CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH 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) 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.

Only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Lipodystrophy (LD) is a rare, progressive, chronic, and life-threatening disease characterized by selective absence of adipose tissue. Complications of lipodystrophy also frequently include multi-organ 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 phase 2/3, open-label, single arm study (NIH 991265/20010769), demonstrated that treatment with metreleptin results in added clinical benefit for patients with LD. Patients in the NIH 991265/20010769 (N = 107) study received metreleptin for a maximum of up to 14 years. Actual change from baseline in HbA1c and percent change from baseline in fasting triglyceride (TG) levels to Month 12 were the co-primary efficacy endpoints. Patients with GL that received metreleptin showed a mean change from baseline in HbA1c of -2.2% (95% CI, -2.7 to -1.6) and fasting TG levels of -32.1% (95% CI, -51.0 to -13.2). While patients with PL that received metreleptin showed a mean change from baseline in HbA1c of -0.6% (95% CI, -1.0 to -0.2) and fasting TG levels of [redacted], more favourable outcomes were observed in HbA1C and fasting TG in patients with severe PL (as defined by baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) that received metreleptin, where the mean change from baseline in this subgroup of patients in HbA1c 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 991265/20010769 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 generalized lipodystrophy, as well as patients with partial lipodystrophy aged 12 years or older with persistent significant metabolic abnormalities, 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		
1. In patients with any of the following: • with confirmed congenital generalized LD (Berardinelli-Seip syndrome) or acquired generalized LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD (PL) or acquired PL, in adults and children 12 years of age and above with persistent significant metabolic abnormalities (as defined by baseline HbA1c ≥6.5% and/or fasting triglycerides ≥5.65 mmol/L) for whom standard treatments have failed to achieve adequate metabolic control, after at least 12 months since initiating standard treatments.	In the NIH 991265/20010769 trial, treatment with metreleptin demonstrated clinical benefit in patients with generalized LD and partial LD. Patients in the PL subgroup had to have baseline HbA1c ≥ 6.5% and/or fasting triglycerides ≥5.65 mmol/L. CDEC noted that one year is a reasonable duration to establish if supportive therapies are able to achieve adequate metabolic control, in addition, in study NIH 991265/20010769 actual change from baseline in HbA1c and percent change from baseline in fasting TG levels to month 12 were the co-primary efficacy endpoints.	The physician must provide the baseline HbA1c and fasting triglycerides when the initial request for reimbursement occurs. The clinical experts noted to CDEC that patients are currently managed using supportive care for comorbid conditions or complications of lipodystrophy (i.e., diet and exercise, anti-hyperglycemic, and lipid-lowering medications) and that these standard treatments aimed at achieving metabolic control in order to reduce comorbidities.
2. Diagnosis needs to be confirmed by genetic testing	In the trial, information on LD genetic mutations was available for [redacted] patients with GL and [redacted] patients with PL. Given the challenges in confirming the diagnosis, the price of metreleptin, and to avoid over-prescribing, genetic testing to confirm diagnosis is recommended	CDEC noted that genetic testing can be helpful to confirm a diagnosis of familial lipodystrophy; however, genetic testing to confirm familial lipodystrophy 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.
3. Patients should not be pregnant or lactating or have HIV associated LD.	No evidence was identified to support the use of metreleptin in patients that are pregnant or lactating or patients that have HIV associated LD.	—
4. The maximum duration of initial authorization is 12 months	In study NIH 991265/20010769 actual change from baseline in HbA1c and percent change from baseline in fasting TG levels to month 12 were the co-primary efficacy endpoints.	—
Renewal		
5. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting	Based on results from the NIH 991265/20010769 trial and clinical expert opinion, improvements should be expected to be demonstrated by 6 months, with	—

Reimbursement condition	Reason	Implementation guidance
continuation of reimbursement, defined as both: 5.1. Actual HbA1c reduction of at least 0.5% from baseline, and 5.2. Percent fasting TG reduction of at least 15% from baseline	0.5% change from baseline in HbA1c and 15% change from baseline in fasting TG levels viewed as a clinically meaningful benefit. In study NIH 991265/20010769 actual change from baseline in HbA1c and percent change from baseline in fasting TG levels to month 12 were the co-primary efficacy endpoints.	
6. Subsequent renewals should be assessed annually with the same requirements as the initial renewal.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	
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 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 incremental budget impact of metreleptin is expected to be greater than $40 million in year 1, year 2, and year 3.	—

ICER = incremental cost-effectiveness ratio; GL = generalized lipodystrophy; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; LD = lipodystrophy; PL = partial LD; QALY = quality-adjusted life-year; TG = triglyceride.

