Zorginstituut Nederland

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To the Minister of Health, Welfare and Sport
P.O. Box 20350
2500 EJ THE HAGUE

Date 22 April 2025
Re: GVS advice 'Expansion of further conditions' setmelanotide (Imcivree®)

Dear Ms Agema,

The National Health Care Institute advises you on expanding the reimbursement conditions for setmelanotide (Imcivree®) for the treatment of obesity and control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children aged ≥ 6 years. This advice was prompted by your request in the letter of 4 November 2024 (CIBG-24-07512). The National Health Care Institute advises you not to change the reimbursement conditions.

Bardet-Biedl syndrome (BBS) is a rare hereditary disorder in which the cilia in almost all cell types are affected. Because the cilia do not work properly, problems occur in various organs such as the kidneys, eyes (retina) and brain. In addition, patients experience extreme, insatiable hunger ('hyperphagia'). Most people with BBS (72 – 92%) will become morbidly obese. They therefore have an increased risk of liver abnormalities, cardiovascular disease and diabetes. There are an estimated 100 – 150 people with BBS in the Netherlands.

Registered indications
Setmelanotide is indicated for the treatment of obesity and control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC) deficiency, including PCSK1 deficiency, or biallelic leptin receptor (LEPR) deficiency in adults and children aged 2 years and older.

Setmelanotide is already listed in List 1B of the Health Insurance Regulation for the treatment of insured people aged ≥ 6 years with genetically confirmed pro-opiomelanocortin (POMC) deficiency, including proprotein convertase subtilisin/kexine type 1(PCSK1) deficiency, or biallelic leptin receptor (LEPR) deficiency, who have undergone a combined lifestyle intervention (CLI).

Claim by the marketing authorisation holder
Setmelanotide has a therapeutic added value in addition to a continuous, intensive combined lifestyle intervention (CLI), compared to continuous CLI+ alone in patients experiencing an extremely elevated weight-related risk (WRR) despite the use of CLI+ for at least 1 year.

The marketing authorisation holder therefore requests an expansion of the existing List 2 conditions for setmelanotide.

Advice
The National Health Care Institute recommends that the existing List 2 conditions for setmelanotide should not be extended for the indication described.

Substantive assessment
In the Netherlands, an intensive combined lifestyle intervention (CLI+) of at least one year is the initial standard treatment for patients with an extremely elevated WRR. The MAH's claim is based on results from a study of patients aged ≥ 6 years. Of these, 32 had BBS and 6 had Alström syndrome (AS)[1]. They were first treated in a blind study with setmelanotide or placebo for 14 weeks[2]. After that, they received setmelanotide for 52 weeks. It is not clear whether they had been treated with CLI+ for at least one year prior to participating in the study. They also did not receive setmelanotide as an addition to CLI+ treatment. In order to assess the effect of setmelanotide as purely as possible, it was assessed only in patients aged ≥ 12 years and not in the entire study population aged ≥ 6 years. The weight of children < 12 years may change (significantly) as a result of their physical growth. In the AS patients, the study outcome did not meet the study objective. Positive effects of setmelanotide were demonstrated in BBS patients.

A pre-planned subgroup analysis of BBS patients ≥ 12 years showed that their baseline weight had decreased by ~3% in the first 14 weeks, compared to placebo. In the following 52 weeks, this weight loss averaged ~6%. However, the effect of setmelanotide could no longer be compared with the effect of placebo. Although the result met the research target of 5% weight loss, its reliability is strongly challenged scientifically. In a later, unplanned subgroup analysis in BBS patients aged ≥ 18 years, a weight loss of ~8% was observed. Again, the effect of setmelanotide could not be compared with the effect of placebo. As a result, it cannot be determined with scientific reliability which part of this effect is based only on treatment with setmelanotide. This is esential because it is well known that treatment with placebo alone can be effective in many conditions. Finally, at the specific request of the National Health Care Institute, the MAH compared the effect of setmelanotide with the effect of placebo on age-related weight development[3] in BBS patients aged < 18 years during the blinded first 14 weeks of the aforementioned study. There was a small difference in favour of setmelanotide. That was also true after the following non-blinded 52 weeks. However, evaluation of the 'pure' effect of setmelanotide was also not possible here, as this effect could not be compared with the placebo effect.
Due to the very low scientific quality of the evidence in these three subgroups, the National Health Care Institute, supported by its Scientific Advisory Board (WAR), has many doubts as to whether the described effects of setmelanotide are also accompanied by health gains. Especially since in a large proportion of these patients these effects diminished over time. During the long-term follow-up study, more than half of them discontinued treatment within 3 years, although no

[1] Alström syndrome (AS), like BBS, is a hereditary disease of the cilia. Some characteristics (e.g. overweight/obesity at a very early age) match the characteristics of BBS.

[2] This means that neither the patients nor the researchers knew whether the treatment consisted of setmelanotide or placebo.

[3] According to the World Health Organisation (WHO) standard for the development of the Body Mass Index (BMI) in children.

(serious) adverse effects occurred. Overall, it cannot be scientifically reliably determined whether the effects described will also be achieved in BBS patients in Dutch clinical practice. As already described, Dutch practice differs from the study design in particular with regard to the use of CLI+.

In this context, the National Health Care Institute, also supported by its WAR, has considered that medicinal products such as liraglutide and semaglutide[4] are also applicable to patients with obesity caused by BBS from the age of 12 or 18 years on the basis of their registered indication. In the assessment of semaglutide for the treatment of adult obese patients (2024), the National Health Care Institute found that after 68 weeks of treatment, an average weight loss of 15.8% was achieved, compared with an average weight loss of 6.4% with liraglutide. The registration studies of semaglutide and liraglutide for obesity did not distinguish between general obesity and genetic obesity. The National Health Care Institute considers it possible that the effect of these medicinal products can also be achieved in patients with obesity due to BBS. It cannot be excluded that they are already being treated with this, as the symptoms of BBS are not always directly recognised as such in clinical practice.

Overall, the National Health Care Institute does not consider it sufficiently plausible in this context, and in particular due to the very low quality of the available evidence, that the addition of setmelanotide to a continuous CLI+ is of sufficient added value in patients aged ≥ 6 years with an extremely elevated WRR and with obesity due to BBS.

As such, setmelanotide does not comply with the established medical science and medical practice as an addition to a continuous CLI+ in adults and children aged ≥ 6 years with genetically confirmed BBS.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report is attached.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

[4] In the scientific literature, these medicinal products are categorised as GLP-1 agonists. Semaglutide can be used as obesity treatment under the brand name Wegovy®.