



Zorginstituut Nederland

Relative effectiveness report metreleptin (Myalepta®) for treatment of lipodystrophy

Element of the assessment of drugs for incorporation into the
drug reimbursement system

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Abbreviations

Abbreviation	Description
AGL	Acquired Generalized Lipodystrophy
APL	Acquired Partial Lipodystrophy
BID	Twice daily
CI	Confidence Interval
CFAS	Controlled Concomitant Medication Full Analysis Set
CGL	Congenital Generalized Lipodystrophy
CHMP	Committee for Medicinal Products for Human Use
CRM	Commission Reimbursement of Medicines
CTG	Commissie Tegemoetkoming Geneesmiddelen
EAP	Expanded Access Program
EMA	European Medicine Agency
EMR	Electronic Medical Record
EPAR	European public assessment reports
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
FPL	Familial Partial Lipodystrophy
FU	Follow up
GL	Generalized Lipodystrophy
HbA1C	Glycohemoglobin
LD	Lipodystrophy
LOCF	Last Observation Carried Forward
LUMC	Leiden University Medical Center
MCID	Minimal clinically important difference
MMRM	Mixed-effects model for repeated measures
NAFLD	Non-Alcoholic Fatty Liver Disease
NHS	National Health Service
PL	Partial Lipodystrophy
PCOS	Polycystic Ovarian Syndrome
QD	Once daily
QoL	Quality of Life
RCT	Randomised controlled trial
RIZIV	Rijksinstituut voor Ziekte- en invaliditeitsverzekering
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
UK	United Kingdom
UMC	University Medical Center
WAR	Wetenschappelijke Adviesraad / Scientific Advisory Board
ZIN	Zorginstituut Nederland (National Health Care Institute)

Summary

In this relative effectiveness report, Zorginstituut Nederland (ZIN) and the Belgian Commission Reimbursement of Medicines (CRM) describe the substantive assessment of the value of metreleptin (Myalepta®) for the treatment of patients two years of age and older with confirmed, congenital, generalized lipodystrophy (Berardinelli-Seip syndrome) or acquired generalized lipodystrophy on the one hand and in patients 12 years and older with familial partial lipodystrophy or acquired partial lipodystrophy (Barraquer-Simons syndrome) without adequate metabolic control under standard treatment on the other hand. Metreleptin was compared with standard supportive care based on the criteria favorable effects, unfavorable effects, experience, applicability and usability. Zorginstituut Nederland has been advised in this regard by its Scientific Advisory Board (WAR). The evaluation is part of a common evaluation in the context of the BeNeLuxA project. This report, as well as the Budget Impact Analysis will be used both by ZIN and by the CRM. The relative effectiveness report has been prepared by the Belgian Rijksinstituut voor Ziekte- en invaliditeitsverzekering (RIZIV), the Budget Impact Analysis by ZIN. Both assessment procedures are running in parallel according to the national legislation.

Lipodystrophy syndromes are clinically heterogeneous inherited or acquired ultra-rare disorders characterised by selective but variable loss of adipose tissue. Deficient adipose mass may result in ectopic lipid storage in the liver, muscle and other organs. Lipodystrophies can be classified according to the distribution of fat loss (generalized or partial) and as congenital or acquired. This yields 4 major categories: congenital generalized lipodystrophy (CGL; or Berardinelli-Seip syndrome), acquired generalized lipodystrophy (AGL; or Lawrence syndrome), familial partial lipodystrophy (FPL; or Kobberling syndrome or Dunnigan syndrome), and acquired partial lipodystrophy (APL; or Barraquer-Simons syndrome). In GL patients, metabolic complications are common and can be severe. Also in FPL patients metabolic complications are common in adulthood. In APL patients metabolic complications are uncommon. Patients with lipodystrophy, especially generalized forms, are typically hyperphagic which makes it difficult to achieve dietary restriction.

Registration of Myalepta® was based on two clinical, single arm trials in 148 patients [75 (66+9) GL and 73 (41+32) PL]. No specific data are collected about the effects of metreleptin on mortality or (disease related) quality of life. As a proxy (surrogate parameter) of micro- or macrovascular complications, metabolic disturbances (glycaemic control, normalisation of hypertriglyceridemia) were evaluated. Metreleptin was intended to be used as an adjunct to diet and best supportive care in optimal dose. HIV patients were excluded from the clinical trials.

Improvements in both HbA1c and fasting triglycerides were observed at 12 Months in the GL population and in a post-hoc defined PL subgroup (patients with baseline leptin <12 ng/ml and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/l). The effects were more pronounced in GL patients (compared with the PL subgroup), attaining near normal mean values for HbA1c at Month 12. Finally, in the overall PL population the observed effects were considerably lower and not supported by statistically significant changes in the CFAS population.

The registered indication concerns GL patients (2 years and above) and PL patients (12 years and above) not achieving adequate metabolic control by standard treatments. This population is broader than the post hoc defined PL subpopulation discussed in the EPAR. However, the limited dataset did not allow to determine clear

thresholds on metabolic parameters in order to define a target PL subpopulation. For that reason, the CHMP has also not set a threshold to define the PL target population. The registered PL population was finally defined as PL patients "without adequate metabolic control" under standard treatment. Registration was not requested for in the overall PL population.

The quality of the evidence is very low due to a limited setup of the trials: single arm studies without controls, long enrolment period (up to 14 years), limited number of patients, especially in the PL subpopulation [n=39 (31+7); PL subgroup]. Even data about matching historical controls is lacking. Moreover, the PL subpopulation in the clinical trials has been defined post hoc and not fully reflects the eligible PL population, as the study population was limited to patients with baseline leptin <12 ng/ml and HbA1c \geq 6.5% and/or triglycerides \geq 5.65 mmol/l. The uncertainties on the magnitude of the effects are considerable. Diet and the use of concomitant medication have not been optimized before study onset. So it is not clear whether these standard treatments have been sufficiently utilized in the study population to regulate their metabolic disorders. Generally, long term data are supportive for those patients still on treatment after 36 Months, but the number is very limited (GL; n=17 and PL subgroup; n=6 for data at 36 Months). In general the safety profile of metreleptin is acceptable, but there are some concerns regarding the development of neutralizing antibodies. They could potentially bind on metreleptin, but also against endogenous leptin (especially important in PL patients).

Finally, administration of metreleptin by subcutaneous injections may be difficult in patients with minimal subcutaneous adipose tissue and jeopardize treatment compliance, especially in patients already in need for insulin who have to administer subcutaneously too.

Generalized lipodystrophy

To treat the complications of leptin deficiency in adults and children 2 years of age and above with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome), the usual care is diet supplemented with antidiabetics and/or lipid-lowering agents if needed.

Metreleptin as an adjunct to diet has a therapeutic lower value compared to standard treatment with antidiabetics and/or lipid-lowering agents due to insufficient data. Because of the limited design of the clinical studies, it is not possible to assess whether the measured favorable effects can be attributed to metreleptin. Based on current data, it is not clear to what extent the standard treatment (at baseline and during the study period) has contributed to the measured effects.

In contrast to metreleptin, the standard treatments are proven to be effective in metabolic syndrome and the long-term effects are well known. Due to the lack of a matching (historical) control group, the effect of natural course is not clear either.

Partial lipodystrophy

Based on the actual data it is not possible to conclude on an added value for metreleptin as an adjunct to diet compared with standard treatment to treat the complications of leptin deficiency in adults and children 12 years of age and above with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in whom standard treatments (diet supplemented with antidiabetics and/or lipid-lowering agents in an optimal dosage) have failed to achieve adequate metabolic control. Improvements in both HbA1c and fasting triglycerides were observed in a post-hoc defined PL subpopulation (with clearly defined metabolic baseline thresholds). However, the observed effects were less pronounced compared with GL patients and the uncertainties on the magnitude of the effects are still higher because of very limited patient numbers. Additionally, data in the overall PL

population were not convincing. Also in the case of PL, the therapeutic value is lower as compared to standard treatment due to insufficient data.

Conclusion

Taking into account the uncertainties in the favorable effects and the concern regarding the development of neutralizing antibodies, ZIN and the Belgian CRM conclude it is not possible to conclude on an added value for metreleptin (Myalepta®) in patients with generalized lipodystrophy and partial lipodystrophy. Due to insufficient data it is concluded that metreleptin has no added benefit ('a lower therapeutic value') in comparison with standard treatment.

The discussion of the concept of this relative effectiveness report was completed by the Scientific Advisory Board of Zorginstituut Nederland at its meeting on 23th September 2019 and by the Belgian Commission Reimbursement of Medicines at its meeting on 8th October 2019.

Nederlandse samenvatting

In dit farmacotherapeutisch rapport beschrijven Zorginstituut Nederland en de Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) de inhoudelijke beoordeling van de waarde van metreleptine (Myalepta®) enerzijds bij de behandeling van patiënten van twee jaar en ouder met bevestigde, congenitale, gegeneraliseerde lipodystrofie (Berardinelli-Seip syndroom) of verworven gegeneraliseerde lipodystrofie en anderzijds bij patiënten van 12 jaar en ouder met familiale partiële lipodystrofie of verworven partiële lipodystrofie (Barraquer-Simons syndroom) zonder adequate metabole controle onder de standaardbehandeling. Metreleptine is daarbij vergeleken met beste ondersteunende zorg op de criteria gunstige effecten, ongunstige effecten, ervaring, toepasbaarheid en gebruiksgemak. Zorginstituut Nederland heeft zich hierbij laten adviseren door haar Wetenschappelijke Adviesraad (WAR). De evaluatie maakt deel uit van een gemeenschappelijke beoordeling in het kader van het BeNeLuxA-project. Het rapport, evenals de Budget Impact Analyse, zal zowel gebruikt worden door het ZIN als door de CTG. Het farmacotherapeutisch rapport werd voorbereid door RIZIV, het Budget Impact Analyse door het ZIN. Beide beoordelingsprocedures lopen parallel en volgen de nationale wetgeving.

Lipodystrofiesyndromen zijn klinisch heterogene, erfelijke of verworven ultra-zeldzame aandoeningen die worden gekenmerkt door selectief maar variabel verlies van vetweefsel. Een tekort aan vetweefsel kan resulteren in de ectopische opslag van lipiden in de lever, spieren en andere organen. Lipodystrofieën kunnen worden geclassificeerd volgens de verdeling van vetverlies (gegeneraliseerd of gedeeltelijk) en als aangeboren of verworven. Dit levert 4 hoofdcategorieën op: aangeboren gegeneraliseerde lipodystrofie (CGL of Berardinelli-Seip-syndroom), verworven gegeneraliseerde lipodystrofie (AGL of Lawrence-syndroom), familiale partiële lipodystrofie (FPL of Kobberling-syndroom of Dunnigan-syndroom) en verworven partiële lipodystrofie (APL of Barraquer-Simons-syndroom). Bij GL patiënten treden frequent metabole complicaties op die potentieel ernstig zijn. Ook bij FPL patiënten komen metabole complicaties vaak voor op volwassen leeftijd. Bij APL patiënten komen metabole complicaties zelden voor. Patiënten met lipodystrofie, vooral gegeneraliseerde vormen, hebben doorgaans hyperfagie, waardoor het moeilijk is om dieetbeperkingen te bereiken.

De registratie van Myalepta® was gebaseerd op twee klinische, eenarmige studies bij 148 patiënten [75 patiënten met GL (66 + 9) en 73 met PL (41 + 32)]. Er werden geen specifieke gegevens verzameld over de effecten van metreleptine op mortaliteit of (ziekte gerelateerde) levenskwaliteit. Als een proxy (surrogaatparameter) van micro- of macrovasculaire complicaties, werden metabole stoornissen (glykemische controle, normalisatie van hypertriglyceridemie) geëvalueerd. Metreleptine werd gebruikt als een aanvulling op dieet en best ondersteunende zorg (in de optimale dosis). HIV patiënten werden geëxcludeerd uit de klinische studies.

Verbeteringen van zowel HbA1c als nuchtere triglyceriden na 12 maanden, werden waargenomen in de GL-populatie en in een post-hoc gedefinieerde PL-subgroep (patiënten met baseline leptine <12 ng/ml en HbA1c ≥6,5% en/of triglyceriden ≥5,65 mmol/l). Deze effecten waren meer uitgesproken in de GL populatie (vergeleken met de PL-subgroep), waarin bijna normale gemiddelde waarden voor HbA1c bereikt werden. De geobserveerde effecten in de totale PL-populatie lagen aanzienlijk lager en werden niet ondersteund door statistisch significante veranderingen in de CFAS populatie.

De geregistreerde indicatie betreft enerzijds GL-patiënten (vanaf 2 jaar) en anderzijds PL-patiënten (vanaf 12 jaar) die geen adequate metabole controle bereiken met standaardbehandelingen. Deze PL populatie is breder dan de post hoc gedefinieerde PL-subpopulatie in de EPAR. De beperkte dataset liet echter niet toe om duidelijke drempels voor metabole parameters vast te stellen teneinde een doel-PL-subpopulatie te definiëren. Om die reden heeft de CHMP ook geen grens gesteld om de groep met PL af te bakenen. De geregistreerde PL populatie werd uiteindelijk gedefinieerd als PL patiënten "zonder adequate metabole controle" onder standaardbehandeling. Registratie werd niet gevraagd voor de totale PL-populatie.

