CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

metreleptin (Myalepta)

(Medison Pharma Canada Inc.)

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.

August 04, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Patient Group Input

Name of Drug: Metreleptin

Indication: Lipodystrophy

Name of Patient Group: Lipodystrophy Canada Foundation

Author of Submission: Sonia Rehal

1. About Your Patient Group

Lipodystrophy Canada Foundation is a non-for profit foundation with the main vision of providing support and resources to lipodystrophy patients and caregivers.

2. Information Gathering

Patient 1: Canada

Patient 2: UK

3. Disease Experience

Patient 1: Severe insulin resistance at puberty, displaying as loss of menstruation, hirsutism and acanthosis nigricans was followed by a pediatric endocrinologist in Montreal. Both my sister (5 years elder than me) and myself were affected by this severe insulin resistance, diabetes and hypertriglyceridemia at such a young age (I was 13, and my sister was 18), leaving our endocrinologist and medical team perplexed. We were finally referred to medical genetics when I was 17 for a suspected diagnosis of type A insulin resistance syndrome or partial lipodystrophy, the latter being confirmed through sequencing.

The striking loss of fat during my pubescent years made school life very difficult, as I was bullied for looking different that the other girls. The bullying severely affected my mental health, and I was placed on antidepressants since the age of 15. During my teen years, instead of enjoying time with friends, I was shuffling between doctor's appointments, medical imaging and blood tests. I also was started on insulin sensitizers, fenofibrates and medication for hypertension, making it very difficult to relate to others (except for my sister who was going through the same thing as I).

Our family support was non-existent, and my sister and I experienced the progression of lipodystrophy throughout our teens to our adulthood, with the further diagnosis of heart arrythmias and other metabolic abnormalities such as fatty liver. Along with bradycardia, requiring the placement of a pacemaker in my elder sister; the severe insulin resistance was particularly hard to control, and my sister developed renal failure requiring dialysis at the age of 33. Both these disease took her life at the age of 35. I myself have had multiple strokes and a massive myocardial infarct due to underlying atrial fibrillation. A cardiac device was implanted in me in 2018.

Despite the profound medical consequences of having lipodystrophy, the lack of subcutaneous fat, causing my habitus to be more male-like was the most disruptive to my overall quality of life. Social relationships were extremely difficult for me and I was also abused by my stepmother due to my altered body habitus.

Patient 2: Lipodystrophy is a multi-system disease that has a significant impact on every aspect of my life. I was diagnosed with familial partial lipodystrophy, type 2 (LMNA) when I was 17 following disruptions of my menses. It turned out this was caused by a hormonal imbalance resulting from PCOS, caused by severe insulin resistance. Upon diagnosis, my insulin levels were 50x normal in order to maintain a balanced blood glucose. Unfortunately, my condition progressed rapidly and I was diagnosed with lipoatrophic diabetes at 22 years old, requiring insulin injections a year later (from 23 y.o). Due to my severe insulin resistance, I require large insulin doses, using 300+ units per day. Due to the high volume of insulin injected, and the lack of subcutaneous fat making such injections very painful, I was started on an insulin pump ~6 years ago (age 34). My diabetic control is very important to me as I am

acutely aware that having insulin-resistant diabetes from such a young age, the possibility of serious secondary complications is high. This causes me a large amount of health anxiety. I suffer multiple lipodystrophy-related metabolic complications, including fatty liver, high cholesterol, high triglycerides, high blood pressure – for all of which I have been medicated. I follow a low fat, reduced carb diet.

Most lipodystrophy patients (particularly partial patients) wait on average seven years to get the correct diagnosis and often have several misdiagnoses along the way.

