleptin to achieve an ICER of \$50,000 per QALY compared to supportive care.	—
Feasibility of adoption		
9. The feasibility of adoption of metreleptin must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption because of the difference between the sponsor's estimate and our estimate.	The prevalence of LD is highly uncertain, and the projected budgetary impact fluctuates substantially depending on the published source used to derive the number of prevalent cases in Canada.

CDEC = Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; GL = generalized lipodystrophy; LD = lipodystrophy; PL = partial lipodystrophy; QALY = quality-adjusted life-year; TG = triglyceride.

Discussion Points

- The sponsor requested a reconsideration of the initial CDEC draft recommendation to reimburse with conditions metreleptin as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in patients with LD. CDEC discussed 3 issues outlined by the sponsor in the request for reconsideration. The sponsor requested we reconsider the prevalence estimate used to derive the eligible patient population in the budget impact analysis model, that genetic testing not be a mandatory requirement for reimbursement, and that for renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as actual hemoglobin A1C reduction of at least 0.5% from baseline and/or percent fasting TG reduction of at least 15% from baseline.
- There was uncertainty with the clinical evidence; therefore, the committee deliberated on metreleptin considering the criteria for significant unmet need that are described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews*. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence reasonably suggests that metreleptin could substantially reduce metabolic parameters from baseline.

- CDEC discussed the small number of included patients in the clinical trials and the open-label noncomparative study design that limited the ability to draw conclusions regarding the efficacy of metreleptin. Given the rarity of the condition and the lack of effective options for patients, it was decided that the limitations and uncertainty were balanced with the significant unmet need and the rarity of the condition.
- CDEC discussed the appropriateness of hemoglobin A1C and fasting TG levels as surrogate outcomes for outcomes that are important to patients, such as hunger, HRQoL, and the emotional and/or social impact of their physical appearance. Although it would be preferable to have these outcomes included in the submitted evidence, based on discussion with the clinical experts, hemoglobin A1C and fasting TG levels were considered reasonable outcomes to evaluate for meaningful clinical benefits.
- CDEC discussed the 2 supportive analyses submitted by the sponsor that aimed to provide comparative estimates of the relative treatment effects of metreleptin versus standard-of-care therapy. The limitations of these analyses were such that no conclusions could be drawn regarding the estimated comparative efficacy, although the direction of the results suggesting positive outcomes in favour of metreleptin were consistent with the convictions of the clinical experts with experience treating LD that metreleptin would be a treatment with clinical benefit.
- During the initial meeting, the clinical experts noted to CDEC that genetic testing can be helpful to confirm a diagnosis of familial LD; however, often there is not a perfect correlation between what is considered a true positive in terms of genetic testing and the clinical presentation of what would be diagnosed as LD. While the clinical experts did not consider that a confirmed genetic test result should be required before initiating therapy for this patient population, CDEC discussed that given the challenges in confirming the diagnosis, the price of metreleptin, and to avoid overprescribing, genetic testing to confirm diagnosis should be implemented for the purposes of reimbursement. During the reconsideration meeting, CDEC acknowledged that confirmatory genetic testing is helpful in suspected familial LDs, but it does not determine the diagnosis in all cases with genetic LDs nor is it applicable in acquired forms of LDs. Hence, CDEC recommended that if genetic testing did not confirm diagnosis, treatment can be initiated in patients with confirmed clinical diagnosis based on a comprehensive clinician assessment and the following fasting leptin levels:
 - patients aged 5 years and older
 - less than 12.0 ng/mL in females
 - less than 8.0 ng/mL in males
 - children aged 6 months to 5 years
 - less than 6 ng/mL.
- During the reconsideration meeting, CDEC acknowledged that not all patients with LD have abnormalities in both hemoglobin A1C and fasting TG and that clinical benefits due to metreleptin can only be observed if the patient exhibits abnormal values at baseline; otherwise, no significant changes are anticipated. Because of the heterogeneity of the patient population, CDEC modified

the renewal criteria to require proof of beneficial metabolic benefits in hemoglobin A1C and/or fasting TG.

- During the reconsideration meeting, CDEC noted that in pediatric patients with GL, there is no evidence available on the efficacy of metreleptin to maintain good metabolic health (with respect to hemoglobin A1C and/or fasting TG levels) in patients who do not have metabolic abnormalities, hence CDEC did not recommend that treatment be initiated in pediatric patients with normal metabolic levels.
- The clinical expert noted to CDEC that over time due to the natural disease course and the progression of disease, hemoglobin A1C and/or fasting TG levels could fluctuate after initial response. However, CDEC recommended that response achieved after the initial 12 months of treatment has to be maintained for patients to be eligible for subsequent renewal.
- CDEC discussed ethical and equity considerations for metreleptin, including the misdiagnosis and underdiagnosis of LD, especially for male patients, as well as the physical, psychosocial, and financial burdens of this condition for patients and their families. Given the uncertainty of the trial evidence, the committee noted the importance of collecting long-term data on safety, efficacy and HRQoL, such as through patient registries, for clinical and health systems decision-making. The committee discussed weighing the potential benefits of requiring confirmatory genetic testing for prescribing metreleptin (e.g., preventing indication creep, especially given the high cost) with the potential harms (e.g., a potential barrier for patients without known variants or in the absence of accessible testing). The committee highlighted that ensuring equitable access to metreleptin will require making genetic testing accessible across jurisdictions. CDEC noted the importance of informed consent discussions and shared decision-making, including for pediatric patients and as patients transition from pediatric to adult care. The committee also noted that health equity is an important consideration when assessing the uncertainty of the evidence of long-term safety and efficacy for metreleptin, since LD is a rare and severe condition, and metreleptin satisfies some important unmet needs for a vulnerable population with limited treatment options; however, these considerations are also balanced against the consideration of high opportunity costs of reimbursing metreleptin at the submitted price.
- Following the initial CDEC meeting, the sponsor requested we reconsider the prevalence estimate used to derive the eligible patient population in the budget impact analysis model. The sponsor presented an argument featuring multiple forms of evidence (i.e., clinical expert opinion, real-world evidence, and international comparisons) suggesting that the prevalence estimate used by us was high. We and CDEC recognize the uncertainty surrounding the prevalence of LD and we have adjusted its base case estimate to align with the original sponsor's submission while also incorporating an alternative estimate in a scenario analysis.