De kwaliteit van het bewijsmateriaal is zeer laag vanwege het beperkte opzet van de klinische studies: studies met één arm zonder controles, lange inclusieperiode (tot 14 jaar), beperkt aantal patiënten, vooral in de PL subpopulatie [39 patiënten (31 +7)]. Zelfs data van gematchte historische controles ontbreekt. Bovendien werd de PL-subpopulatie post-hoc gedefinieerd en weerspiegelt deze niet volledig de geregistreerde PL-populatie. De post-hoc gedefinieerde PL studiepulatie was namelijk beperkt tot patiënten met baseline leptine <12 ng/ml en HbA1c \geq 6,5% en/of triglyceriden \geq 5,65 mmol/l. De onzekerheden over de grootte van de effecten zijn aanzienlijk. Dieet en comedicaties werden niet geoptimaliseerd vóór het begin van de studies. Het is dus niet duidelijk of deze standaardbehandelingen voldoende zijn gebruikt in de studiepulatie om hun metabolische stoornissen te reguleren. Over het algemeen zijn de lange termijngegevens ondersteunend voor de effectiviteit bij patiënten die nog steeds in behandeling zijn na 36 maanden. Het betreft echter een uitermate beperkt aantal patiënten (GL; n = 17 en PL-subgroep; n = 6 voor gegevens na 36 maanden). Over het algemeen is het veiligheidsprofiel van metreleptine aanvaardbaar, maar er is bezorgdheid over de ontwikkeling van neutraliserende antilichamen. Ze kunnen potentieel binden aan metreleptine, maar ook aan endogene leptine (hetgeen vooral belangrijk is bij PL-patiënten). In de praktijk kan het toedienen van metreleptine door middel van subcutane injecties lastig zijn in een populatie met minimaal subcutaan vetweefsel. Dit kan een impact hebben op de therapietrouw, vooral bij patiënten die insuline nemen, eveneens subcutaan toegediend.

Gegeneraliseerde lipodystrofie

Om complicaties van leptinedeficiëntie te behandelen bij volwassenen en kinderen van 2 jaar en ouder met bevestigde congenitale gegeneraliseerde LD (Berardinelli-Seip-syndroom) of verworven gegeneraliseerde LD (Lawrence-syndroom) worden deze patiënten behandeld met dieet, aangevuld met antidiabetica en/of lipidenverlagende middelen indien nodig.

Metreleptine als aanvulling op dieet heeft geen toegevoegde waarde ('een therapeutische minderwaarde') in vergelijking met standaardbehandeling met antidiabetica en/of lipidenverlagende middelen door onvoldoende gegevens.

Door de beperkte opzet van de klinische studies is het niet mogelijk te beoordelen of de gemeten gunstige effecten toe te schrijven zijn aan metreleptine. Op basis van de huidige gegevens is het niet duidelijk in hoeverre de standaardbehandeling (zowel op baseline als tijdens de onderzoeksperiode) heeft bijgedragen aan de gemeten effecten.

In tegenstelling tot metreleptine zijn de standaardbehandelingen bewezen effectief bij metabool syndroom, ook de lange termijn effecten zijn bekend. Door het ontbreken van een gematchte (historische) controle groep is het effect van natuurlijk beloop evenmin duidelijk.

Partiële lipodystrofie

Op basis van de huidige gegevens is het niet mogelijk om een meerwaarde toe te kennen aan metreleptine (Myalepta®) als aanvulling op dieet, vergeleken met de gebruikelijke behandeling (dieet, aangevuld met antidiabetica en/of lipidenverlagende middelen in een optimale dosis) om de complicaties van leptinedeficiëntie te behandelen bij volwassenen en kinderen van 12 jaar en ouder met een bevestigde familiale partiële LD of verworven partiële LD (Barraquer-Simons-syndroom), bij wie onvoldoende metabole controle bereikt wordt met de standaardbehandelingen. Verbeteringen van zowel HbA1c als nuchtere triglyceriden werden waargenomen in een post-hoc gedefinieerde PL-subpopulatie (met baseline HbA1c $\geq 6,5\%$ en/of triglyceriden $\geq 5,65$ mmol/l). De waargenomen effecten waren echter minder uitgesproken in vergelijking met GL-patiënten en de onzekerheden over de omvang van de effecten zijn nog hoger vanwege de uitermate beperkte patiënten aantallen en onduidelijkheid over de optimale inzet van de benodigde comedicaatie. Bovendien waren de data in de totale PL-populatie niet overtuigend. Ook bij PL is sprake van geen toegevoegde waarde ('een therapeutische minderwaarde') ten opzichte van standaardbehandeling door onvoldoende gegevens.

Conclusie

Rekening houdend met de onzekerheden in de gunstige effecten en met de bezorgdheid over de ontwikkeling van neutraliserende antilichamen concluderen Zorginstituut Nederland en de CTG dat het niet mogelijk is om een therapeutische meerwaarde toe te kennen aan metreleptine (Myalepta®) bij patiënten met gegeneraliseerde lipodystrofie en partiële lipodystrofie.

Door onvoldoende gegevens is geconcludeerd dat metreleptine geen toegevoegde waarde ('een therapeutische minderwaarde') heeft ten opzichte van standaardbehandeling.

De bespreking van dit farmacotherapeutisch rapport is door de Wetenschappelijke Adviesraad van Zorginstituut Nederland afgerond in haar vergadering van 23 september 2019 en door de Belgische Commissie Tegemoetkoming in haar vergadering van 8 oktober 2019.

1 Introduction

1.1 Occasion

In this report Zorginstituut Nederland (ZIN) and the Belgian Commission Reimbursement of Medicines evaluate the value of metreleptin (Myalepta®) for the treatment of lipodystrophy compared with standard or usual care. The evaluation is part of a common evaluation in the context of the BeNeLuxA project. The report, as well as the Budget Impact report will be used both by ZIN and by the Belgian Rijksinstituut voor Ziekte- en invaliditeitsverzekering (RIZIV). The relative effectiveness report has been prepared by RIZIV, the Budget Impact report by ZIN. Both assessment procedures are running in parallel according to the national legislation.

<i>Metreleptin (Myalepta®)</i> <i>Powder for solution for injection; 3mg, 5.8mg and 11.3mg</i>																	
<i>Registered indication:</i>	<p>Myalepta® is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:</p> <ul style="list-style-type: none"> 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 or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. 																
<i>Posology:</i>	<p>The recommended daily dose of metreleptin is based on body weight as provided in Table 1.</p> <p>In order to ensure patients and carers understand the correct dose to be injected, the prescriber should prescribe the appropriate dose both in milligrams and the volume in millilitres. In order to avoid medication errors including overdose, dose calculation and dose adjustment guidelines below should be followed. A review of the patient's self-administration technique is recommended every 6 months whilst using Myalepta®.</p> <p>Actual body weight at initiation of treatment should always be used when calculating the dose.</p> <p>Table 1 Metreleptin recommended dose</p> <table border="1"> <thead> <tr> <th>Baseline weight</th> <th>Starting daily dose (injection volume)</th> <th>Dose adjustments (injection volume)</th> <th>Maximum daily dose (injection volume)</th> </tr> </thead> <tbody> <tr> <td>Males and females ≤ 40 kg</td> <td>0.06 mg/kg (0.012 mL/kg)</td> <td>0.02 mg/kg (0.004 mL/kg)</td> <td>0.13 mg/kg (0.026 mL/kg)</td> </tr> <tr> <td>Males > 40 kg</td> <td>2.5 mg (0.5 mL)</td> <td>1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)</td> <td>10 mg (2 mL)</td> </tr> <tr> <td>Females > 40 kg</td> <td>5 mg (1 mL)</td> <td>1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)</td> <td>10 mg (2 mL)</td> </tr> </tbody> </table> <p><i>Dose adjustments</i> Based on clinical response (e.g. inadequate metabolic control) or other consideration (e.g. tolerability issues,</p>	Baseline weight	Starting daily dose (injection volume)	Dose adjustments (injection volume)	Maximum daily dose (injection volume)	Males and females ≤ 40 kg	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)	Males > 40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)	Females > 40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
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	<p>excessive weight loss especially in paediatric patients), the dose may be decreased, or increased to the maximum dose listed in Table 1. The maximum tolerated dose may be less than the maximum daily dose, outlined in Table 1, as evidenced by excessive weight loss, even if metabolic response is incomplete.</p> <p>A minimum clinical response is defined as at least:</p> <ul style="list-style-type: none"> ○ 0.5% HbA1c reduction and/or 25% reduction in insulin requirements and / or ○ 15% reduction in triglycerides (TGs)
<i>Particularities:</i>	Orphan drug, registration under exceptional circumstances.
<i>Mechanism of action:</i>	<p>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. Only the metabolic effects of metreleptin have been studied. No effects on the distribution of subcutaneous fat are expected.</p>
<i>Claim of the company:</i>	Reimbursement of Myalepta® for the registered indication.

1.2 Background

1.2.1 Disease

Lipodystrophy (LD) syndromes are clinically heterogeneous inherited or acquired ultra-rare disorders characterised by selective but variable loss of adipose tissue, primarily subcutaneous fat (EPAR). Reduced capacity and dysfunction of adipose mass may result in reduced leptin release and hypoleptinemia, in contrast to obese patients, presenting with elevated leptin release (Jazet 2013). The leptin deficiency observed in patients with LD results in a significant reduction in the ability to regulate hunger and energy, as well as glucose and fat metabolism (EPAR).

Lipodystrophies can be classified according to the distribution of fat loss (generalized or partial) and as congenital or acquired. This yields 4 major categories: congenital generalized lipodystrophy (CGL; or Berardinelli-Seip syndrome), acquired generalized lipodystrophy (AGL; or Lawrence syndrome), familial partial lipodystrophy (FPL; or Kobberling syndrome or Dunnigan syndrome), and acquired partial lipodystrophy (APL; or Barraquer-Simons syndrome) (Gupta 2017). Lipodystrophy syndromes caused by HIV or antiretroviral treatments won't be discussed, as patients with HIV were not included in Myalepta® registration studies.

The only true diagnostic determination of the subtype among the 4 major categories of LD is an identified genetic mutation. Without that, the subtype is determined by age of onset (generally earlier in generalised versus partial; generally earlier in congenital/familial versus acquired), patient presentation (more evenly distributed fat loss in generalised versus partial), and awareness of concomitant variables (predilection to autoimmune diseases in acquired versus congenital/familial) (EPAR). According to the clinical expert in the Netherlands treating patients with lipodystrophy [Leiden University Medical Center (LUMC)], diagnosing acquired partial lipodystrophy is challenging. Patients can be diagnosed through different routes: geneticist,

cardiologist (cardiomyopathy), neurologist (neuropathy) or internist (metabolic abnormalities / liver disease). Acquired LD can even occur after chemotherapy.

Differential diagnosis includes conditions presenting with severe weight loss (malnutrition, anorexia nervosa, uncontrolled diabetes mellitus, thyrotoxicosis, adrenocortical insufficiency, cancer cachexia, HIV-associated wasting, chronic infections) (Brown 2016).

1.2.2 *Symptoms and severity*

The disease is associated with increased morbidity and mortality, as well as impaired quality of life (EPAR).

Deficient adipose mass may result in ectopic lipid storage in the liver, muscle and other organs and cause insulin resistance, which may lead to diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD). Hypertriglyceridemia may predispose patients to serious conditions such as acute pancreatitis. Described major causes of mortality in lipodystrophy syndromes include heart disease, liver disease, kidney failure, acute pancreatitis and sepsis (Brown 2016). Lifespan in patients with Berardinelli-Seip CGL may be cut by 30 or more years. The majority of these young patients die of liver disease and infection (Lima 2018).

Patients with lipodystrophy, especially generalized forms, are typically hyperphagic due to leptin deficiency. Dietary restriction is challenging to achieve (Brown 2016).

Generalised lipodystrophy (GL) (Brown 2016)

CGL and AGL are characterized by near total absence of body fat, with generalized muscularity in CGL.

CGL is an autosomal recessive disorder with near-complete lack of fat starting at birth or infancy. Multiple genetic causes have been identified. Metabolic complications are frequent and may be severe. Patients can present with cardiomyopathy or rhythm disturbances.

AGL is more common in females (females:males, 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat. It is often associated with autoimmune disease and as in CGL metabolic complications are frequent and can be severe.

Partial lipodystrophy (PL) (Brown 2016)

FPL is usually inherited in an autosomal dominant way. The disease is characterized by loss of fat affecting the limbs, buttocks, and hips. Loss of fat usually occurs around puberty. Muscular hypertrophy is common. Metabolic complications are common in adulthood, with increased risk of coronary heart disease and occasionally early cardiomyopathy.

APL is more frequent in females (females:males, 4:1) and usually begins in childhood or adolescence. It's characterised by absence of fat in the upper body with increased fat in the lower body. Metabolic complications are uncommon.

1.2.3 *Prevalence and incidence*

Not uncommon with rare diseases is the difficult estimation of LD prevalence and incidence, which is hard due to the small patient numbers and the possible underdiagnoses and underreporting of lipodystrophy. As a result, patients are often diagnosed late during the course of their disease. This is partly related to the lack of firm diagnostic criteria.

A literature search carried out by Aegerion resulted in one study in which the prevalence of LD was estimated using data of electronic medical record databases in Germany and the United Kingdom (UK). Generalized lipodystrophy (GL) was estimated to be 0.23-0.9/million and partial lipodystrophy (PL) (all subgroups included) prevalence was 1.2-2.5/million (Chiquette 2017).

Extrapolating the prevalence of GL to the Netherlands (17.1 million inhabitants) and Belgium (11.3 million inhabitants) would yield in 4 to 15 GL patients in the Netherlands and 3 to 10 GL patients in Belgium. The estimated number of patients with PL is 20 to 43 patients in the Netherlands and 13 to 28 in Belgium. Not all PL patients will be treated with metreleptin. It is expected that about 10 to 20% of all PL patients are eligible for treatment with metreleptin as they are able to manage their disease with the other treatments for their comorbidities.

Data from the expanded access program in the UK indicate that currently 26 patients are being treated in this program. Of these 26 patients there are 9 patients with GL and 17 patients with uncontrolled PL. It is expected that the number of patients on this expanded access program is a good representation of the number of eligible patients in the UK.

Extrapolating this UK data to the Netherlands and Belgium would yield in 6 to 8 patients (2-3 GL and 4-5 uncontrolled PL) in the Netherlands and 4 to 5 patients in Belgium (1-2 GL and 3 uncontrolled PL).