Growing up, we had no idea I had lipodystrophy, but I always struggled with my appearance. I have 'typical' partial lipodystrophy features, with a very muscular physique (hypermusculartrophy in my arms and legs), and excess fat on my face and neck. I was bullied from a young age for looking masculine, and this continues to have a huge impact on my self-esteem and body confidence. It's hard to dress the way you want when people literally point and stare. Some days I have the confidence to be myself and wear what I feel comfortable in, even if that means my arms and legs are visible, other days when I feel more fragile, I will cover up to avoid the stares. Aside from the body confidence issues, the biggest impact lipodystrophy has had on me is the insatiable hunger. It's hard to describe just how much of an impact this has on your daily life. We're talking starvation-level hunger. I could eat a three-course meal and still feel like my stomach was so empty it could turn inside out. Constant pain, feeling sick, food-seeking panic behavior's – it consumes your every waking moment: where is my next meal coming from, when can I eat again, I'm so hungry. You plan your day around it. You become obsessed with food and panic when you don't have easy access to it. It makes it very difficult to eat well with a condition that is predominantly managed by diet! In addition, living with lipodystrophy leaves me with terrible fatigue. Everyday activities can be a struggle, and it is hard to stay motivated when you feel exhausted all the time. It's like walking through treacle. Daily life is more hectic than ever, but when you are living with a chronic disease, there are dozens of extras that you have to keep track of – tightly regulated diet, blood glucose checks, blood pressure checks, daily pill regimes, insulin injections, exercise, doctor's appointments (so many appointments), medication deliveries, energy reserves to do everything, planning ahead/contingencies, etc. Let alone worrying about long-term complications, disease progression, explaining to friends/family/colleagues. It impacts all social activities – do I have the energy for this, when will I have access to food, will this activity expose parts of my body I am uncomfortable about, will I have to explain why I can't eat something, did I pack enough snacks/emergency glucose, will I be expending more energy than usual, do I have enough meds, when will I be able to sit down (will the chairs be padded to support my boney butt), will the brain fog caused by my fatigue get noticed – why can't I be normal? Lipodystrophy is an extremely difficult condition to live with, and anything that can be done to support patients and their families, offer some respite, and/or ideally treat the condition and alleviate some of the suffering, should be a priority.

4. Experiences With Currently Available Treatments

Patient 1: I am currently treated by:

- Metformin, Invokana, Ozempic and 300+ units of insulin/day (currently using the Entuzity insulin formulation, which is very expensive)
- Multiple daily insulin injections a day are a struggle with my lack of subcutaneous fat, and I have considerable malabsorption due to fibrosis of the skin
- Fenofibrates and Vascepa (about 3$/capsule, and I take 4 a day) to control elevated triglycerides
- ACE inhibitor for hypertension, Apixaban for anticoagulation
- Sertraline for depression
- Untreated fatty liver disease

Patient 2: I am currently treated with a multitude of diabetes-related medication to address the secondary side effects of my condition. Following diagnosis at 17 I was started on metformin and unfortunately suffered years of severe GI upset as a result, which had a massive impact on my life, particularly as it coincided with my time at University. I was 22 by the time I developed lipoatrophic diabetes and I started injecting insulin just a year later. It was a real shock for me; my condition was progressing more rapidly than I had expected or hoped. It was quite an adjustment to start injecting insulin and it had a massive impact on my day-to-day life. Constant injections and blood glucose checks plus all the pills to help me control high cholesterol and high blood pressure, amongst other things. As a young adult, your peers rarely appreciate your diet restrictions or a need to avoid excessive alcohol consumption!

Now that my hunger levels are being managed by metreleptin therapy, my biggest daily challenge is fatigue. I suffer from this severely and it has a tremendous impact on my daily life. It makes it very difficult for me to do my job and employers only have so much patience. Once I get home from work, I'm so tired I'm lucky if I have the energy to cook myself a proper meal, which inevitably impacts my ability to take care of myself properly (I live alone). It also means I have little energy for anything else and so my routine becomes a repeat of work and sleep without much time to enjoy life with family and friends. This has a knock-on effect in terms of low mood and I have struggled with depression as a result.

I also experience a lot of pain related to my increased muscle mass and I've had to source a private physio for monthly sessions to ease the tension and make the pain bearable.

Unfortunately, lipoatrophic diabetes is extremely treatment resistant and metreleptin is so far the first and only treatment option available to patients that directly treats the primary condition, rather than the secondary consequences. There is a clear need for new treatments directly targeting lipodystrophy. Using conventional treatments alone, my fatty liver was 70% (at age ~25). Nothing was available to impact my hyperphagia. I was struggling to control my blood glucose, with sky high insulin requirements. There is currently nothing available to help alleviate my fatigue.

