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Minister of Health, Welfare and Sport
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Date 12 July 2024
Subject GVS advisory report on semaglutide (Wegovy®)

Dear Ms Agema,

In the letter of 1 August 2023 (CIBG-23-05818), your predecessor asked the National Health Care Institute to assess whether semaglutide (Wegovy®) could be placed on List 1A of the Medicine Reimbursement System (hereinafter "GVS"). The National Health Care Institute has now completed this assessment. The considerations are included in the report attached to this letter.

Licensed indication
Semaglutide is a glucagon-like peptide (GLP-1) analogue and the registered indication is:
As an addition to a low-calorie diet and greater physical exercise for weight management, including weight loss and weight maintenance, in adults with an initial BMI of:
- ≥ 30 kg/m^2 (obesity), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) who have at least one weight-related comorbidity, such as dysglycaemia (prediabetes or diabetes mellitus type 2), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.

Claim by the marketing authorisation holder
The marketing authorisation holder is applying for reimbursement for the entire registered indication and claiming that semaglutide has added value over currently available treatments (combined lifestyle intervention [hereinafter also "CLI"], liraglutide and naltrexone/bupropion).

Package advice
The National Health Care Institute recommends that semaglutide (Wegovy®) should not be included in the basic health insurance package at this time.

Semaglutide (Wegovy®) does comply with established medical science and medical practice but the cost-effectiveness is not currently sufficiently substantiated. This is why the National Health Care Institute's current advice about including Wegovy® in the health insurance package is negative.

The National Health Care Institute is aware that this outcome of its assessment will be disappointing for both patients and treating physicians. Given the current shortages of the medicinal product and the potentially large impact on the pharmacy budget, it is particularly important to understand how to utilise these medicines most appropriately. This is because not reimbursing potentially cost-effective medicines can also make care less accessible. The National Health Care Institute is therefore asking the marketing authorisation holder to modify the pharmacoeconomic analysis and substantiate it better.
There is also a broader issue for society as a whole about reimbursing medicines for overweight and obesity. Work needs to be done on a normative framework for tackling overweight and obesity in Dutch society. In the context of access to care, we would like to stress to you that it is important to start this dialogue soon.

Established medical science and medical practice
The National Health Care Institute concludes that semaglutide (Wegovy®) meets established medical science and medical practice in weight management in adults with a BMI of ≥ 30 kg/m² (obesity) or ≥ 27 kg/m² to < 30 kg/m² (overweight) who have at least one weight-related comorbidity[1], as an addition to a CLI. Semaglutide has added value over liraglutide in patients **without** type 2 diabetes (DM2). A clinically relevant weight reduction of 9.4% was reported in favour of semaglutide. In patients **with** DM2, semaglutide has added value over placebo. A clinically relevant weight reduction of 6.1% was reported compared to placebo.

In the clinical trials of semaglutide, a CLI was started at the same time. These studies therefore only provide evidence for the efficacy of semaglutide in combination with a CLI. In addition, there is no data on the use of semaglutide after 2 years. On immediate discontinuation of treatment, weight was regained. There are no studies into responsible phasing out semaglutide after achieving sufficient weight loss. The effectiveness of semaglutide use for long-term weight loss is uncertain.

Cost-effectiveness
This is the first time that the National Health Care Institute has assessed the cost-effectiveness of a weight-reducing drug for overweight and obesity. Previous advisory reports in this field of indications involved exemption from the economic evaluation, because it was estimated (based on input from the physicians' association) during the assessments of liraglutide and naltrexone/bupropion that the budget impact would be less than 10 million euros.

The cost-effectiveness of semaglutide was analysed by the marketing authorisation holder in a highly complex disease model for overweight/obesity. Despite the efforts of both the marketing authorisation holder and the National Health Care Institute, the conclusion is that the pharmacoeconomic model is currently still insufficient in terms of quality and therefore unusable for decision-making. The National Health Care Institute believes that the model is not transparent enough; there is (likely to be) some bias and there is a lack of evidence. Please refer to the attachment to this letter for a technical explanation of this point. The enclosed pharmacoeconomic report details the crucial points and uncertainties.

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[1] Such as dysglycaemia (prediabetes or diabetes mellitus type 2), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.

Unfortunately, the National Health Care Institute can also therefore not issue advice on possible price negotiations you might conduct. This is essential for you and for the National Health Care Institute, because reimbursement of semaglutide at the current price demanded by the marketing authorisation holder would lead to a very high and potentially socially unjustifiable budgetary impact.