Dutch expert opinion indicates that currently 40 to 45 PL patients have been diagnosed in the Netherlands of which 4 to 6 patients could become candidates for treatment with metreleptin in the coming three years. However, as a result of education of clinicians about LD, the knowledge could increase awareness and could result in some additional eligible patients. This results according to Aegerion in maximum 3 GL patients and 8 uncontrolled PL patients that are eligible for treatment with metreleptin in the coming three years.

According to Belgian expert opinion, there are 15 patients LD patients in Belgium. Currently, 3 patients are treated with metreleptin (2 GL and 1 PL patients) and two more PL patients might be candidates for metreleptin treatment. According to Aegerion, a maximum of 3 GL patients and 5 uncontrolled PL patients might be in need of treatment with metreleptin in the coming three years.

1.2.4 *Standard treatment or usual care*

There are no Dutch or Belgian guidelines for the management of lipodystrophy. However, in 2016 a multi-society practice guideline has been published (Brown 2016).

There is actually no cure for lipodystrophy. Current therapies aim to prevent or ameliorate the comorbidities due to lipodystrophy syndromes. Diet is recommended as the cornerstone of therapy for metabolic complications of lipodystrophy. Complementary, exercise should be encouraged. However, some subtypes of lipodystrophy predispose to cardiomyopathy. Those patients should undergo cardiac evaluation before initiating exercise. In case of hepatosplenomegaly and lytic bone lesions strenuous exercise should be avoided as well.

The table below (of the submission file) provides an overview of the recommended additional treatments for specific co-morbidities being outlined in the multi-society practice guideline (Brown 2016). The national treatment guidelines for diabetes (and other metabolic disorders) may diverge from this multi-society practice guideline.

Co-morbid condition arising as a result of LD	Management
Diabetes	Metformin is a first-line agent for diabetes and insulin resistance. Insulin is effective for hyperglycaemia. In some patients, concentrated preparations and high-doses may be required. Thiazolidinediones may improve metabolic complications in PL but should only be used with caution in GL.
Dyslipidaemia	Statins should be used concomitantly with lifestyle modification (after consideration of age, reproductive status, and tolerance). Fibrates and/or long-chain omega-3 fatty acids should be used for triglycerides >500 mg/dL and may be considered for triglycerides >200 mg/dL.
Hypertension	Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line treatments for hypertension in patients with diabetes.
Liver disease	In NAFLD not associated with LD, diet and exercise are first-line treatments, and among pharmacological treatments, vitamin E (in children and adults) and pioglitazone (in adults) have shown the most consistent benefit for liver histopathology. However, these treatments have not been studied in patients with LD and are not approved for NAFLD.
Cosmetic treatment	Patients should be assessed for distress related to LD and referred as necessary to mental health professionals and/or plastic surgeons.
Abbreviations: GL, generalised lipodystrophy; LD, lipodystrophy; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; PL, partial lipodystrophy	

The guideline recommends the use of metreleptin (with diet) in **generalized lipodystrophy** as a first-line treatment for metabolic and endocrine abnormalities. Furthermore it may be considered for prevention of these comorbidities in children and for hypoleptinemic (leptin < 4 ng/ml) patients with partial lipodystrophy and severe metabolic derangements [HbA1c > 8% and/or triglycerides > 500 mg/dl (5.65 mmol/l)].

The guideline was published before market authorisation of Myalepta® in Europe. The Summary of Product Characteristics (SmPC) of Myalepta® mentions “only the metabolic effects of metreleptin have been studied. No effects on the distribution of subcutaneous fat are expected.” This means that metreleptin has no cosmetic effects.

The registered indication is broader than the guideline recommendations (no thresholds for baseline leptin, HbA1c and TG in PL patients).

2 Method of systematic literature search

2.1 Question

What is the therapeutic value of metreleptin (Myalepta®) as an adjunct to diet and best supportive care for patients with lipodystrophy compared with standard treatment / usual care?

2.1.1 PICO

Table 1: PICO

Patient population	<p>1. Patients \geq 2 years old with confirmed generalized lipodystrophy</p> <p>2. Patients \geq 12 years old with confirmed partial LD for whom standard treatments have failed to achieve adequate metabolic control. (= registered indication)</p> <p>Exclusion; patients being diagnosed with HIV</p>
Intervention	Metreleptin (registered posology), as an adjunct to diet and best supportive care. Medications in optimal (or maximal tolerable) dose
Control	<p>Best supportive care (standard treatments in optimized dosages, to achieve metabolic control).</p> <p>In case a direct comparison is lacking, a comparison with matching historical controls can be considered.</p>
Outcomes	<p>Important outcome measures</p> <ul style="list-style-type: none"> ○ Most relevant outcome measures in LD patients are mortality and macro- and microvascular complications due to diabetes / metabolic dysregulation. As mortality, macro- and microvascular complications are long term outcome measures, surrogate endpoints on metabolic dysregulation, as glycohemoglobin (HbA1c) and triglycerides (TG) are acceptable. ○ Safety ○ Quality of life <p>Many other outcome measures are possible in LD patients, as hyperphagia, non-alcoholic steatohepatitis, effects on growth and puberty, etcetera. As they are correlated with parameters on metabolic dysregulation and/or quality of life, they will not be considered separately.</p>
Relevant follow-up period	In order to have insight in the effects on mortality, macro- and microvascular complications, a time span of several years is necessary. A follow-up period of at least one year is acceptable to measure short term effects using surrogate biochemical endpoints as a measure of metabolic dysregulation.
Study design	In order to support the therapeutic value of metreleptin compared with best supportive care, preference is given to direct comparative randomised controlled phase 3 trials. Considering the rare nature of the disease, indirect comparisons or non-comparative studies can support the evidence.

2.1.2 *Outcome measures and clinical relevance*

Overall survival

As metabolic complications are common in patients with lipodystrophy, overall survival is a crucial outcome measure. Potential effects on mortality are not expected to be measurable in short term trials. Long term (registry) studies are necessary to collect mortality data.

Macro- and microvascular complications

Also, macrovascular (coronary, cerebrovascular, and peripheral vascular diseases) and microvascular complications (retinopathy, nephropathy, and neuropathy) of metabolic dysregulation are crucial long term outcome measures. As diabetes and hypertriglyceridaemia are the primary metabolic abnormalities in patients with LD, glycohemoglobin (HbA1C) and fasting serum triglycerides (TG) are acceptable surrogate endpoints. These surrogate endpoints are considered clinically relevant by the CHMP in view of the role of metabolic abnormalities in morbidity and mortality associated with LD. Fasting plasma glucose (FPG) levels can be supportive. Those parameters are measurable in a shorter time span. However, even though these surrogate parameters have been established in diabetes and cardiovascular diseases, their exact predictive value in lipodystrophy has not been validated. A distinct correlation of these parameters with patient relevant outcomes in leptin deficiency has not been established.

In people without diabetes, HbA1c values are between 4 and 6%. HbA1c values of 7% and over are associated with long term complications of diabetes. Normal fasting serum TG are below 1.7 mmol/l. Values between 2.0 and 6.0 mmol/l are considered slightly to moderately elevated. Highly elevated values above 11.3 mmol/l are associated with an elevated risk for pancreatitis. Normal values for FPG are between 4.4 and 6.4 mmol/l (<https://www.nvkc.nl/>).

In the SmPC of Myalepta® a minimum clinical response in order to increase the dose is defined as "a 0,5% HbA1C reduction and/or 25% reduction in insulin requirements" and/or "a 15% reduction in TGs". However, no clear cut minimal clinically important differences (MCIDs) for HbA1c and fasting serum TGs have been defined and validated. Concerning HbA1C, it should be considered that even apparently small reductions have been shown to be clinically relevant in terms of risk reduction of diabetic complications, according to the EMA guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1). However, effects should be evaluated in relation to baseline values. In the responder analyses in the registration studies, a HbA1c reduction of at least 1% was used as a lower border, which is supported by a clinical expert (LUMC). In view of the clear correlation between diabetes complications and HbA1c, a HbA1c reduction of at least 1% can generally be considered as a clinically relevant lower border in those populations with LD.

For fasting serum TG a reduction of at least 30% was used in the responder analyses of the registration studies. Obviously, data to support a 30% reduction as being clinically relevant are lacking.

Both for HbA1c and fasting serum TG, it should be interesting to have insight into the percentage of people reaching normal or near-normal values.

Quality of life (QoL)

As quality of life in patients with lipodystrophy can be reduced in many different ways, improvement in QoL can be considered an important outcome. However, no specific QoL scales have been developed and validated in patients with lipodystrophy. More generic scales to measure the impact on QoL are acceptable.

Serious adverse events

Serious adverse events are also considered crucial outcomes. Therefore the incidence of adverse events grade 3-5, as well as discontinuations due to adverse events will be analysed as short term parameters. Long term follow-up and registry data are necessary in order to evaluate the potential low frequency serious adverse events, as well as detrimental effects in the long term.

2.2 Search strategy

In the evaluation, the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) have been used.

In order to obtain relevant data out of scientific research we performed a literature search in PubMed and the Cochrane library in April 2019 concerning publications on metreleptin treatment in LD patients. The exact search strategy has been described in annex 1.

2.3 Selection criteria

In- and exclusion of detected literature was based on abstracts. If articles could not be excluded based on the abstract, whole articles were viewed.

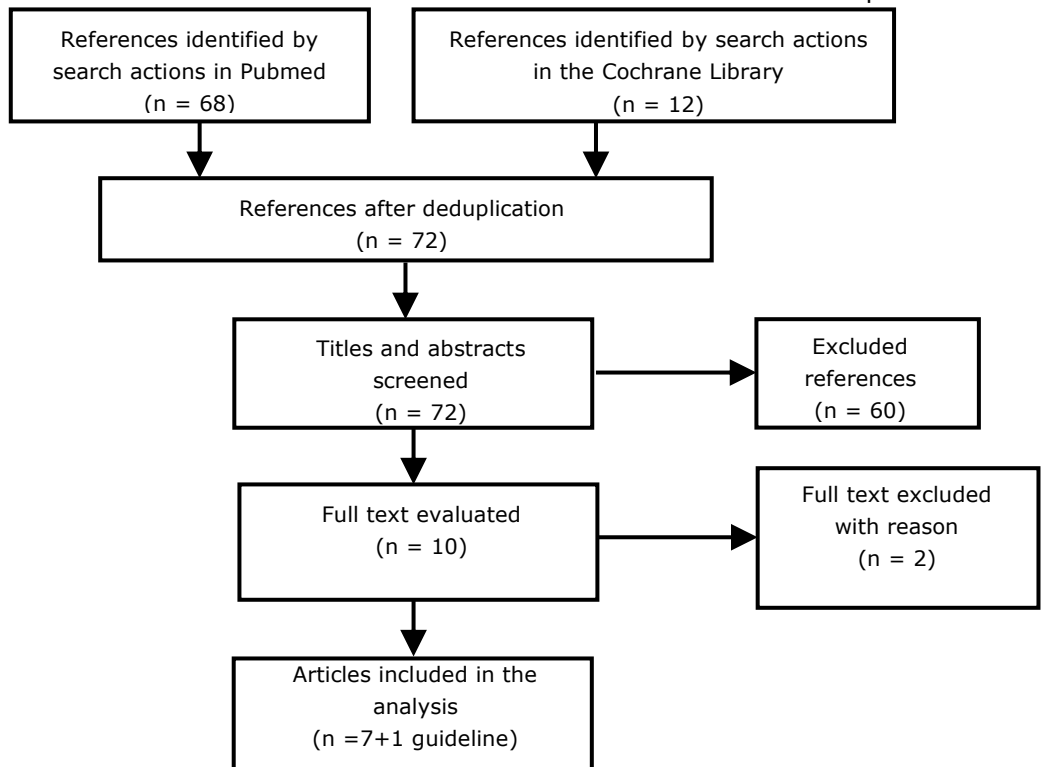
Clinical trials evaluating the efficacy on mortality, macro- and microvascular complications and/or quality of life, as well as trials evaluating adverse events of metreleptin in patients with lipodystrophy were included. Also guidelines on the use of metreleptin in patients with lipodystrophy were included.

Case reports (≤ 5 patients), (Conference) abstracts, studies concerning HIV-related lipodystrophy, and animal studies were excluded.

3 Results

3.1 Results search strategy

The search strategy resulted in 72 references. 8 published references met the inclusion criteria. The PRISMA flowchart below visualizes the selection process.



The characteristics of the selected studies are shown in annex 2. The excluded studies with reason are shown in annex 3. The included guidelines and other sources are shown in annex 4.

Two relevant clinical trials have been identified; study NIH 991265/20010796 and study FHA101, which have been used for registration. The selected publications (7) all report results of the 2 trials. The company has also provided the clinical study reports of both clinical trials (FHA101 without additional tables) to support the published data.

Besides the data in the EPAR, long term results published after registration, were evaluated.