5. Improved Outcomes

Patient 1: Ever since our diagnosis, we were told there is no targeted therapy for lipodystrophy, and that it was to be medically managed for each of its metabolic and cardiovascular pathologies. This approach has never been ideal, as these treatments, at maximum dosage and frequency, still keep our parameters at suboptimal numbers.

However, metreleptin therapy is different; it is a targeted therapy for lipodystrophy.

Patient 2: The metabolics are obviously important, but documenting changes in HbA1c and triglycerides does not capture the impact a new therapy can have on the quality of life of patients and their families/carers. Without understanding/experiencing the all-consuming hyperphagia caused by lipodystrophy, there is really no way you can understand the seminal, life-changing impact removing that disabling symptom can be. In such a rare disease, it can be very difficult to obtain the required number of case studies and data points to make solely evidence-based decisions. Please don't make the mistake of making the evidence-burden too high. You just need to talk to the patients who have benefitted from this treatment. It is life-changing. It means everything to them. Quality of life (and hope for the future) – while hard to measure empirically – is key.

6. Experience With Drug Under Review

Patient 1: In my search for treatments for lipodystrophy, I came across an NIH study for the effect of metreleptin on lipodystrophy taking place in Bethesda, MD under the supervision of Dr. Philip Gorden. I was a participant of this clinical trial and received metreleptin therapy for my lipodystrophy for a duration of about 18months, from 2007-2009. I was eligible for this study as my serum leptin levels were very low. Use of the drug terminated with the clinical study ending and I was never able to get back on the therapy.

While I was on Metreleptin therapy, I experienced the following benefits:

- Almost complete reversal of moderate-severe fatty liver
- Normalization of serum triglycerides
- Complete cessation of insulin therapy, being maintained only on metformin and januvia
- Restoration of menses and improvement in acanthosis nigricans
- Improvement in satiety and not feeling hungry all the time.
- Improvement in overall perception of health.

Patient 2: Commencement of metreleptin treatment has made a huge difference to my wellbeing. One of the most noticeable benefits was the change in my satiety levels. Now I can eat a modest meal and actually feel full, a new sensation for me. No more snacking all the time to fill the constant void. I can enjoy a meal and not be looking for more. Not only does this improve my quality-of-life, but it also makes it much easier for me to keep my levels under control; blood glucose, triglycerides, etc.

As well as the reduced food intake, the metabolic effects of metreleptin have made considerable differences. My insulin requirements have dropped by over 40%. When you are severely insulin resistant you have to inject large volumes of insulin in order to get the job

done. This can be very painful and uncomfortable to do, especially when you have very little subcutaneous fat, so a reduction in insulin requirements has a big impact. The fat on my liver has dropped by almost 75%, which given the prevalence of liver disease in the lipodystrophy community, is a really positive change. Metreleptin treatment has made a massive difference to my quality-of-life and I hope to continue to see improvements in my metabolic status. Metreleptin plays a big part in helping me win the battle against my condition.

Since I was already injecting insulin, the twice-daily injections were not new to me, and this certainly helped! There is a lot of paraphernalia that comes alongside leptin administration, as the powdered drug needs to be reconstituted before it can be injected. This is mainly an issue when travelling as sometimes half my case can be taken up with all my medication and the associated equipment. However, in terms of side effects, they have all been positive: decreased hyperphasia, weight loss (associated with a reduction of visceral fat), increased insulin sensitivity, and improved diabetic control. This treatment has changed (and saved) my life. I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

7. Companion Diagnostic Test

N/A

8. Anything Else?

<u>Diabetes Canada Patient Group support letter for the Submission to CADTH for Metreleptin</u>

Diabetes Canada represents the 11.9 million Canadians living with diabetes [1],which includes those living with diabetes as a result of lipodystrophy. Lipodystrophy leads to severe insulin resistance[2] which requires individuals living with the condition to use several antidiabetic drugs and insulin. Those living with lipodystrophy often experience extremely high rates of insulin resistance which results in the use of high does of insulin, often much greater than normally required to treat diabetes[3].