Background

LD is a rare, progressive, chronic, and life-threatening disease characterized by selective absence of adipose tissue. GL and PL encompass a heterogeneous group of disorders featuring complete or partial loss of

adipose tissue; these disorders may be congenital (congenital GL or familial PL) or acquired (acquired GL or acquired PL). The lack of adipose tissue is also associated with leptin deficiency, which results in the early development of serious metabolic disorders such as severe insulin-resistant diabetes and hypertriglyceridemia. Complications of LD also frequently include multiorgan damage that may become irreversible, affecting organs such as the liver, kidneys, and pancreas.

In addition to the clinical burden, lipodystrophy also has a major detrimental emotional, psychological, and physical burden on patients, reducing life expectancy and HRQoL, and compromising the ability to carry out even basic daily activities. Additionally, patients with LD often have insatiable hunger and hyperphagia which causes distress to them and caregivers, especially those who care for children with LD to ensure they do not eat inedible objects. The impact of LD also leads to a high direct and indirect economic burden.

The lack of precise diagnostic criteria for LD makes it hard to firmly establish the diagnosis of lipodystrophy; overestimation or underestimation of disease prevalence is likely. The prevalence of GL has been estimated to be 0.23 to 0.96 people per million, and the prevalence of PL has been estimated to be 1.67 to 2.84 people per million. There are no Canadian-specific epidemiology studies of LD; however, it is estimated that there are fewer than 30 people with GL and fewer than 200 people with PL in Canada.

Metreleptin mimics the physiological effects of leptin by binding to and activating the human leptin receptor, which belongs to the class I cytokine family of receptors that signal through the JAK and STAT transduction pathway. Metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in:

- adults and children aged 2 years and older with confirmed congenital GL (Berardinelli-Seip syndrome) or acquired GL (Lawrence syndrome)
- in adults and children aged 12 years and older with confirmed familial PL or acquired PL (Barraquer-Simons syndrome) who have persistent significant metabolic disease and standard treatments have failed to achieve adequate metabolic control.

Metreleptin is contraindicated in patients with general obesity not associated with confirmed generalized leptin deficiency or confirmed PL. Metreleptin is also contraindicated in patients with HIV-related LD.

Metreleptin is administered as a once-daily subcutaneous injection. The recommended daily dose is based on body weight. Based on clinical response (e.g., inadequate metabolic control) or other considerations (e.g., tolerability issues, excessive weight loss, especially in pediatric patients), the dose may be adjusted:

- All patients 40 kg or less: Starting daily dose 0.06 mg/kg, adjustments of 0.02 mg/kg/day to a maximum daily dose of 0.13 mg/kg
- Male patients greater than 40 kg: Starting daily dose 2.5 mg, adjustments of 1.25 mg to 2.5 mg per day to a maximum daily dose of 10 mg
- Female patients greater than 40 kg: Starting daily dose 5 mg, adjustments of 1.25 mg to 2.5 mg per day to a maximum daily dose of 10 mg

Sources of Information Used by the Committee

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

- a review of 2 single-arm clinical studies in patients with LD
- patients' perspectives gathered by 1 patient group, the Lipodystrophy Canada Foundation
- input from public drug programs that participate in our review process
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with LD
- input from 1 clinician group of endocrinologists, medical geneticists, lipidologists, and internal medicine specialists from across Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to metreleptin from published literature
- Information submitted as part of the sponsor's request for reconsideration (described subsequently)
- stakeholder feedback on the draft recommendation.

Stakeholder Perspectives

Patient Input

One patient group, Lipodystrophy Canada Foundation, responded to our call for input for the current review of metreleptin as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in patients with LD. Information for this input was gathered from 2 patients – 1 from Canada and 1 from the UK – who live with PL.

According to both patients, LD tremendously affects their physical and mental health and affects every aspect of their life. Patients have hormonal imbalances, insulin resistance, diabetes, uncontrolled hunger, hypertriglyceridemia, hypertension, the emotional and/or social impact of their physical appearance, low self-esteem, and fatigue.

According to the patients' input, symptoms associated with the disease affect school life and social relationships and contribute to bullying because of their masculine appearance, which increases their symptoms of depression. The patients noted that disease symptoms and management affect their everyday activities and HRQoL.

Both patients manage their disease by addressing comorbid conditions, and they agreed that the currently available treatments do not adequately control key symptoms and there is no available treatment that can directly target LD. Both who had an experience with metreleptin reported significant improvements in their disease symptoms and quality of life.

Clinician Input

Input From the Clinical Experts We Consulted

The information in this section is based on input received from a panel of 4 clinical specialists we consulted for the purpose of this review.

The clinical experts explained that there is an unmet need for effective therapies that control metabolic parameters for patients with GL and an unmet need for effective therapies that control metabolic parameters for patients with PL whose metabolic parameters are not controlled with current standard-of-care therapies. The experts expect metreleptin to become first-line therapy for patients with GL and to be used in patients with PL whose metabolic parameters are not controlled with current standard-of-care therapies. The clinical experts noted that although genetic testing can be helpful to confirm a diagnosis of familial GL, often there is not a perfect correlation of what is considered a true positive in terms of genetic testing and the clinical presentation of what would be diagnosed as GL. As such, the clinical experts did not consider that a confirmed genetic test result should be required before initiating therapy for this patient population. To identify patients with PL who would be suitable for treatment with metreleptin, the clinical experts suggested that elevated hemoglobin A1C and fasting TG levels are an adequate substitute given the impracticalities of measuring leptin levels directly. It was noted by the experts that the levels used in the submitted pivotal trial to define severe PL (baseline hemoglobin A1C $\geq 6.5\%$ and/or TGs ≥ 5.65 mmol/L) would be an appropriate criterion for identifying patients with PL who have uncontrolled disease while receiving standard-of-care therapies. The clinical experts noted that to assess response to metreleptin for patients with LD, hemoglobin A1C and fasting TG levels would be monitored to determine whether metabolic control has improved. The experts suggested that determining a clinically meaningful response would be context dependent on a number of factors, including baseline hemoglobin A1C and fasting TG levels as well as the background therapies that the patient was receiving at the time of metreleptin initiation. The clinical experts suggested that the prescribing of metreleptin should be done by an endocrinologist specialist or a pediatric endocrinologist specialist.