Discussion Points

- 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 non-comparative 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 HbA1c 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 physical appearance. While it would be preferable to have these outcomes included in the submitted evidence, based on discussion with the clinical experts, HbA1c and fasting TG levels were considered reasonable outcomes to evaluate for meaningful clinical benefits.

- CDEC discussed the two 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, though 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.
- The clinical experts noted to CDEC that genetic testing can be helpful to confirm a diagnosis of familial lipodystrophy; 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 lipodystrophy. 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 over-prescribing, genetic testing to confirm diagnosis should be implemented for the purposes of reimbursement.
- CDEC discussed ethical and equity considerations for metreleptin, including the misdiagnosis and underdiagnosis of lipodystrophy, especially for males, 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 lipodystrophy 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.

Background

Lipodystrophy (LD) is a rare, progressive, chronic, and life-threatening disease characterized by selective absence of adipose tissue. Generalized lipodystrophy (GL) and partial lipodystrophy (PL) encompass a heterogeneous group of disorders featuring complete or partial loss of adipose tissue; these disorders may be congenital (congenital GL [CGL] or familial PL [FPLD]) or acquired (acquired GL [AGL] or acquired PL [APL]). 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 lipodystrophy also frequently include multi-organ 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 health-related quality of life (HRQoL), and compromising the ability to carry out even basic daily activities. Additionally, patients with lipodystrophy often suffer from insatiable hunger and hyperphagia which causes distress to them and caregivers, especially those who care for patients who are children to ensure they do not eat inedible objects. The impact of lipodystrophy also leads to a high direct and indirect economic burden.

The lack of precise diagnostic criteria for lipodystrophy 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 cases per million and the prevalence of PL has been estimated to be 1.67 to 2.84 cases per million. There are no Canadian-specific epidemiology studies of lipodystrophy; however, it is estimated that there are <30 GL cases and <200 PL cases 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/STAT transduction pathway. Metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in 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.

Metreleptin is contraindicated in patients with general obesity not associated with confirmed generalised leptin deficiency or confirmed partial lipodystrophy. Metreleptin is also contraindicated in patients with HIV-related lipodystrophy.

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 paediatric patients), the dose may be adjusted:

Patients (males and females) ≤40 kg: Starting daily dose 0.06 mg/kg, adjustments of 0.02 mg/kg/day to a maximum daily dose of 0.13 mg/kg

Males >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

Females >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 plans and cancer agencies that participate in the CADTH 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

Stakeholder Perspectives

Patient Input

One patient group, Lipodystrophy Canada Foundation, responded to CADTH's 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 lipodystrophy. Information for this input was gathered from two patients from Canada (Patient 1) and the UK (Patient 2) who live with partial lipodystrophy.

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

According to the patient's input, symptoms associated with the disease affect school life and social relationships and contribute to bullying of their male-like appearance, which increases their symptoms of depression. 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, with no available treatment that can directly target lipodystrophy. The two patients who had an experience with metreleptin reported significant improvements in their disease symptoms and quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The information in this section is based on input received from a panel of 4 clinical specialists consulted by CADTH 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 used in patients with PL whose metabolic parameters are not controlled with current standard of care therapies. The clinical experts noted that while 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 that would be suitable for treatment with metreleptin, the clinical experts suggested that elevated HbA1c 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 HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) would be an appropriate criterion for identifying PL patients that have uncontrolled disease while receiving standard of care therapies. The clinical experts noted that to assess response to metreleptin for patients with LD, HbA1c and fasting TG levels would be monitored to determine whether metabolic control has been improved. The experts suggested that determining a clinically meaningful response would be context dependent on a number of factors including the baseline HbA1c 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 CADTH's 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 Canadian patients with various forms of lipodystrophies.