3.2 Characteristics of the included studies

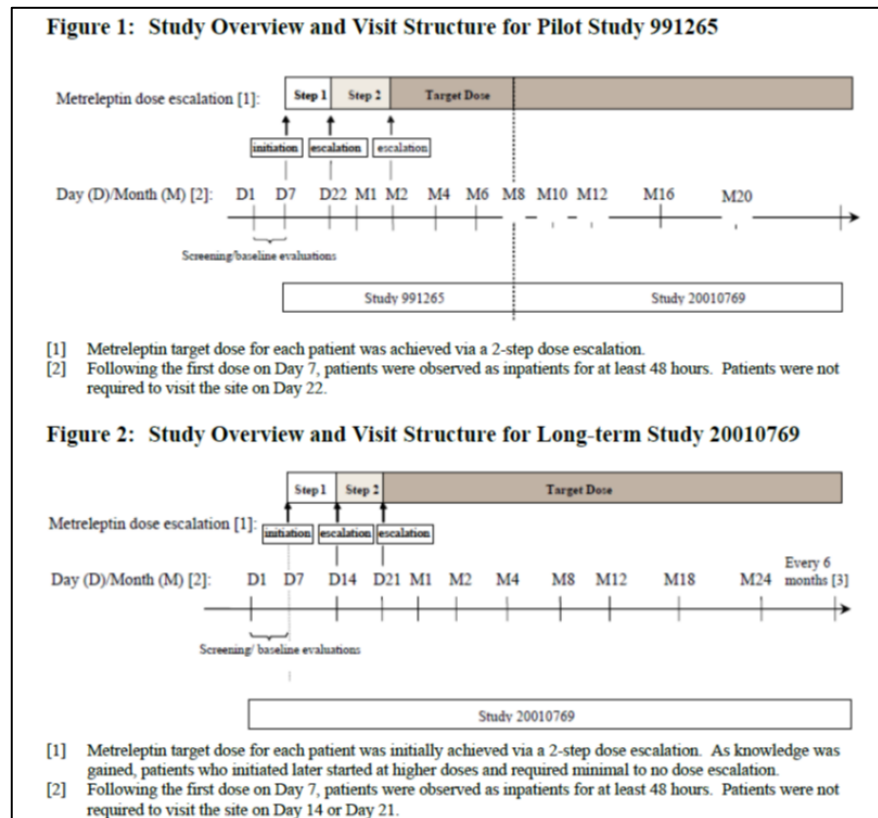
3.2.1 Study design

Main study: NIH 991265 / 20010769

Study NIH 991265 was a pilot, open-label, single-arm, dose-escalation study to determine the safety and efficacy of short-term leptin replacement (up to 8 months). Study 20010769 allowed for the rollover of patients from the pilot study, as well as

for direct enrolment of new patients. Both studies are considered together. Patients were enrolled between 2010 and 2014.

The study design is depicted below (EPAR):



Dosing of metreleptin in studies 991265/20010769 was empirical and evolved to the registered posology. Anti-hyperglycaemic and lipid-lowering regimens were modified if clinically indicated.

Based on the NIH study the dosing recommendations below were proposed:

SEX/ WEIGHT	STARTING DAILY DOSE (INJECTION VOLUME)	DOSE ADJUSTMENTS (INJECTION VOLUME)	MAXIMUM DAILY DOSE (INJECTION VOLUME)
Males and Females ≤40 kg	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Males >40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Females >40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

The primary efficacy analyses were performed using the Full Analysis Set (FAS), defined as all patients who received at least 1 dose of study drug and who had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit. In study NIH 991265/20010769, one patient in the PL subgroup had a >1000% increase from baseline to Month 12 for TG levels (from 3.0 mmol/l to 37.7 mmol/l). The patient was excluded from the study by the investigator 2 days prior to Month 12 assessment for noncompliance with study drug administration. The results for the co-primary endpoints are shown for the FAS, excluding this patient.

Post-hoc subgroup analyses were performed in patients with PL who appeared to have clinically similar metabolic disturbances as patients with GL (further denoted as PL subgroup), according to the original indication being sought: HbA1c $\geq 6.5\%$ and/or triglycerides ≥ 5.65 mmol/L at baseline (note: not anymore specified in the final indication).

Statistics: As described in the EPAR "Actual change from baseline in HbA1c and actual and percent change from baseline in fasting triglyceride levels were summarised using descriptive statistics and 95% confidence intervals (CIs). P-values were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α -level of 0.025. A last observation carried forward (LOCF) method was used to impute any missing Month 12 results. The imputation only included results that were at least 6 months (180 days) post-baseline."

FHA101

The supportive study FHA101 was an open label, single arm study with GL and PL patients ≥ 5 years, diagnosed with diabetes mellitus and/or hypertriglyceridemia with TG > 200 mg/dl.

Dosing was empirical and evolved to the registered posology.

A retrospective analysis was also performed for the PL subgroup. Study NIH 991265/20010769 included specific eligibility criteria for leptin levels (< 12 ng/mL for females and < 8 ng/mL for males > 5 years). As study FHA101 did not have set leptin levels for study entry, the PL subgroup definition for this study required patients to have leptin levels < 12 ng/mL to be consistent with the entry criteria for Study NIH 991265/20010769. Only patients enrolled at one study site (the University of Michigan study site) had baseline leptin levels measured; all patients in the PL subgroup are from that single study site.

Statistics: The initial purpose of the treatment 'Investigational New Drug (IND)' study was descriptive, so no statistical inferences were planned.

Endpoints

The co-primary efficacy endpoints in both trials were defined as:

- Actual change from baseline in HbA1c at Month 12, and
- Percent change from baseline in fasting serum triglycerides at Month 12

Key secondary efficacy endpoints were responder analyses at Month 12, and a change from baseline in fasting plasma glucose levels:

- Proportion of patients achieving target actual decreases of:
 - $\geq 1\%$ decrease in HbA1c or $\geq 30\%$ decrease in fasting serum triglycerides at Month 12;
 - $\geq 1,5\%$ decrease in HbA1c or $\geq 35\%$ decrease in fasting serum triglycerides at Month 12;
 - $\geq 2\%$ decrease in HbA1c or $\geq 40\%$ decrease in fasting serum triglycerides at Month 12
- Actual and percent change from baseline in fasting plasma glucose levels at Month 12.

3.2.2

Study population

Key inclusion criteria in the NIH study are shown in table 2.

Table 2: Main inclusion criteria study NIH 991265/200108769

NIH 991265	NIH 20010769
> 5 years of age with clinically significant LD (modified from > 14 years)	≥ 6 months of age with clinically significant LD (modified from >5 years)
Circulating leptin ≤8 ng/ml (females) and ≤6 ng/ml (males) [modified from <4 ng/ml (females) and <3 ng/ml (males)]	Circulating leptin <12 ng/ml (females) or <8 ng/ml (males) for patients aged > 5 years; in males and females aged 6 months to 5 years leptin <6 ng/ml (modified for males from <3 and <4 to <6 ng/ml)
At least one metabolic abnormality: <ul style="list-style-type: none"> • Presence of diabetes (1997 ADA criteria) • Fasting insulin >30 µU/ml • Fasting TGs >200 mg/dl (>2,26 mmol/l) 	At least one metabolic abnormality: <ul style="list-style-type: none"> • Presence of diabetes (2007 ADA criteria) • Fasting insulin >30 µU/ml • Fasting TGs >200 mg/dl (>2,26 mmol/l) (modified from >300 ng/dl) or postprandially elevated TGs > 500 mg/dl (> 5.65 mmol/l) when fasting not clinically indicated (modified with inclusion of children 0<5 years old)

The most important exclusion criteria were:

- Pregnant women, women in their reproductive years who did not use an effective method of birth control, and women who were nursing or who were lactating within 6 weeks of having completed nursing;
- Known infectious liver disease (in Study 99165, known liver disease due to causes other than NASH);
- Known human immunodeficiency (HIV) infection (added with Amendment to Protocol 2001769).

The FHA101 study included patients 5 years of age and older with physician-confirmed lipodystrophy (GL and PL) who had diabetes mellitus and/or hypertriglyceridemia with triglycerides >200 mg/dl. The main exclusion criteria were the same.

3.2.3

Discussion study characteristics

The open-label single arm study design of both studies was considered appropriate by the CHMP, given the rarity of the disease and the lack of therapeutic options. As the efficacy endpoints are objective measurements, including HbA1c, TG and fasting plasma glucose levels, the CHMP stated the treatment effects can be appropriately evaluated within a single-arm (baseline-controlled, within patient design). However, an uncontrolled before-after design is prone to bias. It's not clear whether beneficial effects should be attributed to metreleptin or to improvements of diet or enhanced compliance with concomitant antihyperglycemic or lipid lowering medications (by being observed). Diet and concomitant medication were not systematically optimized before study onset, so it's also not clear in which manner treatment failure would be present in optimized circumstances.

Finally, the inclusion period is considerable (time span of 14 years). According the applicant it was due to the rarity of the condition (EPAR).

3.3 Favorable effects of intervention

3.3.1 Patient characteristics and patient disposition

Table 3: Number of patients included in LD studies, classified by LD subtype

	CGL	AGL	PL subgroup	Overall PL
NIH991265/20010769	45	21	31	41
FHA101*	2	6	7	32

* The GL subtype of one GL patient in the FHA study has not been further specified.

A total of 107 patients was enrolled in study NIH 991265/20010769; 66 patients with GL and 41 patients with PL, 31 of them belonging to PL subgroup. In study FHA101 41 patients were enrolled; 9 patients with GL (of which one patient cannot be further classified to CGL or AGL) and 32 patients with PL, of which 7 being evaluated in the PL subgroup.

Detailed baseline characteristics of the study population are shown in annex 5.

Almost 3 out of 4 patients were using antidiabetic medications at baseline. Lipid-lowering medications were used at baseline by 48% of the GL population and by 73% of the PL population.

In the PL population, data for patients under 12 years old are lacking and only 5 patients were analysed in the age group 12-18 years.

Over the 14 year study period, 23 GL patients (34.8%), 15 patients (36.6%) in the overall PL population and 11 (35.5%) patients in the PL subgroup discontinued the study. Reasons for discontinuation included non-compliance, lack of efficacy, transfer to another metreleptin treatment program, death, ineligibility, an adverse event, lost to follow-up, and other reasons (bipolar disorder, gastric bypass surgery).

3.3.2 Primary endpoints

No data are available upon the effect of metreleptin on mortality or quality of life of patients with lipodystrophy.

Surrogate endpoints

As a surrogate outcome for the micro- and macrovascular complications, metabolic disorder (glycemic control and lipid dysregulation) has been evaluated.

HbA1C

Tables 4 and 5: Results on HbA1c in study NIH 991265/20010769 and study FHA 101

NIH 991265/20010769		GL	PL*	
			PL subgroup	Overall
Baseline	Number of subjects	62	29	39
	Mean HbA1c % (SD)	8.6 (2.33)	8.8 (1.91)	8.0 (2.18)
Month 12	Number of subjects	59	27	36
	Mean HbA1c % (SD)	6.4 (1.68)	8.0 (1.83)	7.5 (1.84)
Baseline vs 12 months therapy	Number of subjects	59	27	36
	Mean actual change from baseline (SD)	-2.2 (2.15)	-0.9 (1.23)	-0.6 (1.22)
	[95% CI]	[-2.7; -1.6]	[-1.4; -0.4]	[-1.0; -0.2]
	P-value (paired t-tests)	<0.001	<0.001	0.005

*The mean actual change in HbA1C from baseline in the FAS population of the NIH study without excluding the patient with a >1000% increase of TG was -0.9% [-1.4; -0.4] in the PL subgroup and -0.6% [-1.0; -0.2] in the overall PL group.

FHA101		GL	PL	
			PL subgroup	Overall
Baseline	Number of subjects	9	7	29
	Mean HbA1c % (SD)	7.7 (1.99)	7.8 (1.71)	8.1 (1.77)
Month 12	Number of subjects	5	7	26
	Mean HbA1c % (SD)	6.2(1.96)	7.0 (0.76)	7.8 (1.76)
Baseline vs 12 months therapy	Number of subjects	5	7	26
	Mean actual change from baseline (SD)	-1.2 (2.53)	-0.8 (1.85)	-0.4 (1.49)
	[95% CI]	[-4.3, 2.0]	[-2.5, 0.9]	[-1.0, 0.2]
	P-value (paired t-tests)	0.360	0.289	0.210

In study NIH 991265/20010769 mean change in **HbA1C** to Month 12/LOCF was -2.2% (95% CI: -2.7 to -1.6; p< 0.001) for GL patients, -0.9% (95% CI: -1.4 to -0.4; p<0.001) in the PL subgroup and -0.6% (95% CI: -1.0 to -0.2; p=0.005) in the overall PL group. The mean HbA1c level at Month 12 was respectively 6.4% in GL patients, 8.0% in the PL subgroup and 7.5% in the overall PL group. As mentioned before, HbA1c values between 4 and 6% were considered as non-diabetic. HbA1c values of 7% and over are associated with long term complications of diabetes.

In study FHA101, reductions were observed for HbA1c to Month 12/LOCF in both the overall GL group and the PL subgroup. However, none of the changes reached statistical significance. Compared with the main study baseline HbA1C levels in the FHA GL and PL subpopulation were lower.

Tables 6 and 7: Results on fasting TG in Study NIH 991265/20010769 and study FHA 101

NIH 991265/20010769		GL	PL*	
			PL subgroup	Overall
Baseline	Number of subjects	61	29	39
	Mean fasting TG (mmol/l) (SD)	14.7 (25.66)	15.7 (26.42)	12.5 (23.35)
Month 12	Number of subjects	58	27	36
	Mean fasting TG (mmol/l) (SD)	4.5 (6.10)	6.0 (8.41)	5.4 (7.37)
Baseline vs 12 months therapy	Number of subjects	57	27	36
	% change from baseline (mmol/l) (SD)	-32.1 (71.28)	-37.4 (30.81)	-20.8 (47.93)
	[95% CI]	[-51.0; -13.2]	[-49.6; -25.2]	[-37.1; -4.6]
	P-value (paired t-tests)	0.001	<0.001	0.013

*The mean actual change in fasting TG from baseline in the FAS population of the NIH study without excluding the patient with a >1000% increase of TG was 5.7% [-83.5; 94.9] in the PL subgroup and 11.3% [-55.8; 78.4] in the overall PL group.

FHA101		GL	PL	
			PL subgroup	Overall
Baseline	Number of subjects	8	7	29
	Mean fasting TG (mmol/l) (SD)	19.9 (40.90)	4.0 (4.54)	8.5 (12.37)
Month 12	Number of subjects	6	7	26
	Mean fasting TG (mmol/l) (SD)	7.6 (11.10)	3.6 (3.57)	6.4 (10.06)
Baseline vs 12 months therapy	Number of subjects	5	7	26
	% change from baseline (mmol/l) (SD)	-26.9 (78.32)	-8.5 (30.22)	8.7 (93.39)
	[95% CI]	[-124.1; 70.4]	[-36.4; 19.5]	[-29.1; 46.4]
	P-value (paired t-tests)	0.486	0.485	0.640

The mean percent change in **TG** to Month 12/LOCF was -32.1% (p = 0.001) in the GL group, -37.4% (p<0.001) in the PL subgroup and -20.8% (p = 0.013) in the overall PL group excluding the one outlying noncompliant patient. At Month 12 the mean TG levels were 4.5% in GL patients, 6.0% in the PL subgroup and 5.4% in the overall PL group.