Current treatments for lipodystrophy only treat the symptoms of the illness, not the root cause. As such, the current treatment for the complication of diabetes are antidiabetic drugs and insulin, both of which come with their own side effects. Diabetes itself is costly to manage and adherence to treatment is affected by costs which are not covered by their public drugs and devices coverage[4]. Even with recommended adherence to antidiabetic drugs insulin, many of those living with lipodystrophy still experience hyperglycemia which may lead to hospital admission and in some severe instances, mortality[5], Combined with the other complications people with lipodystrophy must manage because of their condition, individuals require several different treatment and medication regimes which can be difficult to co-manage.

Metreleptin is the only medication for those living with lipodystrophy that treats the cause of the condition rather than its associated complications. For individuals living with lipodystrophy, this medication means that those living with lipodystrophy may improve their quality of life through better diabetes management, as well as better management of other associated complications. This medication

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[1] Canadian Diabetes Cost Model. Ottawa: Diabetes Canada; 2016.

[2] Bindlish, S., Presswala, L. S., & Schwartz, F. (2015). Lipodystrophy: Syndrome of severe insulin resistance. *Postgraduate medicine*, *127*(5), 511–516. https://doi.org/10.1080/00325481.2015.101592

[3] Gunhan, H. G., Elbasan, O., Imre, E., & Yavuz, D. G. (2022). LIPODYSTROPHY FREQUENCY ACCORDING TO INSULIN TREATMENT REGIMEN IN TYPE 2 DIABETIC PATIENTS: IS INSULIN INJECTION FREQUENCY MATTERS IN ANALOG INSULIN ERA?. *Acta endocrinologica (Bucharest, Romania : 2005)*, *18*(2), 202–208. https://doi.org/10.4183/aeb.2022.202

[4] Diabetes and Diabetes-Related Out-of-Pocket Costs: 2022 Update. Diabetes Canada; 2022.

[5] Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1:S325.

provides the opportunity for those living with lipodystrophy to treat the cause of their condition, rather than its symptoms and as a result improve quality of life and clinical symptoms[6].

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   YES, Diabetes Canada provided a support letter (see above, section 8)

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   NO

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures
Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
<Enter Name Here>				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Sonia Rehal
Position: Director
Patient Group: Lipodystrophy Canada Foundation
Date:August 4th, 2023

[6] Cook, K., Adamski, K., Gomes, A., Tuttle, E., Kalden, H., Cochran, E., & Brown, R. J. (2021). Effects of Metreleptin on Patient Outcomes and Quality of Life in Generalized and Partial Lipodystrophy. *Journal of the Endocrine Society*, *5*(4), bvab019. https://doi.org/10.1210/jendso/bvab019

Clinician Group Input

CADTH Project Number: **SR0784-000**

Generic Drug Name (Brand Name): Metreleptin (Myalepta)

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

- With confirmed congenital generalised lipodystrophy (GL or 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 for whom standard treatments have failed to achieve adequate metabolic control.

Name of Clinician Group: <Enter Response here>

Author of Submission: Robert A. Hegele MD FRCPC Cert Endo FACP

Distinguished University Professor of Medicine

University of Western Ontario

1. About Your Clinician Group

We are a group of endocrinologists, medical geneticists, lipidologists and internal medicine specialists from across Canada linked by our common interest in the care of patients with rare lipodystrophies, a serious group of disorders for which there is no cure and which can lead to severe life-threatening complications. All geographical ancestries are represented among patients with inherited lipodystrophies, including Indigenous peoples and immigrant populations, and lipodystrophy patients receive care in specialty clinics across Canada.