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

The clinician group stated that there are significant unmet therapeutic needs for patients living with lipodystrophy, as there is no cure for this disease, and available treatments address the associated metabolic complications. Conventional therapies are considered inadequate due to the severity of metabolic abnormalities in patients with GL and 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, 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 PL patients with more severe metabolic diseases and 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 consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Response
Relevant comparators	
There is no direct comparator as there is no treatment for LD. There were some indirect comparators used such as lifestyle modification (diet and exercise, cosmetic surgery – facial reconstruction with free flaps and silicone to replace adipose tissue, liposuction/lipectomy), hyperphagia therapy (Anorexigenic agents, appetite suppressants, bariatric surgery), antihyperglycemic agents (insulin, TZDs, metformin, DPP-4i, GLP-1 agonist, SGLT2i, SUs), hypertriglyceridemia therapy (statins, fibrates, fish oils).	Comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
There was no genetic testing to confirm familial LD (one 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 where a genetic test would be required in order to initiate therapy?	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 Partial Lipodystrophy would be considered to be diagnostic of Familial Partial Lipodystrophy, provided that that variant (or variants) was not annotated exclusively to another disorder such as limb-girdle muscular dystrophy. While 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 given the challenges in confirming the diagnosis, the price of metreleptin, and to avoid over-prescribing, genetic testing to confirm diagnosis should be implemented for the purposes of reimbursement.
Should patients be required to have been prescribed standard of care prior to becoming eligible for metreleptin?	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 an incident PL patient, 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.
Considerations for continuation or renewal of therapy	
What monitoring parameters should be in place to consider patients for renewal? (lipid panel, A1c, etc.?)	The clinical experts and CDEC agreed that monitoring for improvements in HbA1c and fasting triglyceride levels should be required for renewal of therapy.
Considerations for prescribing of therapy	
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?	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. Noting that for patients with PL, consultation can be done virtually for patients that are remote and unable to easily access specialists. The experts noted that patients with GL should be seen in person by a specialist.

Drug program implementation questions	Response
Generalizability	
In the submitted trial, patients with HIV were excluded, should metreleptin be used in this patient population?	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 to CADTH and is outside the scope of the current review.
Care provision issues	
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.	Comment from the drug plans to inform CDEC deliberations.
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 plans to inform CDEC deliberations.

GL = generalized lipodystrophy; HIV = human immunodeficiency virus; LD = lipodystrophy; PL = partial lipodystrophy; SU = sulfonylureas; TZD = thiazollidinediones.

Clinical Evidence

Systematic Review

Description of Studies

NIH 991265/20010769 was a Phase 2/3, open-label, single-arm, single-centre, investigator-sponsored study. Study 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 lipodystrophy and to determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with clinically significant lipodystrophy. Study 20010769 was a long-term study conducted to determine the long-term safety and efficacy of metreleptin treatment for patients with lipodystrophy. Patient enrolment occurred between 24 July 2000 and 26 March 2014; the data cut-off date was in December 2014. Study 20010769 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 the NIH. Although these studies were conducted at the NIH, patients were also enrolled from countries outside the US, including Canada. Nine of the 107 patients were enrolled in the pilot Study 991265; of these, 8 rolled over to receive metreleptin in Study 200010769, and 98 patients enrolled directly into Study 20010769. A total of 66 of the 107 patients had GL and 41 had PL. There were 31 patients in a specified PL subgroup, i.e., those PL patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L.

Actual change from baseline in HbA1c and percent change from baseline in fasting TG levels to Month 12 were the co-primary efficacy endpoints. Month 12 was considered by the clinical experts an appropriate time point for analysis as 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. In order to account for patients who may have discontinued treatment prior to that time last observation carried forward (LOCF) methods were used for determination of changes from baseline to Month 12. Specifically, samples for HbA1c and triglycerides 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 HbA1c at 12 months

In the GL cohort, mean (standard deviation [SD]) baseline HbA1c was 8.6% (2.33) and at month 12 the mean (SD) HbA1c was 6.4% (1.68) for a mean change from baseline of -2.2% (95% confidence interval [CI], -2.7 to -1.6). In the overall PL cohort, mean (SD) baseline HbA1c was 7.9% (2.16) and at month 12 the mean (SD) HbA1c was 7.4% (1.82) for a mean change from baseline of -0.6%