In study FHA101, reductions were observed for triglycerides to Month 12/LOCF in both the overall GL group and the PL subgroup. In the overall PL population % change from baseline was positive. None of the changes reached statistical significance. Compared with the main study, baseline values in the FHA PL population and PL subgroup were considerably lower.

3.3.3 *Supportive outcome measures* Fasting plasma glucose (FPG)

In study NIH 991265/20010769 (statistically significant) reductions in mean fasting glucose levels in GL patients and in the PL subgroup support the findings on the primary outcome measures (at Month 12). In the overall PL population, however, the FPG levels augmented (not statistically significant).

Target reductions in HbA1c or TG

In study NIH 991265/20010769 respectively 80% of GL patients and 68% of patients in the PL subgroup achieved a ≥ 1% decrease in HbA1c or a ≥ 30% decrease in fasting serum TG at Month 12. Respectively 66% of GL patients and 43 % of patients in the PL subgroup achieved a ≥ 2% decrease in HbA1c or a ≥ 40% decrease in fasting serum TG at Month 12. The results in de overall PL group were less remarkable. In study FHA101 3 out of 6 GL patients and 2 out of 7 patients achieved the first target; 1 out of 7 patients in the PL subgroup achieved a ≥ 2% decrease in HbA1c or a ≥ 40% decrease in fasting serum TG at Month 12.

3.3.4 *Long-term data NIH 991265/20010769*

Long-term data are limited. The publication of Brown on long term data in **GL patients** mentions many patients lacked 36-month data (no laboratory value within the 36-month window, enrolment in the final 3 years of the study, transfer to another site before 36 months of metreleptin treatment) (Brown 2018). In GL patients, significant mean changes from baseline in HbA1c, FPG, and TG levels are reported for months 24 (n=25), 36 (n=17), and 48 (n=11) with no loss of efficacy over time (p < 0.001 for all parameters).

In **PL population** data at month 24 were only available for 8 patients in the overall PL population and for 6 patients in the PL subgroup. At month 36 it concerns 7 and 5 patients, respectively. In the PL subpopulation the mean actual decrease in HbA1c was 0.9%, 1.3%, and 1.0% at months 12, 24, and 36, respectively. Fasting TG reductions were 36.2%, 31.7%, and 13.7%. FPG decreased by 1.9, 2.4, and 3.0 mmol/l, respectively. In the overall PL population mean HbA1c reductions at 24 (0.7%) and at 36 months (0.6%) were not statistically significant, nor percent changes in fasting TG (-9.4% and 4.4% at 24 and 36 months, respectively).

3.3.5

Other considerations

Effect of metreleptin on the use of concomitant medications

Data on the effects of metreleptin on the use of concomitant medications are limited. Among the 39 GL patients receiving insulin at baseline in the NIH study, 91% achieved a $\geq 1\%$ decrease in HbA1c or $\geq 30\%$ decrease in TGs by month 12/LOCF; of these patients, 16 (41.0%) were able to discontinue insulin during the study and 11 did so within the first year of metreleptin use. Among patients taking oral antidiabetic and lipid-lowering medications at baseline, 7 out of 32 (22%) and 8 out of 34 (24%), respectively, were able to discontinue the use of those drugs with metreleptin treatment (Brown 2016).

None of the 19 patients in the overall PL population who received insulin at baseline in the NIH study were able to discontinue it after starting metreleptin. One patient who received oral glucose-lowering medications at baseline and another who received lipid-lowering medications at baseline were able to discontinue these medications with metreleptin treatment (Oral 2019).

Sensitivity analyses (NIH 991265/20010769)

Effects of concomitant medication use on efficacy parameters:

Sensitivity analyses were performed in the "Controlled Concomitant Medication FAS (CFAS)": all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12.

In the GL population of the NIH study, efficacy results of FAS and CFAS were similar, with a HbA1c reduction of 1.9% ($p \leq 0.001$), a TG reduction of 26.5% ($p \leq 0.001$) and a FPG reduction of 2.3 mmol/l ($p = 0.026$) in the CFAS. In the overall PL population, although reductions from baseline were observed for HbA1c, fasting TGs, and FPG in the CFAS, these were not statistically significant. In the PL subgroup, results in the CFAS were similar to those in the FAS for HbA1c and fasting TG, with an actual decrease in HbA1c of 0.7% ($p = 0.008$) and a reduction of fasting TG by 34 ($p < 0.001$). FPG did not significantly change (-1.1 mmol/l; $p = 0.6$).

Effect of missing data:

Other sensitivity analyses were performed in the "Efficacy Evaluable Analysis Set" (EEAS) and the "Controlled Concomitant Medication EEAS" (CEEAS). It concerns patients in the FAS and CFAS, respectively, who have either efficacy parameter of interest measured at Month 12 and have no major protocol violations. Only results for the GL population and PL subgroup are shown in the EPAR. The EEAS results for HbA1c Fasting TG in both populations (GL and PL subgroup) are similar to the FAS results. The CEEAS results for HbA1c in the PL subpopulation are very limited and not statistically significant. HbA1c results in the GL population, as well as Fasting TG results in both populations are in line with the FAS results.

Table 8: Sensitivity analyses (NIH 991265/20010769)

CFAS	Comparison groups	Baseline vs 12 months therapy in GL	Baseline vs 12 months therapy in PL subgroup
	Number of subjects	54	23
HbA1c	Mean actual change from baseline (SD)	-1.9 (1.81)	-0.7 (0.69)
	[95% CI]	[-2.6, -1.2]	[-1.2, -0.2]
	P-value (paired t-tests)	<0.001	0.008
Fasting TG	Mean % change from baseline (SD)	-26.5 (76.17)	-34.0 (31.44)
	[95% CI]	[-49.7, -3.3]	[-49.6, -18.3]
	P-value (paired t-tests)	0.026	<0.001
EEAS	Comparison groups	Baseline vs 12 months therapy in GL	Baseline vs 12 months therapy in PL subgroup
	Number of subjects	38	19
HbA1c	Mean actual change from BL (SD)	-2.2 (2.19)	-0.9 (1.45)
	[95% CI]	[-2.9, -1.5]	[-1.6, -0.2]
	P-value (paired t-tests)	<0.001	0.011
Fasting TG	Mean % change from BL (SD)	-49.8 (42.14)	-41.3 (27.73)
	[95% CI]	[-63.9, -35.8]	[-54.7, -27.9]
	P-value (paired t-tests)	<0.001	<0.001
CEEAS	Comparison groups	Baseline vs 12 months therapy in GL	Baseline vs 12 months therapy in PL subgroup
	Number of subjects	33	13
HbA1c	Mean actual change from BL (SD)	-1.8 (1.75)	-0.5 (0.75)
	[95% CI]	[-2.6, -1.0]	[-1.4, 0.4]
	P-value (paired t-tests)	<0.001	0.194
Fasting TG	Mean % change from BL (SD)	-46.6 (42.74)	-39.1 (25.43)
	[95% CI]	[-62.2, -30.9]	[-56.2, -22.1]
	P-value (paired t-tests)	<0.001	<0.001

Baseline HbA1c and TG levels

Subgroup analyses by baseline metabolic abnormalities showed a positive correlation between efficacy results and patient’s baseline level of HbA1c or TG: patients with more abnormal (higher) values for HbA1c and TC will reach greater decreases from baseline. However no robust conclusions could be drawn by the CHMP to define a PL subgroup in need for treatment.

Baseline leptin levels

Subgroup analyses by the applicant did not demonstrate statistical significant differences in HbA1c reduction or TG reduction between patients with different baseline leptin levels. The CHMP concluded that, based on literature and subgroup analyses, no robust conclusions could be made in order to determine the use of metreleptin in PL by baseline leptin levels.

Children

Results on primary endpoints were less pronounced in GL children <6 years. Baseline HbA1c values were in the normal range in this age group. Mean decreases from baseline to Month 12/LOCF in TG for GL children were noted in all ages groups with larger mean changes in the older age groups (-43% and -35%) compared with the younger age groups (-11% and -14%).

3.3.6

Discussion favorable effects

Registration of Myalepta® was based on one observational, single arm, open label study and one supportive open label study. No meta-analysis / pooling of study results was considered which could enhance precision of the effect estimate. The evidence is limited. There is no information about a direct comparison. Data from matching historical controls are also missing.

In summary, in the main study improvements in both HbA1c as fasting TG were observed in the GL population (-2.2% HbA1c; -32.1% TG) and a post hoc PL subgroup (-0.9% HbA1c; -37.4% TG) at 12 Months/LOCF. Based on the results, registration has not been asked for in the overall PL population. Reductions in FPG supported the primary findings. In general, the results of study FHA101 were in line with the results of the main study. Some patients, especially GL patients, were able to discontinue use of insulin, oral antidiabetic medications and/or lipid-lowering therapies. It is noted that the use of standard treatments at baseline and the associated effects are not further clarified.

Important **outcome measures** in patients with LD are mortality, macro- and microvascular complications and quality of life. However, none of these parameters has been measured directly. Mortality, as well as macro- and microvascular complications can't be measured within a limited time span. As macro- and microvascular complications are caused by metabolic dysregulation, surrogate endpoints as HbA1c and fasting TG are acceptable short term outcome measures. However, long term studies are necessary to confirm the effects on clinically relevant parameters. Additionally, the lack of data on quality of life is regrettable.

Generally, the **quality of the efficacy data** should be considered very low, due to the open label nature of the studies, the lack of a control group and the limited number of patients. Given the rare nature of the disease, open label, non-controlled trials can be supportive. However, the quality of the data could have been biased and ameliorated, as diet and concomitant medication were not systematically optimized before study onset. On the one hand it is unclear to which extent metabolic control could have been reached by optimized standard treatment on its own, on the other hand it is unclear to which extent an optimization of diet and standard treatments during the studies could have been attributed to the observed effects. Sensitivity analysis in the CFAS population suggests no major effect due to optimization of concomitant medication during the studies. However, those analyses don't cover potential effects of optimized diet measures during the study, and they cannot correct for the lack of optimized standard treatments at baseline. Due to the small number of patients investigated and the lack of control, available data are not considered sufficient to fully characterise the magnitude of effect.

Additionally, long term data are supportive, but very limited. Study discontinuation is an important issue, it hampers the generalizability of long term results and questions the usability of metreleptin in the clinical practice.

Finally, not all PL patients are in need for metreleptin, as not all of them present with metabolic dysregulation and part of them can be well-controlled with standard treatment. Registration in PL population is based on post hoc subgroup analyses in a population defined by strict thresholds concerning baseline HbA1c, TG and leptin. As it was impossible for the CHMP to conclude on baseline leptin levels and metabolic thresholds to define a target PL population in need for treatment, finally no thresholds were withheld. Consequently, the registered indication in PL patients did not fully reflect the PL subgroup study population.

Minimal clinically important differences are not well-defined for the primary outcome measures. A HbA1C reduction of at least one 1% can generally be considered as an acceptable lower border for the treatment of LD. However, a minimal relevant change in fasting TG is less obvious. The lack of well-defined MCIDs hampers strong conclusions on responder percentages, as responder were defined by either HbA1c or TG reductions.

In GL patients, the findings on HbA1c at Month 12 support diabetes control, as the mean HbA1c level in GL patients was reduced from 8.6% to 6.4%. In people without diabetes, HbA1c values are between 4 and 6%. However, in PL patients, as well in the PL subgroup, the mean HbA1c values at Month 12 remain high (7.5% and 8.0 respectively). Considering fasting TG, the observed main values at Month 12 were considered slightly to moderately elevated, with the best results being observed in GL patients.

Data in **children** are limited. Given the lack of data in PL patients under 12 years old, registration has been limited to PL patients of 12 years and over.

In GL patients, the observed treatment effects increase with age. Despite a small treatment effect in young children, treatment of GL patients of 2 years and above can be considered acceptable in order to prevent or delay onset of complications. The severity of disease in inadequately treated GL patients worsens over time.

No conclusions could be made on **HIV-related LD**, as people being diagnosed with HIV were excluded from the clinical trials.

3.4 Unfavorable effects

Safety data discussed in the EPAR were derived from the two registration studies. Supportive safety data were extracted from 5 Phase II trials in obese patients (two of them recruited explicitly diabetic patients) that had aimed to investigate the effectiveness of treating obesity with metreleptin. (Metreleptin was originally developed for the treatment of obesity, but turned out to be ineffective.)

Across the two LD studies, a total of 148 patients were enrolled (75 GL and 73 PL). The vast majority of these patients were treated for at least 1 year and about half for more than 3 years. Very few patients older than 65 or younger than 6 were included.

Table 9: Incidence drug-related adverse events (>1 patient in the Overall GL or PL Groups)

	Generalized lipodystrophy N (%)	Partial lipodystrophy N (%)
NIH Study (SAS)	N=66	N = 41
Weight decrease	15 (22.6)	1 (2.4)
Hypoglycaemia	8 (12.1)	3 (7.3)
Decreased appetite	4 (6.1)	0
Fatigue	4 (6.1)	3 (7.3)
Neutralising antibodies	4 (6.1)	0
Alopecia	2 (3.0)	2 (4.9)
Injection site reaction	2 (3.0)	2 (4.9)
Menorrhagia	2 (3.0)	0
Nausea	2 (3.0)	0
FHA101 (SAS)	N = 9	N = 32
Weight decrease	1 (11.1)	1 (3.1)
Hypoglycaemia	2 (22.2)	8 (25.0)
Muscle spasms	0	2 (6.3)
Headache	0	3 (9.4)
Injection site reaction	4 (44.4)	11 (34.3)
Nausea	0	8 (25.0)
Abdominal pain	1 (11.1)	1 (3.1)

Treatment-related adverse events (>=1%) mentioned in the Obesity Studies Pool were injection site reaction, headache, fatigue, hypoglycaemia, nasopharyngitis, urticaria, nausea and pyrexia.