2. Information Gathering

There is a longstanding history of medical diagnosis and care of Canadian patients with inherited lipodystrophies by Canadian doctors, including some signatories of this submission. This history goes back to at least the year 2000, when a laboratory in London, Ontario discovered the causative genes for two forms of partial lipodystrophy – FPLD2 and FPLD3 - in several Canadian families from the Maritimes, Ontario and Quebec (1,2). Also, Canadian patients with generalized lipodystrophy were among the first participants in the pivotal clinical trial of metreleptin in that patient group, travelling to the US National Institutes of Health to receive the treatment (3). Since that time, clinical registries of Canadian patients with various forms of lipodystrophies have been maintained as part of research databases for projects funded by CIHR, Heart and Stroke Foundation, Genome Canada and Diabetes Canada. Many members of the clinical network of Canadian physicians who provide medical care for lipodystrophy patients are also academic collaborators. Information and experience gathered about the clinical features and natural history of lipodystrophies in Canadian patients are derived from the grass-roots academic and community collaborative network of care providers.

3. Current Treatments and Treatment Goals

Lipodystrophy refers to a rare, heterogeneous group of syndromes characterised by complete or partial loss, or absence of, subcutaneous adipose tissue known as generalized lipodystrophy (GL) and partial lipodystrophy (PL) respectively (4). Without sufficient adipose tissue there is profound disruption of the body's system for regulating energy use and storage. This results in lipid accumulation in abnormal sites such as the liver, skeletal muscle, heart and pancreas. Metabolic abnormalities often occur with lipodystrophy, including insulin resistance and diabetes; hepatic steatosis; and dyslipidemia with severe hypertriglyceridemia at an early age which can cause potentially life-threatening acute pancreatitis (5).

The absolute or relatively low concentrations of leptin, due to subcutaneous adipose tissue loss, leads to symptoms such as hyperphagia which may also contribute to the metabolic abnormalities. Standard treatments for these complications, which do not

target the underlying pathophysiology are often unsuccessful. Statins, fibrates and omega 3 fatty acids are only partially helpful to control the dyslipidemia; and there is no available drug that currently targets the hepatic steatosis. In Canada we do not have a specific treatment for lipodystrophy and this represents a significant unmet need for therapy that is actually targeting the underlying pathophysiology and has been proven to ameliorate the downstream metabolic complications. Patients living with lipodystrophy in Canada are generally managed with supportive care of comorbid conditions or complications.

The 2016 Multi-society Lipodystrophy guidelines recommend diet and exercise as the foundation of care (6). All lipodystrophy patients are encouraged to consume a balanced diet and maintain a regular exercise routine but unfortunately these general measures do not correct the underlying metabolic issues. Lipodystrophy patients also have difficulty maintaining diet due to uncontrolled appetite that develops in the absence of a proper leptin signal.

Antihyperglycemic medications such as metformin, sulfonylureas or thiazolidinediones, which may be useful in some patients, and insulin is needed in most patients (4). Diabetes can be difficult to control despite the use of high doses of insulin (up to 500 - 1000 units/day). Recently, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium/glucose cotransporter 2 (SGLT2) inhibitors have bee added to the treatment to manage hyperglycemia but they are only partially helpful in some patients and do not eliminate the need for insulin (4). Furthermore, these agents do not address underlying leptin deficiency.

Also, severe hypertriglyceridemia and previous history of pancreatitis can be limiting factors for the GLP-1 agonist use in lipodystrophy. These available medications offer general supportive care for the comorbid complications of lipodystrophy but leave an unmet medical need since these conventional therapies fail to achieve adequate metabolic control in vast majority of patients with GL and in a clinically relevant subset of patients with PL. Further, conventional therapies, such as insulin can exacerbate hyperphagia, making it difficult to maintain an adequate diet and further fuelling the surplus of energy that becomes abnormally stored as ectopic fat deposition in the liver and/or muscle. These patients become resistant or refractory to supportive care and require numerous medications to manage comorbid conditions of lipodystrophy (6). Conventional therapies do not address the fundamental root cause which is a deficiency of leptin and despite supportive care patients face the risk of early mortality as a result of uncontrolled metabolic disease (6).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There are no approved drugs in Canada for the treatment of either generalized lipodystrophy (GL) or partial lipodystrophy (PL). There is no cure for lipodystrophy (LD) and no currently approved treatment that can regrow adipose tissue. The current supportive care consists of the treatment of metabolic complications associated with the disease and includes the following: low fat diet, antidiabetic medications (metformin, sulfonylureas, glitazone, SGLT2 inhibitors, GLP-1 agonists and insulin), and lipid-lowering medications, (fibrates, niacin, fish oils, and statins). These treatments are usually inadequate due to the severity of metabolic abnormalities in patients with GL and more severe forms of PL (4). Conventional therapies also have no effect or can even exacerbate hyperphagia, making it difficult to maintain an adequate diet and further fuelling the surplus of energy that gets stored as ectopic fat deposition in the liver and/or muscle.

