Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

**National Health Care Institute**
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

**Contact**
Ms J.M. van der Waal
T +31 (0)6 120 017 28

*2022021146*

**Our reference**
2022021146

Date 8 July 2022
Re: GVS advisory report re-assessment metreleptin (Myalepta®)

Dear Mr Kuipers,

In the letter of 29 November 2021 (CIBG-21-02903), the Minister of Medical Care and Sport asked the National Health Care Institute to carry out a substantive assessment of whether metreleptin (Myalepta®) is interchangeable with a product that is included in the Medicine Reimbursement System (GVS). The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has since completed this assessment.

Metreleptin (Myalepta®) is indicated in addition to a diet as replacement therapy to treat the complications of leptin deficiency in patients with lipodystrophy:
- With confirmed congenital generalized lipodystrophy (Berardinelli-Seip syndrome) or acquired generalized lipodystrophy (Lawrence syndrome), in adults and children aged 2 and older;
- With confirmed familial partial lipodystrophy or acquired partial lipodystrophy (Barraquer-Simons syndrome), in adults and children aged 12 years and older for whom standard treatments did not achieve adequate metabolic control.

The marketing authorisation holder is asking for inclusion in List 1B of the Healthcare Insurance Regulation for part of the indication: generalized lipodystrophy (GL).

**Background initial assessment (May 2019)**
On 14 May 2019, the National Health Care Institute advised you not to include metreleptin (Myalepta®) in the GVS. Due to the limited study design of the single-arm studies and the absence of a historical control group, long-term data, and data on mortality and quality of life, the National Health Care Institute concluded in the initial assessment that metreleptin for patients with generalized lipodystrophy and partial lipodystrophy had a therapeutic lesser value compared to the standard treatment.

**Outcome of the substantive assessment**
*Review of interchangeability*
To determine the place of a medicinal product in the GVS, its interchangeability with medicinal products already included in the GVS must first be assessed.

**National Health Care Institute**
Care
Medicinal Products

**Date**
7 July 2022

**Our reference**
2022021146

Based on the criteria for interchangeability, metreleptin (Myalepta®) is not interchangeable with another medicinal product included in the GVS.

*Therapeutic value*
Because new data have become available and have been submitted, the National Health Care Institute has carried out a reassessment.
The leptin deficiency observed in patients with GL can result in a significant reduction in the ability to regulate hunger and energy metabolism, as well as in a dysfunction of the glucose and fat metabolism. GL cannot be cured. Currently, these patients are only treated for the comorbidities that arise as a result of the disease. Metreleptin gives these patients a clinically relevant improvement on both HbA1c and fasting triglycerides. An HbA1c reduction of 2.2% is achieved through metreleptin treatment, which can be considered as a major effect in these patients. In addition, improvements in fatty liver disease, menstrual cycle and extreme hunger pangs are also observed. In addition, new research shows that treatment with metreleptin is associated with a significant reduction in mortality risk for the entire group of lipodystrophy patients. However, a larger sample size is required to reliably assess the effect of metreleptin on the mortality risk in the GL subgroup.
Given the rarity and severity of the condition, the safety profile is acceptable, although the administration of metreleptin through subcutaneous injection may be difficult in patients with minimal subcutaneous fat tissue.

The National Health Care Institute concludes that metreleptin complies with the established medical science and medical practice in congenital generalized lipodystrophy (Berardinelli-Seip syndrome) or acquired generalized lipodystrophy (Lawrence syndrome), in adults and children aged 2 and older. The National Health Care Institute concludes, on the basis of the data, that the medicinal product has an added value compared to the current standard treatment.

*Budget impact analysis (BIA)*
Treatment with metreleptin costs €350,804 per patient per year. Taking into account assumptions about the number of patients, their weight distribution, and the market penetration, inclusion in the GVS is expected to be accompanied by additional costs charged to the pharmaceutical budget of approximately €2.8 million in the third year after inclusion in the health insurance package.

*Pharmaco-economic analysis*
Based on the estimated budget impact, the product is exempt from pharmacoeconomic analysis. That is largely because of the very limited number of patients. At the same time, the National Health Care Institute notes that the annually recurring costs per patient are high. As in previous similar situations, the National Health Care Institute also keeps this case in mind when evaluating the criteria for the implementation of a pharmacoeconomic analysis in the future. In addition, the National Health Care Institute considers it desirable that health care insurers make strict purchasing arrangements for metreleptin.

**Advice**

The National Health Care Institute recommends that metreleptin (Myalepta®) be included in List 1B of the GVS, with the following reimbursement condition:
Only for insured persons aged 2 years or older

- With congenital generalized lipodystrophy (Berardinelli-Seip syndrome) or acquired generalized lipodystrophy (Lawrence syndrome);
- If patients with the current treatments for diabetes mellitus or dyslipidaemia and a strict diet cannot meet the target values for HbA1c, triglycerides and LDL cholesterol, or in case of hepatic steatosis with steatohepatitis (increased transaminases) and/or decreased elasticity on the fibroscan.

The treatment should be evaluated every 6 months and terminated in the event of insufficient efficacy.
The treatment must be carried out by an expertise centre.

Yours sincerely,

Sjaak Wijma
*Chairperson of the Executive Board*

**National Health Care Institute**
Care
Medicinal Products

**Date**
7 July 2022

**Our reference**
2022021146