(95% CI, -1.0 to -0.2). In the specified PL subgroup, mean (SD) baseline HbA1c was 8.7% (1.90) and at month 12 the mean (SD) HbA1c was 7.9% (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 (SD) baseline TG level was 14.7 mmol/L (25.66) and at month 12 the mean (SD) was 4.5 mmol/L (6.10) 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 one patient in the PL cohort who was recorded as non-compliant. 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 (SD) baseline glucose level was 10.2 mmol/L (5.05) and at month 12 the mean (SD) was 7.0 mmol/L (3.40) for a relative mean change from baseline of -19.7% (95% CI, -29.4 to -10.0). In the overall PL cohort, mean (SD) baseline glucose level was 8.8 mmol/L (4.39) and at month 12 the mean (SD) glucose level was 7.5 mmol/L (3.28) for a relative mean change from baseline of -6.1% (95% CI, -16.0 to 3.8). In the specified PL subgroup, mean (SD) baseline glucose level was 10.0 mmol/L (4.36) and at month 12 the mean (SD) glucose level was 8.1 mmol/L (3.55) 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 (SD) baseline liver volume was 3357.7 mL (1121.74), the relative mean (SD) change from baseline was -33.8% ([redacted]). In the overall PL cohort (N = 9), mean (SD) baseline liver volume was 2624.6 mL (936.21), the relative mean (SD) change from baseline was -13.4% ([redacted]). In the specified PL subgroup (N = 8), mean (SD) baseline liver volume was 2411.7 mL (731.91), the relative mean (SD) change from baseline was -12.4% ([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 AEs in the GL cohort were weight decreased (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 991265/20010769 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, as 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 an RCT 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 endpoints included are objective laboratory values and therefore are unlikely to have been influenced by this bias. Harms outcomes however may be impacted by the open-label design of the study.

The NIH 991265/20010769 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 the 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 prior to 6 months violates intent-to-treat principles as not all randomized patients have been included in the primary analysis. Additionally, 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 1 error. The co-primary endpoints did not require multiplicity adjustment due to the need for both endpoints to achieve statistical significance to be considered a positive result, however the PL cohort only achieved statistical significance with the removal of a non-compliant patient.

The NIH 991265/20010769 study enrolled patients beginning in July 2000. As this is 23 years from 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 991265/20010769 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 991265/20010769 study is unknown, although the clinical experts consulted by CADTH did not expect the efficacy of metreleptin to be different beyond the time horizon of the NIH 991265/20010769 study. The clinical experts consulted considered the patient characteristics from the NIH 991265/20010769 study to be broadly generalizable to that of the expected Canadian population.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Change from baseline to month 12 in HbA1c
- Change from baseline to month 12 in fasting TG
- Change from baseline to month 12 in fasting glucose
- Change from baseline to month 12 in liver volume

Table 3: Summary of Findings for Metreleptin for patients with leptin deficiency in Generalized Lipodystrophy (NIH991265/20010769)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Mean Change from Baseline in HbA1c, % (95% CI) Follow-up: 12 months	59 (1 single-arm trial)	Actual CFB: -2.2 (95% CI, -2.7 to -1.6)	Very low[a,b]	The evidence is very uncertain about the effects of metreleptin on HbA1c when compared with any comparator
Mean change from baseline in fasting triglycerides, % (95% CI) Follow-up: 12 months	57 (1 single-arm trial)	Percent CFB: -32.1 (95% CI, -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
Mean change from baseline in fasting glucose, mmol/L (95% CI)	59 (1 single-arm trial)	Actual CFB: -3.0 (95% CI, -4.2 to -1.7) Percent CFB: -19.7 (95% CI, -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

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Follow-up: 12 months				
Mean change from baseline in liver volume, mL (SD) Follow-up 12 months	12 (1 single-arm trial)	Actual CFB: -1350.9 ([redacted]) Percent CFB: -33.8 ([redacted])	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 endpoint), 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.

CFB = change from baseline; CI = confidence interval; SAE = serious adverse event; RCT = randomized controlled trial; 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.