There is a significant unmet medical need for a therapy that aims at correcting the underlying pathophysiology of the lipodystrophic state, leptin deficiency, as conventional treatments fail in the majority of patients with GL and in a subset of patients with PL and increase their risk of end organ damage and early death. Natural history studies highlighted the early onset of severe metabolic complications in patients with lipodystrophy and that these patients develop end-organ complications at a young age. Studies have reported the high disease burden in LD patients despite being on conventional therapies (6).

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Metreleptin is the first and only medicine to treat lipodystrophy that targets the underlying cause of lipodystrophy and is considered first line treatment for GL. It has been approved and successfully used clinical in several countries since the mid-2000's (3). 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 signals through the JAK/STAT transduction pathway. Metreleptin ameliorates hyperphagia. In addition it improves hepatic and peripheral insulin sensitivity, via direct effects as well as an indirect effect due to reduced hyperphagia. Metreleptin has been approved for GL and PL in major markets globally for many years and has an established benefit/ risk profile. Further, the published 2016 Multi-Society Lipodystrophy Guidelines have suggested that metreleptin therapy should be considered early to prevent the comorbidities of LD in children with GL (6).

In PL metreleptin therapy would be appropriate for a subgroup of patients, estimated at 10-20%, on the severe side of the spectrum who develop clinical features and complications that can be as severe as in GL. However, the majority of patients with PL can usually be adequately managed with supportive and existing therapies directed at individual components of the multi-system manifestations. However, the most severely affected PL patients have metabolic deficits similar to GL patients in terms of the severity and the refractoriness of their metabolic state and definitely would benefit the most from leptin therapy (7).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Lipodystrophy is diagnosed based on clinical evaluation (6). Physicians have several tools at their disposal to diagnose lipodystrophy, including physical and metabolic signs, patient history (both clinical and family), routine blood tests, serum leptin measurements (on a research basis), skinfold measurements, radiology such as MRI scanning of subcutaneous fat, liver and muscle, and genetic testing. Lipodystrophy syndromes show considerable heterogeneity, and different subtypes have been classified based on the extent of fat loss and the time of symptom onset. The two major categories are generalized lipodystrophy (GL) and partial lipodystrophy (PL).

In most cases, physicians can diagnose lipodystrophy by evaluating clinical features along with laboratory, imaging, and genetic test results, without the need for more complex tests (6). However, it is essential for physicians to recognize that GL and PL have significant differences, and being aware of these distinctions can greatly aid in making an accurate diagnosis.

Metreleptin is the primary first line treatment for GL (6). Conventional treatments cannot address the root cause of the disease, which involves a near complete lack of adipose tissue and a resulting absolute deficiency of leptin. In some patients, even staggeringly high doses of insulin are ineffective due to severe insulin resistance. There is a critical need for a therapy that corrects the fundamental underlying deficiency in lipodystrophy and effectively improves the associated metabolic disorders that arise secondarily.

Patients with GL are at risk of serious, life-threatening metabolic complications, including recalcitrant insulin resistant diabetes and its life-threatening cardiovascular, renal, and neurological complications, liver fibrosis, and life-threatening acute pancreatitis secondary to severe hypertriglyceridemia (5). Patients with Berardinelli-Seip congenital GL can present with these complications at much earlier ages than usual (e.g. Diabetes by age 15-20 years), causing a significant burden on the individuals, their families and the health care system. Clinical studies have documented significant objective improvements with metreleptin, which were further confirmed in real-life situations. Metreleptin treatment leads to substantial enhancements in glycemic control and TG levels. Some patients were able to reduce or even stop using other diabetes and lipid-lowering therapies.