Incidence treatment-related serious adverse events (SAEs)

SAEs included abdominal pain and pancreatitis, infections and worsening liver function. However, only a low number of SAEs were considered drug-related:

- In the NIH study 3 SAEs, all in GL patients, were considered drug-related: one case of hypertension, one case of respiratory distress and one case of anaplastic large-cell lymphoma (ALCL). ALCL was developed 10 months after testing positive for NAbs. Treatment was interrupted for 6 months. After excision of the neoplasm and restart of metreleptin the patient remained neoplasm free for the rest of the study duration.
- In the FAH101 study one SAE of hypoglycaemia in a PL patient was considered drug-related.

Overall death rate was 4% across both trials. No drug-related deaths occurred. In the obesity studies there was one death considered unrelated to the study drug.

From post-marketing data (United States, Japan), the EPAR mentions one case of pancreatitis which was associated with treatment interruption/non-compliance. Anaphylaxes was mentioned twice (24/07/2016).

Discontinuation due to adverse events

The overall withdrawal rates due to treatment-emergent adverse events (TEAEs) in the NIH study and study FHA101 were 6% and 10% respectively.

All TEAEs leading to withdrawal in the NIH study were considered non treatment-related.

In the FHA101 study, one event was considered treatment-related. After 8 months on treatment, the patient experienced muscle spasms. The patient was discontinued from the study 6 months. Equal rates of GL and non-subgroup PL patients withdrew due to TEAEs, but no PL subgroup patients.

Neutralizing antibodies (NABs)

Antibody data were available for 102 patients out of 148 patients enrolled. 38 patients developed NABs. Sixteen (42%) of them did not achieve resolution of neutralizing activity in the follow-up period. No patient had a total failure in efficacy. The CHMP concluded there are not enough data to conclude on the reversibility after cessation of therapy and thus on any potential impact of NABs on endogenous leptin activity, especially important in PL patients.

3.4.1

Conclusions on clinical safety

Given the rarity and severity of the disease the safety profile is acceptable.

The main safety concerns, identified in the EPAR are:

- acute pancreatitis associated with discontinuation of metreleptin,
- hypoglycaemia with concomitant use with insulin and other antidiabetics,
- immunogenicity
- the potential for medication errors

To address the missing safety data in the context of a market authorization under exceptional circumstances two measures were imposed:

- A patient registry to evaluate the long-term safety profile
- An integrated immunogenicity report using validated assays for the detection of anti-drug antibodies from all available data

3.5

Experience

The experience with metreleptin (Myalepta®) is shown in table 10.

Table 10: Experience with metreleptin

	<i>metreleptin</i>
limited: < 3 years on the market or < 100,000 prescriptions (not-chronical indication)/20,000 patient years (chronical medication)	X
sufficient: ≥ years on the market, and > 100,000 prescriptions/20,000 patient years	
broad: > 10 years on the market	

Myalepta® was approved by the EMA in 2014.

3.6 Applicability

Extended information on applicability is available in the SmPC. This paragraph only mentions the most important elements.

Contra-indications

Hypersensitivity to the active substance of one of the excipients.

Specific groups

- **Elderly:** Clinical trials of metreleptin did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, dose selection and modification for an elderly patient should be cautious, although no specific dose adjustment is recommended.
- **Renal and hepatic impairment:** Metreleptin has not been studied in patients with impaired renal or hepatic function. No dose recommendations can be made.
- **Paediatric population:** The safety and efficacy of metreleptin in children aged 0 to 2 years with generalised LD and children aged 0 to 12 years with partial LD has not been established. Very limited data are available for children, especially less than 6 years, with generalised LD.

Interactions

- No interaction studies have been performed in humans.
- Leptin is a cytokine and has the potential to alter the formation of cytochrome P450 (CYP450) enzymes. Since it cannot be excluded that metreleptin may reduce exposure to substrates of CYP3A through enzyme induction, the efficacy of **hormonal contraceptives** may be reduced if co-administered with metreleptin. Therefore, an additional non-hormonal contraceptive method should be considered during treatment. The effect of metreleptin on CYP450 enzymes may be clinically relevant for **CYP450 substrates with narrow therapeutic index**, where the dose is individually adjusted. Upon initiation or discontinuation of metreleptin, in patients being treated with these types of agents, therapeutic monitoring of effect (e.g., warfarin), or drug concentrations (e.g. cyclosporin or theophylline) should be performed and the individual dose of the agent adjusted as needed. When starting therapy with metreleptin there is a risk of hypoglycaemia in patients who are on **anti-diabetic medicinal products**, in particular insulin or insulin secretagogues (e.g. sulphonylureas).

Warnings and precautions

- Generalised hypersensitivity (e.g. anaphylaxis, urticaria or generalised rash) has been reported in patients using metreleptin.
- Non-compliance with, or abrupt discontinuation of, metreleptin may result in worsening hypertriglyceridaemia and associated pancreatitis.
- There is a risk of hypoglycaemia in patients treated with metreleptin who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues.
- Cases of T-cell lymphoma have been reported in clinical studies. A causal relationship between the medicinal product treatment and the development and/or progression of lymphoma has not been established.
- Antidrug antibodies (ADA) to metreleptin occurred very commonly. An association between the development of a blocking activity against metreleptin and serious and severe infections cannot be excluded. Although not being confirmed in clinical trials, neutralising antibodies could in theory

affect the activity of endogenous leptin.

Other

- Pregnancy: metreleptin is not recommended during pregnancy and in women of childbearing potential not using contraception.
- Breast feeding: It is unknown whether metreleptin or its metabolites are excreted in human milk. Endogenous leptin is present in human milk. A risk to newborns/infants cannot be excluded.

Conclusion

Given the severity of the condition, the applicability is acceptable.

3.7

Usability

The usability of metreleptin (Myalepta®) is shown in table 11.

Table 11: Usability of metreleptin

<i>metreleptin</i>	
Route of administration	Subcutaneous injection
Administration frequency	The injection should be administered at the same time every day. It can be administered any time of the day without regard to the timing of meals.

Healthcare professionals should provide patients and carers with training on the reconstitution of the product and proper subcutaneous injection technique, so as to avoid intramuscular injection in patients with minimal subcutaneous adipose tissue.

The reconstituted solution should be injected into the abdomen, thigh or upper arm tissue. It is recommended that patients should use a different injection site each day when injecting in the same region. Doses exceeding 1 ml can be administered as two injections (the total daily dose divided equally) to minimise potential injection site discomfort due to injection volume. When dividing doses due to volume, doses can be administered one after the other at different injection sites.

When small doses/volumes are prescribed (e.g. in children), the vials will remain almost completely filled with product after withdrawal of the required dose. Remaining reconstituted product should be discarded after use.

Discussion / Conclusion

Given the severity of the disease, the usability is acceptable. However, for a treatment intended to be lifelong, compliance is important. Subcutaneous injections in patients with minimal subcutaneous adipose tissue may be challenging, especially in patients being in need for insulin too. The numerous subcutaneous injections can jeopardize compliance. This concern is supported by recent real world data from 20 patients in a compassionate use program in France. Adherence with metreleptin (one daily subcutaneous injection) was poor in 25% of patients. On a 0-to-100 scale, patients' satisfaction scores reached 55.6 (44.4;66.7) for ease/comfort of use. Self-reported side effects were frequent injection site reactions. Six patients added a free text comment related to the practical difficulties linked to the daily reconstitution of the product from powder and/or the subcutaneous route of injection in the absence of a pre-prepared device (Vatier 2019).

4 Final assessment

4.1 Discussion on relevant aspects

Lipodystrophy syndromes are clinically heterogeneous inherited or acquired ultra-rare disorders characterised by selective but variable loss of adipose tissue. Deficient adipose mass may result in ectopic lipid storage in the liver, muscle and other organs. In GL patients, metabolic complications are common and can be severe. Also in FPL patients metabolic complications are common in adulthood. In APL patients metabolic complications are uncommon. Patients with lipodystrophy, especially generalized forms, are typically hyperphagic which makes it difficult to achieve dietary restriction.

Registration of Myalepta® was based on two clinical, single arm trials in 148 patients [75 (66+9) GL and 73 (41+32) PL]. Information about (matching historical) controls is lacking. No data are collected about the effects of metreleptin on mortality or (disease related) quality of life. As a proxy (surrogate parameter) of micro- or macrovascular complications, metabolic disturbances (glycaemic control, normalisation of hypertriglyceridemia) were evaluated. Metreleptin was intended to be used as an adjunct to diet and best supportive care in optimal dose. However, it is not clear whether these standard treatments have been used sufficiently in the study population to regulate their metabolic disorders.

Improvements in both HbA1c and fasting TG were observed at 12 Months in the GL population and in a post-hoc defined PL subgroup (patients with baseline leptin <12 ng/ml and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/l). The effects were more pronounced in GL patients (compared with the PL subgroup), attaining near normal mean values for HbA1c at Month 12. Finally, in the overall PL population the observed effects were considerably lower and not supported by statistically significant changes in the CFAS population.

The registered indication concerns GL patients (2 years and above) and PL patients (12 years and above) not achieving adequate metabolic control by standard treatments. This population is broader than the post hoc defined PL subpopulation in the EPAR. However, the limited dataset did not allow to determine clear thresholds on metabolic parameters in order to define a target PL subpopulation. For that reason, the CHMP has also not set a threshold to define the PL target population. The registered PL population was finally defined as PL patients "without adequate metabolic control" under standard treatment. Registration was not asked for in the overall PL population. HIV patients were excluded from the clinical trials.

The quality of the evidence is very low due to a limited setup of the trials: single arm studies without matching (historical) controls, long enrolment period (up to 14 year), limited number of patients, especially in the PL subpopulation [39 (31+7) PL subgroup]. Moreover, the PL subpopulation in the clinical trials has been defined post hoc and not fully reflects the eligible PL population, as the study population was limited to patients with baseline leptin <12 ng/ml and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/l. The uncertainties on the magnitude of the effects are considerable. Diet and the use of concomitant medication have not been optimized before study onset. Generally, long term data are supportive for those patients still on treatment after 36 Months, but the number is very limited (GL; n=17 and PL subgroup; n=6 for data at 36 Months). In general the safety profile of metreleptin is acceptable, but there is a concern regarding the development of NABs. They could potentially bind on metreleptin, but also against endogenous leptin (especially important in PL patients). Finally, The administration of metreleptin by subcutaneous injections may be difficult

in patients with minimal subcutaneous adipose tissue and jeopardize treatment compliance, especially in patients already in need for insulin which has to be administered subcutaneously too.

4.2 Final conclusion

Generalized lipodystrophy

To treat the complications of leptin deficiency in adults and children 2 years of age and above with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome), the usual care is diet supplemented with antidiabetics and/or lipid-lowering agents if needed.

Metreleptin as an adjunct to diet has a therapeutic lower value compared to standard treatment with antidiabetics and/or lipid-lowering agents due to insufficient data.

Because of the limited design of the clinical studies, it is not possible to assess whether the measured favorable effects can be attributed to metreleptin. Based on current data, it is not clear to what extent the standard treatment (at baseline and during the study period) has contributed to the measured effects.

In contrast to metreleptin, the standard treatments are proven to be effective in metabolic syndrome and the long-term effects are well known. Due to the lack of a matching (historical) control group, the effect of natural course is not clear either.

Partial lipodystrophy

Based on the actual data it is not possible to conclude on an added value for metreleptin as an adjunct to diet compared with standard treatment to treat the complications of leptin deficiency in adults and children 12 years of age and above with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in whom standard treatments (diet supplemented with antidiabetics and/or lipid-lowering agents in an optimal dosage) have failed to achieve adequate metabolic control. Improvements in both HbA1c and fasting triglycerides were observed in a post-hoc defined PL subpopulation (with clearly defined metabolic baseline thresholds). However, the observed effects were less pronounced compared with GL patients and the uncertainties on the magnitude of the effects are still higher because of very limited patient numbers. Additionally, data in the overall PL population were not convincing. Also in the case of PL, the therapeutic value is lower as compared to standard treatment due to insufficient data.

Conclusion

Taking into account the uncertainties in the favorable effects and the concerns regarding the development of neutralizing antibodies, ZIN and the Belgian CRM conclude it is not possible to conclude on an added value for metreleptin (Myalepta®) in patients with generalized lipodystrophy and partial lipodystrophy. Due to insufficient data it is concluded that metreleptin has a lower therapeutic value in comparison with standard treatment.

5 Advice “Farmacotherapeutisch Kompas” (the Netherlands)

5.1 **Nieuw advies**

Lipodystrofie (LD) is een zeldzame, complexe aandoening die vraagt om een specialistische, multidisciplinaire behandeling. Deze dient beperkt te worden tot centra waar voldoende LD expertise aanwezig is.

Er zijn onvoldoende onderzoeksgegevens over het toepassen van metreleptine bij patiënten met gegeneraliseerde of partiële lipodystrofie, bij wie geen adequate metabole controle kan worden bereikt met dieet en standaardbehandeling. Over de effecten op de lange termijn is onvoldoende bekend.

Annex 1: Search strategy

Search strategy literature search

The literature search has been performed in PubMed (68) and the Cochrane Library (12) April 15th 2019 with search terms: metreleptin AND lipodystrophy (all fields).