[a] In 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.

[b] Rated 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.

[c] Rated 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 patients with leptin deficiency in Partial Lipodystrophy (NIH991265/20010769)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Mean Change from Baseline in HbA1c, % (95% CI) Follow-up: 12 months	37 (1 single-arm trial)	Actual CFB: -0.6 (95% CI, -1.0 to -0.2)	Very low[a,b]	The evidence is very uncertain about the effects of metreleptin on HbA1c when compared with any comparator
Mean change from baseline in fasting triglycerides, % (95% CI) Follow-up: 12 months	37 (1 single-arm trial)	Percent CFB: [redacted]	Very low[a,b]	The evidence is very uncertain about the effects of metreleptin on fasting triglycerides when compared with any comparator
Mean change from baseline in fasting glucose, mmol/L (95% CI) Follow-up: 12 months	37 (1 single-arm trial)	Actual CFB: -1.2 (95% CI, -2.1 to -0.3) Percent CFB: -6.1% (95% CI, -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

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Mean change from baseline in liver volume, mL (SD) Follow-up: 12 months	8 (1 single-arm trial)	Actual CFB: -376.8 ([redacted]) Percent CFB: -13.4% ([redacted])	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 endpoint), 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.

CFB = change from baseline; CI = confidence interval; SAE = serious adverse event; RCT = randomized controlled trial; 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.

[a] In 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.

[b] Rated 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.

[c] Rated 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 (SC) compared to SC alone using an inverse probability weighting (IPW) and multivariate regression methods to adjust for differences between patients from the NIH follow-up study and an observational study of GL and PL patients on SC 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 metreleptin-treated and the historical cohort of metreleptin-naïve patients.

Efficacy Results

In the unpublished supportive analysis, after IPW, the mean difference between metreleptin with or without SC compared to SC alone in HbA1c 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 metreleptin treated versus matched metreleptin-naïve patients was 0.35 (95% CI, 0.13 to 0.90). Statistically significant differences in mortality risk between metreleptin-treated and metreleptin-naïve patients 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 (though still not capturing all important factors), however with mortality as the only

endpoint assessed, there were few events captured resulting in imprecise and wide 95% CIs. The Cook et al. (2021) analysis also suffered from missing data given that 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

Study FHA101 was a single-arm, multicentre, open-label, expanded-access conducted at multiple treatment centers in the United States among patients with lipodystrophy. The primary objective was to provide metreleptin, an investigational medication, under a treatment protocol to patients with lipodystrophy that is 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 30 March 2009 and 23 January 2016. A total of 41 patients were enrolled across 6 centres in the United States.

Efficacy Results

This study found that treatment with metreleptin led to sustained improvements in glycaemic control and hypertriglyceridaemia in this small group of patients, both with GL and in the PL subgroup. Among the 9 patients with GL included in the FAS, treatment with metreleptin led to reductions in HbA1c; mean HbA1c was reduced from 7.7% at baseline (n=9) to 6.2% at Month 12/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 HbA1c 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 hypoglycaemia, infections, abdominal pain and increased liver function tests. Most TEAEs were mild to moderate in severity. The adverse event (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 hypoglycaemia, urinary tract infection, upper respiratory tract infection, anxiety, nausea, and sinusitis. Two patients had neoplasms reported but 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 neutralising antibodies.

Over the 5-year study duration, 2 deaths were reported, and 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 Canadian study sites, 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 CADTH review, were reviewed to identify ethical considerations relevant to the use of metreleptin to treat the complications of leptin deficiency in patients with lipodystrophy with confirmed: Congenital GL or acquired GL in adults and children 2 years of age and above; or Familial PL or acquired PL in adults and children 12 years of age and above for whom standard therapies have failed to achieve metabolic control.