Clinician Group Input

One clinician group responded to our call for input by a group of endocrinologists, medical geneticists, lipidologists, and internal medicine specialists. Information for this input was gathered mainly through the clinical registries of patients in Canada with various forms of LD.

The clinician group indicated that the current treatment paradigm for LD, which does not target the underlying pathophysiology, consists of supportive care for comorbid conditions or complications. This includes diet and exercise, antidyslipidemics, and antihyperglycemic medications.

The clinician group stated that there are significant unmet therapeutic needs for patients living with LD because there is no cure for the disease and available treatments only address the associated metabolic complications. Conventional therapies are considered inadequate due to the severity of metabolic abnormalities in patients with GL and those with more severe forms of PL, increasing their risk of end-organ

damage and early death. Therefore, there is a need for a therapy that aims at correcting the underlying pathophysiology of leptin deficiency.

The clinician group noted that metreleptin can ameliorate hyperphagia and improve hepatic and peripheral insulin sensitivity and has an established benefit versus risk profile. According to the clinician group, metreleptin is the primary first-line therapy for patients with GL, including children, and for patients with PL with more severe metabolic diseases who do not respond well to standard treatment approaches.

The clinician group indicated that the outcomes of interest in assessing clinical response are changes in metabolic control. If clinical response is not seen after 6 months of treatment and the patient is compliant with the administration technique, is receiving the correct dose, and is adherent to diet, a dose increase should be considered before stopping treatment.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
<p>There is no direct comparator because there is no treatment for LD. There were some indirect comparators used, such as lifestyle modification (diet and exercise; cosmetic surgery, such as facial reconstruction with free flaps and silicone to replace adipose tissue, liposuction, or lipectomy), hyperphagia therapy (anorexigenic agents, appetite suppressants, bariatric surgery), antihyperglycemic agents (insulin, TZDs, metformin, DPP-4i, GLP-1 agonist, SGLT2 inhibitor, SUs), and hypertriglyceridemia therapy (statins, fibrates, fish oils).</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>
Considerations for initiation of therapy	
<p>There was no genetic testing to confirm familial LD (1 of the indications that is applied for). Diagnosis was as follows: “Clinically significant lipodystrophy identified by the study physician during the physical examination as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient.” Is there any scenario in which a genetic test would be required to initiate therapy?</p>	<p>The clinical experts suggested that an absolute requirement for genetic testing to confirm familial LD is not necessary. Genetic testing can be used to confirm; however, the diagnosis should be made taking the full clinical presentation of the patient into account. The clinical experts also noted that the presence of a pathogenic or likely pathogenic DNA variant in a gene known to cause familial PL would be considered to be diagnostic of familial PL, provided that that variant (or variants) was not annotated exclusively to another disorder such as limb-girdle muscular dystrophy.</p> <p>Although the clinical experts did not consider that a confirmed genetic test result should be required before initiating therapy for this patient population, CDEC recommended that because of the challenges in confirming the diagnosis, the price of metreleptin, and to avoid overprescribing, genetic testing must be conducted for the purposes</p>

Implementation issues	Response
	<p>of reimbursement. If genetic testing is positive, then diagnosis is confirmed and treatment with metreleptin can be initiated. Otherwise, if LD is not confirmed after conducting genetic testing, treatment can be initiated in patients with confirmed clinical diagnosis based on a comprehensive clinician assessment and the following fasting leptin levels:</p> <ul style="list-style-type: none"> • Patients aged 5 years and older <ul style="list-style-type: none"> ◦ < 12.0 ng/mL in females ◦ < 8.0 ng/mL in males • Children aged 6 months to 5 years <ul style="list-style-type: none"> ◦ < 6 ng/mL.
<p>Should patients be required to have been prescribed standard of care before becoming eligible for metreleptin?</p>	<p>The clinical experts and CDEC agreed that for patients with GL, metreleptin would be included as the initial treatment regimen. For patients with PL, it was noted that often patients are already being treated for metabolic disorders with standard-of-care therapies before a diagnosis of PL is made. Therefore, practically speaking, patients with PL will have received standard of care and, if they are not adequately responding to that therapy, metreleptin should be added in an attempt to bring their metabolic parameters under control. In the event of identifying a patient with PL, the clinical experts agreed that existing therapies would still be tried first before moving on to metreleptin if the disease was unable to be controlled.</p>
Considerations for continuation or renewal of therapy	
<p>What monitoring parameters should be in place to consider patients for renewal (e.g., lipid panel, hemoglobin A1C)?</p>	<p>The clinical experts and CDEC agreed that monitoring for improvements in hemoglobin A1C and fasting triglyceride levels should be required for renewal of therapy.</p>
Considerations for prescribing of therapy	
<p>There can be difficulty accessing specialists in endocrinology or pediatric endocrinology in remote areas. Can metreleptin be initiated by internal medicine physicians in consultation with specialists?</p>	<p>The clinical experts and CDEC agreed that initiation of treatment for both patients with GL and patients with PL should be done in coordination with an endocrinology or pediatric endocrinology specialist. They noted that for patients with PL, consultation can be done virtually for patients who are remote and unable to easily access specialists. The experts noted that patients with GL should be seen in person by a specialist.</p>
Generalizability	
<p>In the submitted trial, patients with HIV were excluded, should metreleptin be used in this patient population?</p>	<p>The clinical experts and CDEC agreed that LD associated with HIV is a distinct type of LD with a distinct pathophysiology. Therefore, metreleptin reimbursement for HIV-associated LD would require a separate submission and is outside the scope of the current review.</p>
Care provision issues	
<p>Although not required for an initial diagnosis of familial LD, genetic marker testing is required to make a definitive diagnosis in suspected LD and especially in those with a family history of LD and at-risk family members. This can result in issues with access.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>

Implementation issues	Response
System and economic issues	
Metreleptin is considered to be added to current standard of care. This will have an increased incremental budget impact.	Comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee; DPP-4 = dipeptidyl peptidase 4; GL = generalized lipodystrophy; GLP-1 = glucagon-like peptide 1; LD = lipodystrophy; PL = partial lipodystrophy; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonyleurea; TZD = thiazolidinedione.