Additionally, metreleptin treatment has shown to improve liver function tests and liver volume (7). It also aids in appetite regulation, providing patients with a sense of satiety. Metreleptin offers various clinical benefits, such as improvements in cutaneous acanthosis nigricans, reduced proteinuria, normalized gonadotropin secretion leading to proper puberty progression, and normalized menstrual periods in females. It may also potentially enhance quality of life and survival.

Notably, metreleptin is an important treatment option for pediatric patients as well. It leads to significant improvements in the metabolic profiles of children with lipodystrophy. Current guidelines recommend early treatment with metreleptin in children with GL to prevent serious complications.

In PL, the extent of adipose tissue loss varies more compared to patients with GL, and the presence and severity of metabolic abnormalities also show greater variability than in GL. Clinical studies of PL have demonstrated that metreleptin treatment leads to significant reductions in HbA1c, fasting triglycerides, fasting glucose, and liver volume. Improvements in NASH (non-alcoholic steatohepatitis) histopathology were also reported. These improvements were more prominent in a subgroup of patients with more severe metabolic disease (7). This population of PL patients can exhibit metabolic issues similar to those seen in GL patients. Those with more severe metabolic abnormalities often do not respond well to standard treatment approaches, making them a group with higher unmet medical needs (i.e., insufficient metabolic control despite the use of currently available anti-diabetes and lipid therapies).

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The clinical response to metreleptin is evaluated by monitoring changes in metabolic control. In clinical studies, patients with GL and a subgroup of PL patients with uncontrolled metabolic disease experienced meaningful and statistically significant improvements in HbA1c, indicating improved insulin sensitivity, as well as significant reductions in serum triglycerides. The observed reductions in HbA1c during metreleptin treatment are associated with notable reductions in complications linked to high blood sugar levels.

A minimum clinical response is defined as at least:

- 0.5% hemoglobin A1c (HbA1c) reduction and/or 25% reduction in insulin requirements; and/or
- 15% reduction in serum triglycerides.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

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.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Metreleptin can be administered by the patient once daily at the same time every day. Metreleptin can be administered any time of day without regard to the timing of meals.

6. Additional Information

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Additional information is available upon request from Robert A. Hegele MD, FRCPC, FACP, Professor of Medicine, University of Western Ontario, London ON, email: hegele@robarts.ca

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

4. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

The submission was completed by the clinician group.

5. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

The information was collected by the clinician group.

6. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Robert A Hegele MD FRCPC

Position: Staff Physician, London Health Sciences Centre, London ON

Date: 01-Aug-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acasti	X			
Aegerion	X			
Akcea/Ionis	X			
Pfizer	X			
Regeneron	X			
Sanofi	X			
HLS Therapeutics		X		
Medison	X			
Novartis			X	
Amgen			X	

Declaration for Clinician 2

Name: Tisha Joy MD FRCOC

Position: Associate Professor (Endocrinology & Metabolism), St. Joseph's Health Centre, London, Ontario

Date: August 2, 2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen				X
Continuing Professional Development Network Association		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Tugce Bulakbasi Balci MD FRCPC

Position: Staff Physician, Genetics, London Health Sciences Centre

Date: 1 August 2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Medison	X			

Declaration for Clinician 4

Name: Jean Bergeron MD

Position: Staff Physician, Lipidology and Medical Biochemistry, CHU de Québec-Université Laval

Date: 02-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Akcea/Ionis	X			
Arrowhead	X			
Eli-Lilly	X			
HLS Therapeutics	X			
LIB Therapeutics	X			
Medison	X			
New Amsterdam Pharma	X			
Novartis	X			
Novo Nordisk	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Marie Pigeyre MD FRCPC

Position: Assistant Professor, Medicine department, McMaster University

Date: 03-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Medison	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Satya Dash MD

Position: Staff Physician, University Health Network

Date: 03-Aug-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
NovoNordisk		x		
Eli Lilly	X			
Medison	X			