Ethical considerations identified in this review included those related to:

- **Treatment, Care, and Experiences of Lipodystrophy:** In the context of lipodystrophy, ethical considerations highlighted the significant physical, psychosocial, and financial impact of this rare condition and its associated complications on patients and families. People with lipodystrophy who are male, have PL, have limited agency to self-advocate, are unable to access a general practitioner and specialist care, or live in rural and remote communities may experience disproportionate barriers to timely diagnosis, standard treatment or care, and ultimately, access to therapies like metreleptin. Socioeconomic and cultural factors may also impact the ability of people with lipodystrophy to manage the condition. There is an unmet need for an effective therapy for treating complications of leptin deficiency in GL and severe cases of 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 lipodystrophy 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 lipodystrophy, their families, and health care providers, including changes in subjectively experienced hunger, fertility, and health-related quality of life. 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, 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 under-represented in the studies informing the available clinical evidence (e.g., older adults and pregnant people). Clinical experts also noted that the representation of racial groups within 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; additionally, 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 lipodystrophy, 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 Canadian jurisdictions. Clinical experts anticipated that implementing metreleptin would not increase health care utilization over and above care already received by people with lipodystrophy. 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

Component	Description
Type of economic evaluation	Cost-utility analysis Patient-level simulation consisting of 6 separate Markov sub-models
Target population	Patients with confirmed congenital or acquired generalized lipodystrophy (GL) aged 2 years and older, as well as patients with confirmed familial or acquired partial lipodystrophy (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 supportive care (Metreleptin + SC). Supportive care (SC) consists of antidiabetic therapies (i.e., insulin, metformin, empagliflozin, semaglutide), lipid-lowering therapies (i.e., atorvastatin; rosuvastatin, fenofibrate, bezafbrate), and anti-hypertensive 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
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, Life-years
Time horizon	Lifetime (95 years)
Key data sources	• Metreleptin with or without SC: NIH 991265/20010769 follow-up study (Timeframe: July 2, 2000 to January 22, 2017). • SC: GL/PL Natural History observational chart study (Timeframe: 1960 to March 20, 2018). • Comparative efficacy data were informed from the indirect treatment comparison (ITC) of NIH 991265/20010769 and the GL/PL Natural History study through inverse probability weighting. • Transition probabilities for the 6 organ sub-models were informed by published literature from diseases where lipodystrophy (LD) complications are commonly observed and the ITC.
Key limitations	• In the submitted model, the use of HbA1c, 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 while the relationship between the surrogate and primary endpoints is credible, there is uncertainty regarding the quantification of the associated risk reduction across organ sub-systems, 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 CADTH 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 HbA1c that occur among patients treated with metreleptin + SC were assumed to persist following treatment discontinuation rather than trend towards 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 CADTH from fully exploring and validating the associated uncertainties.

Component	Description
CADTH reanalysis results	• The CADTH base case was derived by making changes to the following model parameters: reversing the HbA1c benefit post-treatment 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 the CADTH base case, metreleptin + SC was associated with an ICER of $5,308,188 per QALY gained compared to SC (incr. costs: $6,895,438; incr. QALYs: 1.30). • CADTH 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 (incr. QALYs: 2.27; incr. 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 (incr. costs: $6,767,340; incr. QALYs: 0.97). • The cost-effectiveness of metreleptin + SC was sensitive to the inclusion of caregiver disutilities. In a scenario where 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 (incr. costs: $6,970,621; incr. QALYs: 3.29) relative to SC. • 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 sub-models impacts survival, the cost-effectiveness results are highly sensitive to the strength of the surrogate relationships between HbA1c, ALT, AST, and disease-specific outcomes.

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; WTP = willingness to pay.

Budget Impact

CADTH 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 SC is underestimated. CADTH conducted re-analyses of the BIA 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 SC in accordance with real-world evidence.

Based on the CADTH base case, the estimated budget impact associated with the reimbursement of metreleptin for the treatment of patients with congenital or acquired GL in adults and children 2 years of age and above, as well as patients 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, is expected to be $400,548,793 in Year 1, $571,194,946 in Year 2, and $661,872,121 in Year 3, for a three-year budgetary impact of $1,633,615,860.

CADTH conducted scenario analyses to address remaining uncertainty. Using earlier prevalence estimates for GL and PL resulted in a 92% decrease in the budgetary impact. In subgroup analyses, the CADTH base case suggests that reimbursing metreleptin for the treatment of patients with GL would be associated with a three-year budgetary impact of $637,646,469, 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 three-year budgetary impact of $995,969,391.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, 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.

Meeting date: December 20, 2023

Regrets:

None

Conflicts of interest:

None