Clinical Evidence

Systematic Review

Description of Studies

NIH 991265 and 20010769 were a phase II and III, open-label, single-arm, single-centre, investigator-sponsored study. NIH 991265 was a pilot, dose-escalation study, with the objectives to determine if metreleptin can be safely administered to a group of patients with clinically significant LD and to determine if metreleptin treatment is effective in lowering plasma glucose and lipid abnormalities in patients with clinically significant LD. NIH 20010769 was a long-term study conducted to determine the long-term safety and efficacy of metreleptin treatment for patients with LD. Patient enrolment occurred between July 24, 2000, and March 26, 2014; the data cut-off date was in December 2014. The NIH 20010769 trial allowed for the rollover of patients from the pilot study as well as for direct enrolment of new patients. A total of 107 patients were enrolled in the studies, which were conducted at NIH. Although these studies were conducted at NIH, patients were also enrolled from countries outside the US, including Canada. Nine of 107 patients were enrolled in the pilot NIH 991265 trial; of these, 8 rolled over to receive metreleptin in the NIH 20010769 trial, and 98 patients enrolled directly into the NIH 20010769 trial. A total of 66 of 107 patients had GL and 41 had PL. There were 31 patients in a specified PL subgroup (i.e., patients with PL with baseline hemoglobin A1C $\geq 6.5\%$ and/or TGs ≥ 5.65 mmol/L).

Actual change from baseline in hemoglobin A1C and percent change from baseline in fasting TG levels to month 12 were the coprimary efficacy end points. Month 12 was considered by the clinical experts to be an appropriate time point for analysis because the effect of metreleptin would be expected to be seen by this time period. The sponsor noted that this time period would allow for individual dose titration to achieve maximum effect in a given patient and an acceptable time frame over which to assess the clinical impact of the treatment. To account for patients who may have discontinued treatment before that time, last observation carried forward (LOCF) methods were used for determination of changes from baseline to month 12. Specifically, samples for hemoglobin A1C and TGs obtained on or after day 180 were used in the analysis for patients who did not have samples obtained within the month 12 window (day 365 ± 65 days).



Efficacy Results

Change From Baseline in Hemoglobin A1C at 12 Months

In the GL cohort, mean baseline hemoglobin A1C was 8.6% (standard deviation [SD] = 2.33%) and at month 12 the mean hemoglobin A1C was 6.4% (SD = 1.68%) for a mean change from baseline of -2.2% (95% CI, -2.7% to -1.6%). In the overall PL cohort, mean baseline hemoglobin A1C was 7.9% (SD = 2.16%) and at month 12 the mean hemoglobin A1C was 7.4% (SD = 1.82%) for a mean change from baseline of -0.6% (95% CI, -1.0% to -0.2%). In the specified PL subgroup, mean baseline hemoglobin A1C was 8.7% (SD = 1.90%) and at month 12 the mean hemoglobin A1C was 7.9% (SD = 1.81%) for a mean change from baseline of -0.9% (95% CI, -1.4% to -0.4%).

Change From Baseline in Fasting TG at 12 Months

In the GL cohort, mean baseline TG level was 14.7 mmol/L (SD = 25.66 mmol/L) and at month 12 the mean was 4.5 mmol/L (SD = 6.10 mmol/L) for a relative mean change from baseline of -32.1% (95% CI, -51.0% to -13.2%). In the overall PL cohort, mean (SD) baseline TG level was [REDACTED] and at month 12 the mean (SD) TG level was [REDACTED] for a relative mean change from baseline of [REDACTED]. In the specified PL subgroup, mean (SD) baseline TG level was [REDACTED] and at month 12 the mean (SD) TG level was [REDACTED] for a mean change from baseline of [REDACTED].

The sponsor, [REDACTED] conducted an ad hoc sensitivity analysis, removing 1 patient in the PL cohort who was recorded as “noncompliant.” The results of this ad hoc analysis showed a mean change from baseline in TG levels of -20.8% [REDACTED] in the PL cohort and -37.4% [REDACTED] in the specified PL subgroup.

Change From Baseline in Fasting Glucose at 12 Months

In the GL cohort, mean baseline glucose level was 10.2 mmol/L (SD = 5.05 mmol/L) and at month 12 the mean was 7.0 mmol/L (SD = 3.40 mmol/L) for a relative mean change from baseline of -19.7% (95% CI, -29.4% to -10.0%). In the overall PL cohort, mean baseline glucose level was 8.8 mmol/L (SD = 4.39 mmol/L) and at month 12 the mean (SD) glucose level was 7.5 mmol/L (SD = 3.28 mmol/L) for a relative mean change from baseline of -6.1% (95% CI, -16.0% to 3.8%). In the specified PL subgroup, mean baseline glucose level was 10.0 mmol/L (SD = 4.36 mmol/L) and at month 12 the mean glucose level was 8.1 mmol/L (SD = 3.55 mmol/L) for a relative mean change from baseline of -13.2% (95% CI, -24.4% to -1.9%).

Change From Baseline in Liver Volume at 12 Months

In the GL cohort (n = 21), mean baseline liver volume was 3,357.7 mL (SD = 1,121.74 mL), the relative mean change from baseline was -33.8% (SD = [REDACTED]). In the overall PL cohort (n = 9), mean baseline liver volume was 2,624.6 mL (SD = 936.21 mL), the relative mean change from baseline was -13.4% (SD = [REDACTED]). In the specified PL subgroup (n = 8), mean baseline liver volume was 2,411.7 mL (SD = 731.91 mL), the relative mean change from baseline was -12.4% (SD = [REDACTED]).