Budget impact analysis (BIA)
In Netherlands, around 7 million people are currently overweight (BMI ≥25 kg/m^2). Looking at the number of adults who could be eligible for semaglutide, based on the EMA label, this could come to about 4.2 million people. According to the guideline, pharmacotherapeutic treatment should currently only be used as an additional treatment on top of a CLI; the licensed indication also states "*as an adjunct to a low-calorie diet and greater physical exercise for weight management*" and this is therefore the starting point for the calculations in the BIA.

A different approach than normal was chosen for the budget impact analysis. Firstly, it is not yet clear how cost-effective this medicinal product is and which patients this treatment is most appropriate for. Additionally, there are many uncertainties about the number of patients who will participate in the CLI in the future and will thereby become eligible for semaglutide. Practice has taught us that there is a very high demand for obesity medicines. There are also numerous questions from the field about how to implement the current List 2 conditions of the weight-reducing medicines already reimbursed from the basic health insurance package. The current List 2 conditions are based on the 2010 Obesity Care Standard[2] and the physicians' association's agreements about appropriate use that are based upon it. This stated that people are only eligible for pharmacotherapeutic treatment *combined with a combined lifestyle intervention (CLI) recognised by the RIVM if the CLI is unsuccessful after 1 year.* The latest multidisciplinary Obesity Care Standard[3] (from 2023) states that pharmacotherapy may be considered earlier in the treatment at the discretion of the healthcare professionals for people with a BMI of ≥ 35 to < 40 *and* an enlarged abdominal circumference and/or comorbidity; *or* in people with a BMI of ≥ 40 kg/m^2.

Producing a realistic estimate of the number of patients actually eligible for semaglutide (Wegovy®) as additional treatment along with a CLI in the future is therefore not only difficult but also based on some crucial choices/assumptions:

- assuming stable growth in the annual number of new CLI participants, or assuming increased growth in the annual number of new CLI participants;
- assuming the current number of people following a CLI or assuming all people eligible for a CLI;
- assuming that a CLI is first followed for 1 year before starting pharmacotherapy (as per current reimbursement conditions), or assuming pharmacotherapy is started at the same time as the CLI.

To inform you as well as possible about the potential budget impact, it was decided to present four scenarios that vary the choices or assumptions listed

[2] *Zorgstandaard Obesitas* (Obesity Care Standard) – Partnerschap Overgewicht Nederland (PON), 2010
[3] *Zorgstandaard Obesitas* (Obesity Care Standard) – Partnerschap Overgewicht Nederland (PON), 2023

above for calculating the number of patients and the corresponding budgetary impact, based on the cost of semaglutide (about €2750 per annum) in the maintenance phase.

	Numbers of patients			Costs*
Scenario	Year 1	Year 2	Year 3	Additional costs in Year 3
1: current number of CLI participants who first follow a CLI for 1 year, with an annual growth of 5%	35,057	45,937	60,754	€59.3 million
2: current number of CLI participants who have first followed a CLI for 1 year, with annual growth figures of 10, 20 and 30% respectively	35,426	48,304	69,214	€62.4 million
3: total head count of the Dutch population eligible for a CLI who first have followed the CLI for 1 year, with annual growth figures of 10, 20 and 30% respectively	42,379	207,520	384,873	€661.1 million
4: total head count of the Dutch population eligible for a CLI, with annual growth figures of 10, 20 and 30% respectively	225,516	433,647	669,880	€1.3 billion

* Assuming market penetration figures of 70, 80 and 90% in years 1, 2 and 3 respectively.

The budget impact analysis shows that semaglutide could potentially have a very major impact on the pharmacy budget. It should be noted here that semaglutide is now the third medicinal product for this area of indications that has been assessed by the National Health Care Institute. However, a large number of other drugs are also under development for this indication that could affect semaglutide's market penetration in the future. The medicinal product tirzepatide (Mounjaro®) was recently approved by the EMA for roughly the same indication and the marketing authorisation holder can now submit a reimbursement dossier to the National Health Care Institute. The budget impact as presented therefore mainly reflects the number of overweight or obese patients eligible for pharmacotherapeutic treatment: under the current reimbursement conditions for the use of pharmacotherapy for overweight/obesity (scenarios 1-3) and if other reimbursement conditions for the use of pharmacotherapy were applied (scenario 4). The additional costs presented are based on the asking price of semaglutide; if products with a similar effect come onto the market in future, that competition will potentially reduce the additional costs. However, the potential advent of even more effective products that could command a higher asking price thanks to their greater effect must also be taken into account.