Annex 2: Included studies

NIH 991265 / 20010769

References	Type of trial, follow-up period	Number of patients	Patient characteristics	Intervention and comparative treatment	Relevant outcome measures	Commentary, risk of bias
Chan J, 2011 Diker-Cohen, 2015 Chan J, 2016 Brown R, 2017 Brown R, 2018a Oral E, 2019	Open label, single arm pilot dose-escalation study and extension study, continuous enrolment over 14 years (2000-2014); longer-term efficacy data till 36 months (maximum)	N = 107 (GL = 66; PL = 41; PL subgroup = 31)	GL and PL patients aged ≥ 6 months with lipodystrophy, low circulating leptin, and ≥ 1 metabolic abnormality (diabetes mellitus, insulin resistance, or hypertriglyceridemia). PL subgroup = patients with baseline HbA1c $\geq 6.5\%$ and/or triglycerides ≥ 5.65 mmol/l	Metreleptin + best supportive care Metreleptin dose (once or twice daily) was titrated to a mean dose of 0.10 mg/kg/day with a maximum of 0.24 mg/kg/day; no comparative treatment (compared with baseline)	1. Change from baseline in HbA1C, percent change from baseline in fasting serum triglycerides 2. Proportion of patients achieving target actual decreases of: <ul style="list-style-type: none"> $\geq 1\%$ decrease in HbA1c or $\geq 30\%$ decrease in fasting serum triglycerides $\geq 1.5\%$ decrease in HbA1c or $\geq 35\%$ decrease in fasting serum triglycerides $\geq 2\%$ decrease in HbA1c or $\geq 40\%$ decrease in fasting serum triglycerides , Actual and percent change from baseline in fasting plasma glucose levels 3. Adverse events	<ul style="list-style-type: none"> Non-comparative study; it's not clear if patients could have reached a benefit over baseline value when optimizing best supportive care for metabolic control Limited number of patients

FHA101

<p>Ajluni, 2016</p>	<p>Open label, single arm, expanded access study</p> <p>Continuous enrolment over 6 years (2008-2014)</p>	<p>N = 41 (GL = 9; PL = 32; PL subgroup = 7)</p>	<p>GL and PL patients ≥5 years, with diabetes mellitus and/or hypertriglyceridaemia with TG >200 mg/dl.</p> <p>PL subgroup = PL patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/l</p>	<p>Metreleptin + best supportive care</p>	<p>Cfr NIH 991265 / 20010769</p>	<ul style="list-style-type: none"> • Non-comparative study; it's not clear if patients could have reached a benefit over baseline value when optimizing best supportive care for metabolic control • Very limited number of patients • Descriptive, no statistical inferences anticipated
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GL= generalized lipodystrophy

PL = partial lipodystrophy

TG = triglycerides

HbA1c = glycohemoglobin

Annex 3: Excluded studies

First author, year of publication	Reason of exclusion
Simha V, 2012	Excluded due to short follow-up: study duration 6 months.
Brown R, 2018b	Excluded due to choice of the endpoints, not corresponding to the PICO: the prespecified primary outcome for glucose metabolism was total body insulin sensitivity (measured as the glucose disposal rate during a hyperinsulinemic-euglycemic clamp), and for lipid metabolism, the prespecified primary outcome was the rate of lipolysis (measured using glycerol stable isotope tracers).

Simha V, Subramanyam L, Szczepaniak L, et al. Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the dunnigan variety. Journal of Clinical Endocrinology and Metabolism. 2012;97(3):785-92.

Brown RJ, Valencia A, Startzell M, et al. Metreleptin-mediated improvements in insulin sensitivity are independent of food intake in humans with lipodystrophy. J Clin Invest. 2018 Aug 1; 128(8): 3504–3516.

Annex 4: Used guidelines and standards

Organisation, reference	Date	Title
EMA	2018	Summary of Product Characteristics Myalepta®
EMA	2018	European Public Assessment Report (EPAR) Myalepta®
Brown R, et al	2016	The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline.
EMA	2012	EMA guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)

Annex 5: Baseline table

Generalized lipodystrophy

Characteristic	NIH 991265/20010769 (N = 66)	FHA101 (N = 9)
Female, n (%)	51 (77.3)	8 (88.9)
Race, n (%)		
Caucasian	31 (47.0)	8 (88.9)
Black	16 (24.2)	1 (11.1)
Asian / Native American / Hispanic / Other	3 (4.5) / 2 (3.0) / 11 (16.7) / 3 (4.5)	0/0/0/0
Age, years, median (range)	15.0 (1.0, 68.0)	25.0 (9.0, 67.0)
<18 years	45 (68.2)	3 (33.3)
>18 years	21 (31.8)	6 (66.7)
LD type, n (%)		
Acquired	21 (31.8)	6 (66.7)
Congenital / Familial	45 (68.2)	2 (22.2)
Fasting leptin, ng/ml, median (range)	1.0 (0.2, 5.3)	
BMI, kg/m ² , median (range)	20.5 (14.0, 29.5)	21.3 (13.9, 38.4)
HbA1c, %		
Median (range)	8.7 (4.5, 13.7)	8.4 (5.1, 10.2)
≥6.5, n (%)	49 (74.2)	6 (66.7)
≥8.0, n (%)	42 (63.6)	5 (55.6)
Fasting plasma glucose, mmol/l, median (range)	10.3 (5.04)	10.4 (4.2, 23.3)
Fasting triglycerides, mmol/l		
Median (range)	14.5 (25.29)	3.3 (1.5, 119.9)
≥2,26 mmol/l	50 (75.8)	6 (66.7)
≥5,65 mmol/l	26 (39.4)	3 (33.3)
ALT, >ULN, n (%)	49 (74.2)	5 (55.6)
AST, >ULN, n (%)	36 (54.5)	4 (44.4)
Anti-diabetic medications at baseline, n (%)	53 (80.3)	2 (22.2)
Lipid-lowering medications at baseline, n (%)	34 (51.5)	2 (22.2)

Partial lipodystrophy

Characteristic	NIH 991265/20010769		FHA101	
	PL subgroup (N = 31)	Overall (N = 41)	PL subgroup (N = 7)	Overall (N = 32)
Female, n (%)	30 (96.8)	40 (97.6)	7 (100.0)	31 (96.9)
Race, n (%)				
Caucasian	26 (83.9)	36 (87.8)	5 (71.4)	22 (68.8)
Black	0	0	2 (28.6)	3 (9.4)
Asian / Native American / Hispanic / Other	1 (3.2) / 0 / 2 (6.5) / 2 (6.5)	1 (2.4) / 0 / 2 (4.9) / 2 (4.9)	0/0/0/0	1 (3.1) / 2 (6.3) / 1 (3.1) / 3 (9.4)
Age, years, median (range)	38.0 (15.0, 64.0)	34.0 (10.0, 64.0)	42.0 (23.0, 57.0)	44.5 (23.0, 67.0)
<18 years	5 (16.1)	8 (19.5)	0	0
>18 years	26 (83.9)	33 (80.5)	7 (100.0)	32 (100.0)
LD type, n (%)				
Acquired	4 (12.9)	6 (14.6)	1 (14.3)	3 (9.4)
Congenital / Familial	27 (87.1)	35 (85.4)	6 (85.7)	29 (90.6)
Fasting leptin, ng/ml, median (range)	5.9 (1.6, 16.9)	5.9 (1.0, 16.9)		
BMI, kg/m ² , median (range)	25.1 (18.6, 33.3)	25.3 (17.7, 33.3)	27.6 (20.9, 30.5)	30.3 (19.1, 41.2)
HbA1c, %				
Median (range)	8.6 (5.7, 13.3)	7.8 (4.6, 13.3)	7.6 (5.7, 11.1)	8.0 (5.6, 12.8)
≥6.5, n (%)	29 (93.5)	29 (70.7)	6 (85.7)	27 (84.4)
≥8.0, n (%)	19 (61.3)	19 (46.3)	2 (28.6)	16 (50.0)
Fasting plasma glucose, mmol/l, median (range)	9.9 (4.33)	8.7 (4.35)	7.4 (5.1, 13.4)	7.8 (2.0, 15.0)
Fasting triglycerides, mmol/l				
Median (range)	14.8 (25.72)	12.0 (22.85)	2.9 (0.7, 14.0)	3.2 (0.7, 50.4)
≥2,26 mmol/l	27 (87.1)	34 (82.9)	4 (57.1)	23 (71.9)
≥5,65 mmol/l	15 (48.4)	15 (36.6)	1 (14.3)	7 (21.9)
ALT, >ULN, n (%)	9 (29.0)	14 (34.1)	5 (71.4)	23 (71.9)
AST, >ULN, n (%)	7 (22.6)	10 (24.4)	2 (28.6)	9 (28.1)
Anti-diabetic medications at baseline, n (%)	30 (96.8)	37 (90.2)	6 (85.7)	19 (59.4)
Lipid-lowering medications at baseline, n (%)	26 (83.9)	34 (82.9)	6 (85.7)	19 (59.4)

- **Abbreviations:** ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; GL = generalised lipodystrophy; LD = lipodystrophy; HbA1c = glycated haemoglobin; PL = partial lipodystrophy; ULN = upper limit of normal
- **PL subgroup:** patients with baseline leptin <12 ng/ml and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/l

Annex 6. Evaluation by other EU-countries

Myalpetra has been evaluated by **other European countries.**

In Germany, the added benefit of an orphan drug is considered as proven by the authorization. Only the extent of the added benefit is assessed by the "Gemeinsame Bundesausschuss (G-BA)". The G-BA concluded both for GL and PL patients (within the registered indication); "overall, a non-quantifiable added benefit of metreleptin is noted" or "In der Gesamtschau wird ein nicht quantifizierbarer Zusatznutzen von Metreleptin festgestellt."

(https://www.g-ba.de/downloads/92-975-2587/2018-10-01_Nutzenbewertung-G-BA_Metreleptin_D-385.pdf)

In France, the "Haute Autorité de Santé (HAS)" allocates an 'SMR' score (Service Médical Rendu) which answers the question: "is the drug of sufficient clinical interest to be supported by national solidarity?". The 'SMR' of Myalepta is considered 'important'. However, the HAS also assesses the relative value of a drug "Does the drug improve patients clinical situation, as compared to existing therapies?". The Improvement in actual benefit (Amélioration du Service Médical Rendu) is represented by a code (Major improvement = ASMR I; Important = ASMR II; Moderate improvement = ASMR III; Minor improvement = ASMR IV; No clinical improvement = ASMR V). The HAS considers that Myalepta provides a minor improvement in actual benefit (ASMR IV) in the management of patients with generalized lipodystrophy and that Myalepta does not provide any improvement in actual benefit (ASMR V) in the management of patients with partial lipodystrophy.

(https://www.has-sante.fr/portail/jcms/c_2913097/fr/myalepta)

In the United Kingdom, the assessment of Myalepta by the "National Institute for Health and Care Excellence (NICE)" is still ongoing. In an evaluation consultation document (July 2018) NICE stated "The committee acknowledged that lipodystrophy, and hyperphagia in particular, has a substantial effect on the quality of life of patients, and their families and carers. It noted that the clinical evidence suggested metreleptin may provide clinical benefits for some patients, but considered this to be highly uncertain because of important limitations in the nature and extent of the evidence."

(<https://www.nice.org.uk/guidance/gid-hst10011/documents/evaluation-consultation-document>)

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Zorginstituut Nederland

Budget impact analysis of metreleptin (Myalepta®) for the indication lipodystrophy

For assessment in the context of a reimbursement request

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Colofon

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Inhoud

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1 Introduction

In this report the (additional) costs for the pharmaceutical budget are estimated, that arise when metreleptin (Myalepta®) will be reimbursed (opgenomen op lijst 1B van het GVS). Starting points for the budget impact analysis (BIA) are: the registered indication, the potential patient population, the official price (apothekinkoopprijs (AIP)), the dosage of the pharmaceutical, treatment duration and the possible substitution of the current treatment.

In this budget impact analysis the patient population is assumed for which in both the Netherlands and Belgium reimbursement has been requested. Both the Dutch Zorginstituut Nederland and the Belgian Commission Reimbursement of Medicines conclude that it is not possible to conclude on an added value for metreleptin (Myalepta®) in patients with generalized lipodystrophy and partial lipodystrophy. Due to insufficient data it is concluded that metreleptin has a lower therapeutic value in comparison with standard treatment.

1.1 Indication

Metreleptin (Myalepta®) is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients¹:

- 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 or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

1.2 Place in treatment algorithm

In both the Netherlands and Belgium there are no guidelines for the management of lipodystrophy. Experts follow the recommendations of the multi-society practice guidelines which were published in December 2016.² Currently, Dutch patients are treated by dr. I. Jazet from the Leiden University Medical Center (LUMC) and dr. J. Rutten from Radboud University Medical Center (RadboudUMC), whereby the LUMC is recognized as Expert Center for Lipodystrophy. In Belgium, patients are treated by prof. dr. B. van der Schueren and prof. dr A. Mertens from University Hospitals Leuven (UZ Leuven).

In the multi-society practice guideline diet is recommended to manage the metabolic complications of LD.² Next to that, patients are encouraged to exercise, whereby it is stated that strenuous exercise should be avoided in patients with cardiomyopathy and contact sports should be avoided in patients with severe hepatosplenomegaly and congenital generalized lipodystrophy (GL) patients with lytic bone lesions.

Recommended additional treatments for the specific co-morbidities related to lipodystrophy can be found in table 1.²

Table 1: Treatments for co-morbidities related to lipodystrophy

Co-morbidities arising from LD	Management
Diabetes	Metformin is a first-line agent for diabetes and insulin resistance. Insulin is effective for hyperglycaemia. In some patients, concentrated preparations and high-doses may be required.

Table 1: Treatments for co-morbidities related to lipodystrophy

Co-morbidities arising from LD	Management
	Thiazolidinediones may improve metabolic complications in partial lipodystrophy (PL)but should only be used with caution in GL.
Dyslipidaemia	Statins should be used concomitantly with lifestyle modification (after consideration of age, reproductive status, and tolerance). Fibrates and/or long-chain omega-3 fatty acids should be used for triglycerides >500 mg/dL and may be considered for triglycerides >200 mg/dL.
Hypertension	Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line treatments for hypertension in patients with diabetes.
Liver disease	In NAFLD not associated with LD, diet and exercise are first-line treatments, and among pharmacological treatments, vitamin E (in children and adults) and pioglitazone (in adults) have shown the most consistent benefit for liver histopathology. However, these treatments have not been studied in patients with LD and are not approved for NAFLD.
Cosmetic treatment	Patients should be assessed for distress related to LD and referred as necessary to mental health professionals and/or plastic surgeons.