Harms Results

Treatment emergent adverse events (TEAEs) occurred in 89.4% of patients in the GL safety cohort and 85.4% of patients in the PL safety cohort. The most common adverse events (AEs) in the GL cohort were decreased

weight (25.8%), abdominal pain (16.7%), and hypoglycemia (15.2%). The most common AEs in the PL cohort were hypoglycemia (17.1%), abdominal pain (14.6%), and nausea (14.6%).

Serious adverse events (SAEs) occurred in 34.8% of patients in the GL safety cohort, [REDACTED]. SAEs occurred in 24.4% of the PL safety cohort, [REDACTED].

TEAEs that resulted in treatment discontinuation occurred in 7.6% of patients in the GL safety cohort and 2.4% of patients in the PL safety cohort.

Death occurred in 4.5% of patients in the GL safety cohort, including death due to renal failure, cardiac arrest, and chronic hepatic failure. Death occurred in 2.4% of the PL safety cohort, including death due to hypoxic-ischemic encephalopathy.

Critical Appraisal

The major limitations associated with the NIH 991265 and 20010769 study include the single-arm, open-label design of the study. Lack of comparative data is a key limitation to the interpretation of the results from a single-arm trial because it is difficult to distinguish between the effect of the intervention relative to that of a placebo effect or the effect of natural history. It is acknowledged that there may be practical limitations to conducting a randomized controlled trial in patients with LD due to the rarity of the condition. The open-label nature of the trial also potentially increases the risk of bias; however, the end points included are objective laboratory values and unlikely to have been influenced by this bias. Harms outcomes may be impacted by the open-label design of the study.

The NIH 991265 and 20010769 study had a large number of dropouts and missing data at the 12-month primary analysis due to the challenges in conducting a clinical study including international participants at NIH. LOCF was used to carry forward the results from 6 months onward. Patients who did not have an observation after 6 months from baseline were considered missing data and not included in the results. Excluding patients with final observations before 6 months violates intention-to-treat principles because not all randomized patients have been included in the primary analysis. In addition, this imputation may underestimate the variance in the results, and hence could have resulted in narrower CIs. There were also interim analyses conducted without adjusting for multiplicity to account for the increased risk of type I error. The coprimary end points did not require multiplicity adjustment due to the need for both end points to achieve statistical significance to be considered a positive result; however, the PL cohort only achieved statistical significance with the removal of a patient who had barriers to adherence.

The NIH 991265 and 20010769 study enrolled patients beginning in July 2000. Because this was 23 years before the time of writing this report, clinical experts suggested that standards of therapy and patient support may have evolved during this time. However, it is anticipated that the clinical benefit of metreleptin would be consistent with that observed in the NIH 991265 and 20010769 study. LD is a chronic disease, and patients would be expected to receive treatment for life. The generalizability of the results beyond the maximum 14-year follow-up of the NIH 991265 and 20010769 study is unknown, although the clinical experts we consulted did not expect the efficacy of metreleptin to be different beyond the time horizon of

the NIH 991265 and 20010769 study. The clinical experts consulted considered the patient characteristics from the NIH 991265 and 20010769 study to be broadly generalizable to that of the expected population in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for the Grading of Recommendations Assessment, Development and Evaluation (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 programs. The following list of outcomes was finalized in consultation with expert committee members:

- change in hemoglobin A1C from baseline to month 12
- change in fasting TG from baseline to month 12
- change in fasting glucose from baseline to month 12
- change in liver volume from baseline to month 12.

Table 3: Summary of Findings for Metreleptin for Leptin Deficiency in Patients With Generalized Lipodystrophy (NIH991265/20010769)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Change from baseline in hemoglobin A1C (%), mean (95% CI) Follow-up: 12 months	59 (1 single-arm trial)	Actual: -2.2 (-2.7 to -1.6)	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on hemoglobin A1C when compared with any comparator.
Change from baseline in fasting triglycerides (%), mean (95% CI) Follow-up: 12 months	57 (1 single-arm trial)	Percent: -32.1 (-51.0 to -13.2)	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on fasting triglycerides when compared with any comparator.
Change from baseline in fasting glucose (mmol/L), mean (95% CI) Follow-up: 12 months	59 (1 single-arm trial)	Actual: -3.0 (-4.2 to -1.7) Percent: -19.7 (-29.4 to -10.0)	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on fasting glucose when compared with any comparator.
Change from baseline in liver volume (mL), mean (SD) Follow-up 12 months	12 (1 single-arm trial)	Actual: -1,350.9 (■■■■) Percent: -33.8 (■■■■)	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on liver volume when compared with any comparator.
Harms				
SAEs (safety end point), n Follow-up: maximum study duration of 14 years	66 (1 single-arm trial)	35 per 100	Very low ^{a,c}	The evidence is very uncertain about the effects of metreleptin on SAEs when compared with any comparator.

CI = confidence interval; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation.


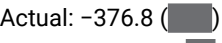
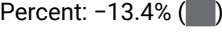
Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. For single-arm trials, all serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

^aIn the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is started at very low and cannot be rated up.

^bRated down 2 levels for very serious imprecision due to the small sample size. Rated down 1 level for a high amount of missing data requiring imputation.

^cRated down 1 level for serious risk of bias due to potential for bias in favour of metreleptin arising from the open-label nature of the study.

Table 4: Summary of Findings for Metreleptin for Leptin Deficiency in Patients With Partial Lipodystrophy (NIH991265/20010769)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Change from Baseline in hemoglobin A1C (%), mean (95% CI) Follow-up: 12 months	37 (1 single-arm trial)	Actual: -0.6 (-1.0 to -0.2)	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on hemoglobin A1C when compared with any comparator.
Change from baseline in fasting triglycerides (%), mean (95% CI) Follow-up: 12 months	37 (1 single-arm trial)	Percent: 	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on fasting triglycerides when compared with any comparator.
Change from baseline in fasting glucose, (mmol/L), mean (95% CI) Follow-up: 12 months	37 (1 single-arm trial)	Actual: -1.2 (-2.1 to -0.3) Percent: -6.1% (-16.0% to 3.8%)	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on fasting glucose when compared with any comparator.
Change from baseline in liver volume (mL), mean (SD) Follow-up: 12 months	8 (1 single-arm trial)	Actual: -376.8  Percent: -13.4% 	Very low ^{a,b}	The evidence is very uncertain about the effects of metreleptin on liver volume when compared with any comparator.
Harms				
SAEs (safety end point), n Follow-up: maximum study duration of 14 years	41 (1 single-arm trial)	24 per 100	Very low ^{a,c}	The evidence is very uncertain about the effects of metreleptin on SAEs when compared with any comparator.

CI = confidence interval; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation.

Note: Study limitations (which refers 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 single-arm trials, all serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

^aIn the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn, and the certainty of evidence is started at very low and cannot be rated up.

^bRated down 2 levels for very serious imprecision due to the small sample size. Rated down 1 level for a high amount of missing data requiring imputation.

^cRated down 1 level for serious risk of bias due to potential for bias in favour of metreleptin arising from the open-label nature of the study.

Indirect Comparisons

Description of Studies

One unpublished supportive analysis was conducted to estimate the comparative treatment effect of metreleptin with or without supportive care compared to supportive care alone using an inverse probability weighting and multivariate regression methods to adjust for differences between patients from the NIH follow-up study and an observational study of patients with GL and patients with PL who were on supportive care alone.

One published supportive analysis by Cook et al. (2021) estimated the treatment effect of metreleptin on mortality among patients with GL or PL using a Cox proportional hazard model to control for differences between patients treated with metreleptin and the historical cohort of patients who had not been treated with metreleptin.

Efficacy Results

In the unpublished supportive analysis, after inverse probability weighting, the mean difference between metreleptin with or without supportive care compared to supportive care alone in hemoglobin A1C was [REDACTED], the mean difference in TG levels was [REDACTED] and the hazard ratio (HR) for all-cause mortality was [REDACTED].

In the Cook et al. (2021) supportive analysis, the Cox model-predicted mortality HR for the overall patients treated with metreleptin group versus matched patients who had not been treated with metreleptin was 0.35 (95% CI, 0.13 to 0.90). Statistically significant differences in mortality risk between patients who had been treated with metreleptin and those who had not been treated with metreleptin in the GL subgroup were not detected from the Cox proportional hazards model (HR = 0.455; 95% CI, 0.150 to 1.387).

Critical Appraisal

The unpublished supportive analysis was associated with major limitations relating to the use of retrospective chart reviews and missing data, inability to adjust for important prognostic covariates, and small sample sizes resulting in imprecise and wide 95% CIs.

The published Cook et al. (2021) historical control arm analysis utilized a more robust methodology for adjusting the patient populations on important prognostic factors (although still not capturing all important factors); however, with mortality as the only end point assessed, there were few events captured resulting in imprecise and wide 95% CIs. The Cook et al. (2021) analysis also had missing data because the details of the standard-of-care therapies received by the historical control arm was not available.

Studies Addressing Gaps in the Evidence From the Systematic Review

FHA101 was a single-arm, multicentre, open-label, expanded-access study conducted at multiple treatment centres in the US among patients with LD. The primary objective was to provide metreleptin, an investigational medication, under a treatment protocol to patients with LD associated with diabetes mellitus and/or hypertriglyceridemia. A secondary objective was to assess the long-term efficacy, safety, and tolerability of metreleptin on diabetes mellitus and/or hypertriglyceridemia. Patient enrolment occurred between March 30, 2009, and January 23, 2016. A total of 41 patients were enrolled across 6 centres in the US.

Efficacy Results

This study found that treatment with metreleptin led to sustained improvements in glycemic control and hypertriglyceridemia in patients with GL and patients in the PL subgroup (i.e., patients with PL with baseline hemoglobin A1C \geq 6.5% and/or TGs \geq 5.65 mmol/L). Among the 9 patients with GL included in the full analysis set (FAS), treatment with metreleptin led to reductions in hemoglobin A1C; mean hemoglobin A1C

was reduced from 7.7% at baseline (n = 9) to 6.2% at month 12, and LOCF (n = 5), a mean change of -1.2%. Results were similar for the 7 patients in the PL subgroup included in the FAS; treatment with metreleptin led to reductions in hemoglobin A1C from 7.8% at baseline (n = 7) to 7.0% at month 12/LOCF (n = 7), a mean change of -0.8%.

Mean fasting glucose levels were reduced from 11.4 mmol/L at baseline (n = 9) to 10.2 mmol/L at month 12/LOCF (n = 6) in the GL group, a mean change of -1.5 mmol/L representing a 7.3% decrease in fasting glucose levels. For the PL subgroup, mean fasting glucose levels were reduced from 8.0 mmol/L at baseline (n = 7) to 6.9 mmol/L at month 12/LOCF (n = 7), a mean change of -1.1 mmol/L, representing a 9.0% decrease from baseline.

Mean fasting TG concentrations were reduced from 19.9 mmol/L at baseline (n = 8) to 7.6 mmol/L at month 12/LOCF (n = 6) in the GL group, corresponding to a mean percent change of -26.9%. In the PL subgroup, mean fasting TG concentrations, which were lower in this group of patients compared to those with GL, were reduced from 4.0 mmol/L (n = 7) at baseline to 3.6 mmol/L at month 12/LOCF (n = 7), a mean change of -8.5%.

Harms Results

Treatment with metreleptin was safe and generally well tolerated in patients with GL and in patients in the PL subgroup. The most common TEAEs in the GL group were hypoglycemia, infections, abdominal pain, and increased liver function tests. Most TEAEs were mild to moderate in severity. The AE profile in patients in the PL subgroup was generally similar to that in patients with GL. The most common TEAEs in patients in the PL subgroup were hypoglycemia, urinary tract infection, upper respiratory tract infection, anxiety, nausea, and sinusitis. Two patients reported neoplasms but these were considered by the investigator as unrelated to metreleptin. A total of 3 patients, including 1 with GL, 1 in the PL subgroup, and 1 with PL (not in the subgroup), developed neutralizing antibodies.