Abbreviations: GL, generalised lipodystrophy; LD, lipodystrophy; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; PL, partial lipodystrophy

When a patient suffers from dyslipidaemia, it is recommended that statins and fibrates should be used with caution because of the increased risk of myopathy. In addition, due to the increased cardiovascular risk, clinicians may consider applying more strict lipid targets even in patients without diabetes.²

Metreleptin is the only drug that is registered for the treatment of lipodystrophy. It is recommended in addition to diet for patients with generalized lipodystrophy (GL) for the treatment of metabolic and endocrine abnormalities. In addition, metreleptin might be an option for hypoleptinaemic patients with PL (partial lipodystrophy) or PL patients with severe metabolic abnormalities despite the best use of standard treatments.¹

2 Starting points

2.1 Number of patients

Not uncommon with rare diseases is the estimation of LD prevalence and incidence difficult due to the small patient numbers and the possible underdiagnoses and underreporting of lipodystrophy. As a result, patients are often diagnosed late in the course of their disease. This is partly related to the lack of firm diagnostic criteria. The multi-society practice guideline recommends that the diagnosis of LD should initially be based on patient history, physical examination including body composition and metabolic status. Confirmatory genetic testing could be helpful in suspected familial LD and is also a consideration in at-risk family members. Differentiation between the different subtypes of LD (genetic and acquired) can be more complicated due to the heterogeneity of subcutaneous adipose tissue loss between the LD types. Patients with congenital generalized LD (CGL) typically have a lack of subcutaneous adipose tissue from infancy whereas patients with acquired generalized LD (AGL) may have normal adipose tissue in infancy. The suspicion of an acquired subtype of LD increases by the presence of an autoimmune disease.²

A literature search carried out by Aegerion resulted in one study in which the prevalence of LD was estimated using data of electronic medical record databases in Germany and the United Kingdom (UK). Generalized lipodystrophy (GL) was estimated to be 0.23-0.9/million and partial lipodystrophy (PL) (all subgroups included) prevalence was 1.2-2.5/million.³

Extrapolating the prevalence of GL to the Netherlands (17.1 million) and Belgium (11.3 million) would yield in 4 to 15 GL patients in the Netherlands and 3 to 10 GL patients in Belgium. The estimated number of patients with PL is 20 to 43 patients in the Netherlands and 13 to 28 in Belgium. Not all PL patients will be treated with metreleptin. It is expected that about 10 to 20% of all PL patients are eligible for treatment with metreleptin as they are able to manage their disease with the other treatments for their comorbidities.

Data from the expanded access program in the UK indicate that currently 26 patients are being treated in this program. Of these 26 patients there are 9 patients with GL and 17 patients with uncontrolled PL. It is expected that the number of patients on this expended access program is a good representation of the number of eligible patients in the UK.⁴

Extrapolating this UK data to the Netherlands and Belgium would yield in 6 to 8 patients (2-3 GL and 4-5 uncontrolled PL) in the Netherlands and 4 to 5 patients in Belgium (1-2 GL and 3 uncontrolled PL).

Dutch expert opinion indicate that currently 40 to 45 PL patients have been diagnosed in the Netherlands of which 4 to 6 patients could become candidates for treatment with metreleptin in the coming three years. However, as a result of education of clinicians about LD could increase awareness and could result in a some additional eligible patients. This results according to Aegerion in maximum 3 GL patients and 8 uncontrolled PL patients that are eligible for treatment with metreleptin in the coming three years.

According to Belgian expert opinion, there are 15 patients LD patients in Belgium. Currently, 3 patients are treated with metreleptin (2 GL and 1 PL patients) and two more PL patients might be candidates for metreleptin treatment. According to Aegerion, a maximum of 3 GL patients and 5 uncontrolled PL patients might be in need of treatment with metreleptin in the coming three years.

Market share

It is expected that metreleptin will be prescribed to patients if they fit the indication criteria. The two patients in the Netherlands and three patients in Belgium who are currently being treated within the expanded access program will remain on treatment.

The market share is expected to be 50% in year 1, 75% in year 2 and 100% in year 3. It is thereby assumed that new patients will start gradually during the year except the patients that are already being treated with metreleptin. Another assumption is that none of the patients will stop treatment or will die during treatment.

Off-label use

The risk of off-label use is negligible as it is not expected that metreleptin will be prescribed beyond the registered indication. Although metreleptin was originally developed for the treatment of obesity, clinical studies have shown that is not effective for the treatment of obesity. In the NIH studies a total of seven patients with congenital leptin deficiency received off-label treatment with metreleptin. However, both in Belgium and in the Netherlands the experts indicated that they do not know any patient with congenital leptin deficiency.

Table 2: Estimated number of patients with lipodystrophy who are eligible for treatment with metreleptin

	Year 1	Year 2	Year 3
Prevalence generalized lipodystrophy	0.23-0.9 cases/million		
Prevalence partial lipodystrophy	1.2-2.5 cases/million		
Calculation for the Netherlands (NL)			
Estimated number of patients with GL in NL	3 patients		
Estimated number of patients with uncontrolled PL in NL	8 patients		
Patients currently treated with metreleptin in the Netherlands (GL + PL)	1 GL + 1 PL		
Market share new patients	50%	75%	100%
Number of patients on treatment in NL	2	6	8
Patients (GL + PL) starting with treatment in NL	4	2	3
Total number of patients who are eligible for treatment with metreleptin in the Netherlands	6	8	11
Calculation for Belgium (BE)			
Estimated number of patients with GL in BE	3 patients		
Estimated number of patients with uncontrolled PL in BE	5 patients		
Patients currently treated with metreleptin in Belgium (GL + PL)	2 GL + 1 PL		
Market share new patients	50%	75%	100%
Number of patients on treatment in BE	3	4	6
Patients (GL + PL) starting with treatment in BE	1	2	2
Total number of patients who are eligible for treatment with metreleptin in Belgium	4	6	8

2.2

Substitution

According to Aegerion it is likely that patients treated with metreleptin will require less standard of care treatment which could result in a reduction of the healthcare costs for these patients. However, patients will continue to receive standard of care but it is possible that the quantity of care will be reduced. It is however not possible to quantify the possible reduction of standard of care needed for each patient and

thus to estimate the possible savings in healthcare resource use. Therefore possible savings in usual care are not included in the calculation of the budget impact.

2.3 Costs per patient per year

At the moment there is no official price set in the Netherlands. Currently there are three different doses available, being: 11.3 mg powder in a vial, 5.8 mg powder in a vial and a 3 mg powder in a vial containing a dose of 10 mg, 5 mg and 2.5 mg respectively. The expected prices of these three vials for both the Netherlands and Belgium can be found in table 3.

Lipodystrophy cannot be cured and as a result patients will require daily injections with metreleptin. Metreleptin is administered once daily and the treatment dose is adjusted to the weight of the patient by patients till 40 kilogram and is also subject to the treatment response.

Table 3: Costs per patient per year

	Netherlands	Belgium	
		Hospital price	Ambulatory price
Vial of 11.3 mg	€2,655	€2,814.30	€2,814.54
Vial of 5.8 mg	€1,340	€1,420.40	€1,420.64
Vial of 3 mg	€673	€713.38	€713.62
Number of vials per day		1	
Treatment duration		365 days per year	
Total costs per year (vial 11.3 mg)	€969,075	€1,027,219.50	€1,027,306.01
Total costs per year (vial 5.8 mg)	€489,100	€518,446.00	€518,532.51
Total costs per year (vial 3 mg)	€245,645	€260,383.70	€261,565.21

As indicated in the SmPC each patient is titrated up to the adequate dose for that specific patient.¹ Dose increase should be not be made more often than every 4 weeks. Dosage decrease due to weight loss is weekly possible. The dosing scheme including starting dose, dose adjustments and maximum dose can be found in table 4.

Table 4: Metreleptin recommended dose as indicated in SmPC

Baseline weight	Starting daily dose (injection volume)	Dose adjustments (injection volume)	Maximum daily dose (injection volume)
Males and females ≤ 40 kg	0.06 mg/kg (0.012 ml/kg)	0.02 mg/kg (0.004 ml/kg)	0.13 mg/kg (0.026 ml/kg)
Males > 40 kg	2.5 mg (0.5 ml)	1.25 mg (0.25 ml) to 2.5 mg (0.5 ml)	10 mg (2 ml)
Females > 40 kg	5 mg (1 ml)	1.25 mg (0.25 ml) to 2.5 mg (0.5 ml)	10 mg (2 ml)

It is not clear from the SmPC which proportion of the patients use which dose of metreleptin. Using information from the expanded access program in the UK Aegerion made an assumption on the proportion of patients using a specific vial. In the UK, a total of 26 patients received metreleptin via the expanded access program. In that program, the majority of the patients (69.23% or 18 patients) used the 5.8 mg vial, only 11.53% (or 3 patients) of the patients used the 11.3mg vial and 19.23% (5 patients) used the 3 mg vial.⁴ The National Health Care Institute

(Zorginstituut Nederland) will use different distributions of the patients over the vials, in the maximum scenario every patient will use the largest vial of 11.3 mg to have the maximum budget impact. In the other scenario or 'current use' scenario the National Health Care Institute will use a distribution that is based on the dosage of the patients that are currently treated in the Netherlands and Belgium, resulting in the following distribution: 40% of patients will use a 11,3 mg vial, 40% will use a 5.8 mg vial and 20% will use a 3 mg vial.

The assumption is made that the treatment adherence rate is 100%. The clinical study report of the NIH studies indicate that noncompliance to the treatment was mentioned as a reason for early discontinuation of the study. Unfortunately, patient compliance with the treatment with metreleptin was not collected in a systematic manner.

There are no additional costs expected related to the treatment with metreleptin. The devices needed to administer metreleptin are provided in conjunction with the medicine supplied in vials.

2.4

Assumptions

The calculations are based on the following assumptions:

- The current 2 patients at LUMC (The Netherlands) and the current 3 patients at UZ Leuven (Belgium) remain stable on their dose with corresponding specific vial (all in expanded access program). The two Dutch patients currently receive the 11.3 mg vial. Two of the Belgian patients receive a 5.8 mg vial and one receives an 11.3 mg vial.
- Market share will be 50% in year 1, 75% in year 2 and 100% in year 3 in both the Netherlands and Belgium
- One year equals 365 days of treatment and patients use 1 vial a day.
- New patients (not yet treated within the expanded access program) will start gradually during each year. In their first year these new patients are treated in average for 0.5 year. In following years they are treated for 1 full year.
- The anticipated prices for both the Netherlands and Belgium for the three different vials (11.3 mg, 5.8 mg and 3 mg) can be found in table 3.
- Two different scenarios with different proportions of patients in need of a specific vial size are calculated. In the maximum scenario all patients will use the largest vial of 11.3 mg. In the current use scenario 40% of the patients will use the 11.3 mg vial, another 40% of the patients the 5.8 mg vial and the final 20% the 3 mg vial. This only applies to new Dutch and Belgian patients on metreleptin.
- Treatment adherence is set at 100%. It is also assumed that all patients remain on treatment, although clinicians may stop treatment due to inadequate response or side effects. It is also assumed that no treated patient will die during treatment.
- No other additional costs associated with the metreleptin treatment.
- No costs savings have been included. It is possible that costs will be saved because of the impact on standard of care treatment and the impact on the progression of organ abnormalities and associated costs.

3 Budget impact analyse

3.1 Budget impact: only pharmaceutical costs

In table 5a (the Netherlands) and table 5b (Belgium) an overview can be found of the total budget impact when metreleptin is added to the current treatment options for the indication lipodystrophy.

Only the pharmaceutical costs are included in the table, potential additional costs or savings to the healthcare budget are not included in the analysis.

Table 5a: Estimation of the total costs of the addition of metreleptin as treatment option for lipodystrophy - the Netherlands

Scenario	Year	Market share	Number of patients - new	Number of patients - on treatment	Total costs/year metreleptin
Maximum ^A	1	50%			€3,876,300
Current use ^B			4	2	€3,034,610
Maximum	2	75%			€6,783,525
Current use			2	6	€4,860,158
Maximum	3	100%			€9,206,213
Current use			3	8	€6,441,155

^A All patients use the largest vial of 11.3 mg

^B Of the new patients use 40% the vial of 11.3 mg, 40% the vial of 5.8 mg and 20% the 3 mg vial

Table 5b: Estimation of the total costs of the addition of metreleptin as treatment option for lipodystrophy - Belgium

Scenario	Year	Market share	Number of patients - new	Number of patients - on treatment	Total costs/year metreleptin (hospital price)	Total costs/year metreleptin (ambulatory price)
Maximum ^A	1	50%			€3,595,268	€3,595,571
Current use ^B			1	3	€2,194,303	€2,195,154
Maximum	2	75%			€5,136,098	€5,136,530
Current use			2	4	€3,097,328	€3,098,855
Maximum	3	100%			€7,190,537	€7,191,142
Current use			2	6	€4,642,993	€4.644.694

^A All patients use the largest vial of 11.3 mg

^B Of the new patients use 40% the vial of 11.3 mg, 40% the vial of 5.8 mg and 20% the 3 mg vial

4 Conclusion

Taking into consideration the assumptions made regarding the number of patients, market share and vials used by the patients will reimbursement in the Netherlands of metreleptin (Myalepta®) (opname op lijst 1B van het GVS) for the treatment of lipodystrophy result in additional costs for the pharmaceutical budget between €6.44 million (current use scenario) to €9.21 million (maximum scenario) in year 3. In Belgium, the budget impact using the hospital price is estimated between €4.6 million and €7.2 million. When using the ambulatory price, the budget impact is estimated between €4.6 million and €7.2 million in year 3. Hereby exists uncertainty on the number of patients and the vial going to be used by the patients.

5 References

1. Annex I. Summary of Characteristics Myalepta/Public Assessment Report. 1A. https://www.ema.europa.eu/documents/product-information/myalepta-epar-product-information_en.pdf. / 1B http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004218/WC500253138.pdf)
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3. Chiquette E, Oral EA, Garg A, et al. Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. *Diabetes Metab Syndr Obes*. 2017;10:375-83.
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