Over the 5-year study duration, 2 deaths were reported; neither of the deaths was assessed as drug related.

Critical Appraisal

The open-label design of Study FHA101 is considered a limitation that could bias the results parameters. The lack of a control arm is considered a key constraint that limits the interpretation of study outcomes. A small number of patients with GL and PL were evaluated; therefore, observed results should be interpreted with caution.

External Validity

There were no study sites located in Canada, so there may be limitations in generalizing these findings to the Canadian context.

Ethical Considerations

Patient group, clinician group, and drug program input, and relevant literature gathered during this review, were reviewed to identify ethical considerations relevant to the use of metreleptin to treat the complications of leptin deficiency in adults and children aged 2 years and older with confirmed congenital GL or acquired GL or adults and children aged 12 years and older with confirmed familial PL or acquired PL and standard therapies have failed to achieve metabolic control.

Ethical considerations identified in this review included those related to:

- **Treatment, care, and experiences of LD:** In the context of LD, ethical considerations highlighted the significant physical, psychosocial, and financial impacts of this rare condition and its associated complications on patients and families. Patients with LD who are male as well as patients with PL, patients who have limited agency to self-advocate, patients who are unable to access a general practitioner and specialist care, and patients who live in rural and remote communities may experience disproportionate barriers to a timely diagnosis, standard treatment or care, and access to therapies like metreleptin. Socioeconomic and cultural factors may also affect the ability of people with LD to manage their condition. There is an unmet need for an effective therapy for treating complications of leptin deficiency in patients with GL and those with severe PL due to the limited efficacy of standard-of-care therapies.
- **Clinical and economic evidence used in the evaluation of metreleptin:** The clinical trial evidence directionally showed improvements from baseline in hemoglobin A1C and triglyceride levels, an expected safety profile according to clinical experts, and that people with LD tolerated metreleptin well during the study period. However, evidence regarding metreleptin's short- and long-term safety and efficacy is deemed very uncertain. Furthermore, the clinical trial evidence did not assess some outcomes important to people with LD, their families, and health care providers, including changes in subjectively experienced hunger, fertility, and HRQoL. These evidentiary limitations present challenges for assessing clinical benefits and harms associated with using, or forgoing the use of, metreleptin, as well as the pharmacoeconomic assessment of cost-effectiveness.
- **Clinical use and implementation of metreleptin:** Despite uncertainties in the currently available clinical evidence, the clinical experts noted they would prescribe metreleptin given its potential to address an unmet need for treating life-altering and life-limiting complications related to leptin deficiency in GL and treatment-refractory cases of PL. Decision-making about the benefits and harms of metreleptin use may be particularly challenging when treating groups that were not included or were underrepresented in the studies informing the available clinical evidence (e.g., older adults and people who are pregnant). Clinical experts also noted that the representation of racial groups within the study population may not fully reflect the Canadian context. Ensuring equitable access to this injectable medication requires addressing potential diagnostic and monitoring-related barriers to access; in addition, it is necessary to consider how geography and limited agency to self-advocate or navigate the health care system may contribute to or exacerbate these barriers. This includes considering whether tests required to determine treatment eligibility are routinely accessible within

Canada. Given the evidentiary uncertainty and that metreleptin does not cure LD, clear and ongoing informed consent conversations are required. This involves open and collaborative communication between the prescribing clinician, patient, and/or their surrogate decision-maker regarding the disease process, the risks and benefits of treatment, uncertainty in and changes to available evidence, and treatment values and goals. Informed consent in pediatric contexts should consider each child's unique vulnerabilities, developing capacity, and the evolving evidence base.

- **Health systems:** Ethical considerations for health systems related to the implementation of metreleptin highlight potential challenges of funding decisions for high-cost drugs for rare diseases. These include challenges to assessing opportunity costs and the fair allocation of scarce resources in the context of limited long-term evidence for the safety, efficacy, and comparative effectiveness of metreleptin. Clinical experts noted the potential for inequities in access to therapy if reimbursement of metreleptin were inconsistent across jurisdictions in Canada. Clinical experts anticipated that implementing metreleptin would not increase health care utilization over and above care already received by people with LD. The experts also noted that metreleptin use might even decrease health care resource needs over a person's lifetime, although there is no long-term evidence to support this expectation.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Patient-level simulation consisting of 6 separate Markov submodels
Target population	Patients with confirmed congenital or acquired GL aged 2 years and older as well as patients with confirmed familial or acquired PL aged 12 years or older for whom standard treatments have failed to achieve adequate metabolic control. The target population is aligned with the proposed Health Canada indication.
Treatment	Metreleptin, in combination with SC. SC consists of antidiabetic therapies (i.e., insulin, metformin, empagliflozin, semaglutide), lipid-lowering therapies (i.e., atorvastatin; rosuvastatin, fenofibrate, bezafibrate), and antihypertensive therapies (i.e., ramipril, losartan).
Dose regimen	The recommended daily dose of metreleptin is based on body weight. Metreleptin should be self-administered once daily at the same time every day.
Submitted price	Metreleptin, 3 mg, 5.8 mg, and 11.3 mg powder for solution, subcutaneous injection: \$803, \$1,605, and \$3,120, respectively.
Treatment cost	The annual per-patient cost of metreleptin according to vial size is \$1,139,730 for patients using the 11.3 mg vial, \$586,066 for patients using the 5.8 mg vial, and \$293,179 for patients using the 3 mg vial.
Comparator	SC

Component	Description
Perspective	Publicly funded health care payers in Canada
Outcomes	QALYs, life-years
Time horizon	Lifetime (95 years)
Key data sources	<ul style="list-style-type: none"> • Metreleptin with or without SC: NIH 991265 and 20010769 follow-up study (time frame: July 2, 2000, to January 22, 2017). • SC: GL and PL natural history observational chart study (time frame: 1960 to March 20, 2018). • Comparative efficacy data were informed from the ITC of NIH 991265 and 20010769 and the GL and PL natural history study through inverse probability weighting. • Transition probabilities for the 6 organ submodels were informed by published literature from diseases in which LD complications are commonly observed and the ITC.
Key limitations	<ul style="list-style-type: none"> • In the submitted model, the use of hemoglobin A1C, ALT, and AST as surrogate outcomes predicted a reduced risk of cardiovascular-, kidney-, liver-, neuropathy-, and retinopathy-related complications among patients treated with metreleptin + SC, which has not been shown in clinical studies. Clinical experts indicated that although the relationship between the surrogate and primary end points is credible, there is uncertainty regarding the quantification of the associated risk reduction across organ subsystems, particularly as it pertains to patients with LD. • Survival gains associated with the use of metreleptin + SC have not been shown in clinical studies. Hence, it is plausible that the prevention of disease-specific complications, and the resulting survival benefit associated with metreleptin + SC may be overestimated. • Inclusion of caregiver disutilities in the submitted base case is highly uncertain. The parameters used to derive the caregiver burden and the assumptions made regarding the caregiver benefit associated with metreleptin + SC have not been shown in clinical studies. Moreover, according to our guidelines, the analysis of health-related quality of life must be focused on the target population; that is, patients with GL, as well as patients with PL who are inadequately controlled with SC. • Reductions in hemoglobin A1C that occur among patients treated with metreleptin + SC were assumed to persist following treatment discontinuation rather than trend toward baseline rates, despite the absence of evidence to support enduring legacy effects of glycemic control associated with long-term use of metreleptin. • Proportions of patients with GL and PL used by the sponsor do not reflect those reported in published literature. • Model lacked transparency and its programming prevented us from fully exploring and validating the associated uncertainties.
Reanalysis results	<ul style="list-style-type: none"> • Our base case was derived by making changes to the following model parameters: reversing the hemoglobin A1C benefit posttreatment discontinuation given the absence of evidence to support legacy effects associated with long-term use of metreleptin; adjusting the proportion of patients with GL and PL in accordance with published estimates; and, removing caregiver disutilities. • In our base case, metreleptin + SC was associated with an ICER of \$5,308,188 per QALY gained compared to SC (incremental costs: \$6,895,438; incremental QALYs: 1.30). • We conducted subgroup base case analyses. For patients with GL, metreleptin + SC was associated with an ICER of \$3,199,437 per QALY gained compared with SC (incremental QALYs: 2.27; incremental costs: \$7,274,459). For patients with PL, metreleptin + SC was associated with an ICER of \$6,979,408 per QALY gained compared with SC (incremental costs: \$6,767,340; incremental QALYs: 0.97). • The cost-effectiveness of metreleptin + SC was sensitive to the inclusion of caregiver disutilities. In a scenario in which the sponsor's estimates were used for spillover quality of life decrements due to caregiver burden, the ICER of metreleptin + SC decreased to \$2,116,901 (incremental costs: \$6,970,621; incremental QALYs: 3.29) relative to SC.

Component	Description
	<ul style="list-style-type: none"> • Clinical uncertainties in the extrapolation period could not be adequately explored due to a lack of clinical data. Given that the probability of disease progression in each of the organ-specific submodels affects survival, the cost-effectiveness results are highly sensitive to the strength of the surrogate relationships between hemoglobin A1C, ALT, AST, and disease-specific outcomes.

ALT = alanine transaminase; AST = aspartate aminotransferase; GL = generalized lipodystrophy; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LD = lipodystrophy; NOC = Notice of Compliance; PL = partial lipodystrophy; QALY = quality-adjusted life-year; SC = supportive care.

Budget Impact

We identified the following limitations in the sponsor’s base case: the prevalence of LD is uncertain, the diagnosis rate for GL is underestimated, and the proportion of patients with PL who are inadequately controlled with supportive care is underestimated. We conducted re-analyses of the budget impact analysis by updating the prevalence of GL and PL in accordance with the most recent published estimates, varying the diagnosis rate of GL in line with the assumption that a proportion of patients with GL may be undiagnosed or misdiagnosed, and changing the proportion of patients with PL who are inadequately controlled with supportive care in accordance with real-world evidence.

Based on our base case, the estimated budget impact associated with the reimbursement of metreleptin for the treatment of adults and children aged 2 years and older with congenital or acquired GL, as well as adults and children aged 12 years and older with confirmed familial PL or acquired PL (Barraquer-Simons syndrome) who have persistent significant metabolic disease and standard treatments have failed to achieve adequate metabolic control is expected to be \$34,557,718 in year 1, \$47,241,427 in year 2, and \$54,144,756 in year 3, for a 3-year budgetary impact of \$135,943,900.

We conducted scenario analyses to address remaining uncertainty. Using alternative prevalence estimates for GL and PL resulted in a 12-fold increase in the budgetary impact. In subgroup analyses, our base case suggests that reimbursing metreleptin for the treatment of patients with GL would be associated with a 3-year budgetary impact of \$55,644,361, while reimbursing metreleptin for the treatment of patients with PL for whom standard treatments have failed to achieve adequate metabolic control would be associated with a 3-year budgetary impact of \$80,299,539.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for metreleptin as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in patients with LD. In their request, the sponsor identified the following issues:

- The sponsor stated that our budget impact analysis reanalysis considerably overestimates the patient population in Canada.
- The sponsor is of the view that the use of genetic testing to dictate reimbursement is inappropriate.
- The sponsor is of the view that renewal criteria are only applicable to patients with abnormal hemoglobin A1C and TGs.



In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- feedback on the draft recommendation from the sponsor
- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in the diagnosing and treating patients with LD
- feedback on the draft recommendation from the public drug programs that participate in our review process.

All stakeholder feedback received in response to the draft recommendation is available on our website.

CDEC Information

Initial Meeting Date: December 20, 2023

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Regrets: None

Conflicts of interest: None

Reconsideration Meeting Date: April 24, 2024

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed

Regrets: Three expert committee members did not attend.

Conflicts of interest: None



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