Appraisal
Given that no statement can currently be made about the cost-effectiveness of semaglutide, this dossier has not yet been discussed according to the usual procedure in a *public* meeting of the Insured Package Advisory Committee (hereinafter "ACP"). The National Health Care Institute, in consultation with the ACP, concludes that the large population potentially eligible for treatment with weight-reducing drugs, including semaglutide, means that a broader public discussion on the use of these products is very much warranted. However, that debate also needs an understanding of the cost-effectiveness and efficacy of these medicines, while it is also currently unclear what reimbursement of this medicinal product will yield for society.

Several other medicinal products will soon come onto the market for this indication area. We are therefore potentially about to medicalise part of the Dutch population. It is as yet unclear how desirable this is. This was also recently endorsed by the Centre for Ethics and Health of the Netherlands, a partnership between the Health Council of the Netherlands and the Council for Public Health & Society. The overview of arguments entitled *Door dik en dun? Gewichtsverlagende medicatie in het basispakket* (Through thick and thin? Weight-lowering medication in the basic health insurance package) focuses on ethical considerations about the desirability of reimbursing weight-lowering medication[4]. Rather than just looking at the dossier for this specific medicine, broader consideration should be given to using preventive resources versus interventions (treatment) for overweight and obesity. The issue of our obesogenic society in fact transcends the care sector and impinges upon finance, economics, education and more. It will only be possible to present a more realistic budget impact estimate to you once it is clearer how cost-effective it is and which patients this treatment is most appropriate for. However, it is now the right time for a multi-party dialogue and we recommend that you initiate one, centred on the potential impact of these medicinal products.

Shortages
There is currently a shortage of semaglutide, which means that not all patients eligible for treatment may have access to it[5]. In particular, this is the case for the low-dose semaglutide product (Ozempic®), which is licensed for diabetes (rather than for overweight and obesity like Wegovy®, which the present document is assessing). The pharmaceutical company Novo Nordisk is the manufacturer and marketing authorisation holder of both semaglutide and liraglutide. To increase production of Ozempic®, the marketing authorisation holder has decided to reduce the supply of liraglutide temporarily. Partly because of the shortage, the Dutch College of General Practitioners has advised prescribing semaglutide (Ozempic®) only for people with diabetes[6]. The shortage underlines the importance all the more of identifying those who would benefit most from pharmacotherapeutic treatment. Reimbursement of semaglutide (Wegovy®) for overweight and obese patients should only come into effect once the shortages of semaglutide and liraglutide have been resolved for the diabetic patients who are currently adjusted to them.

Appropriate care

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[4] https://www.ceg.nl/documenten/publicaties/2024/05/06/argumentenwijzer
[5] https://www.cbg-meb.nl/actueel/nieuws/2023/11/17/aanhoudend-tekort-diabetesmedicijn-ozempic-en-victoza
[6] https://www.nhg.org/actueel/adviezen-tekorten-glp1-agonisten/

The large impact on the pharmacy budget and the current shortages of GLP-1 agonists mean that choices will very likely have to be made about who these medicines can most appropriately be used on. The current cost-effectiveness analysis does not as yet provide enough solid guidance to make any statements about this. Further detailing and validation of a cost-effectiveness analysis or disease model would also be important for appropriate use of the other medicines that will follow for the same indication.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

Appendix

Technical explanation of why the quality of the pharmacoeconomic analysis is insufficient
The health gains reported by the marketing authorisation holder (expressed in QALYs) are calculated using the modelled effects of semaglutide treatment on preventing comorbidities and preventing progression to diabetes. However, these are long-term measures of outcome that could not be measured/observed in the studies assessed. For it still to be possible to say something about health gains, a model is used to make estimates based on surrogate outcomes. The surrogate measures of outcome that were measured in the studies included BMI, SBP, cholesterol and HbA1c. In the model, the effect of semaglutide on these outcome measures is linked to preventing weight-related comorbidities and preventing progression to diabetes. However, there are still little or no direct study data on the effects of semaglutide on comorbidities and preventing progression to diabetes. For this, the surrogate outcome data from the study with a follow-up of at most 2 years were extrapolated in the model to 20 years. The effects on hard outcome measures are consequently highly uncertain. Numerous assumptions and choices have been made in the model that have a large number of effects on the results of the analysis, as can be seen in our analyses of the scenarios. Several of these assumptions and choices are likely to involve bias (e.g. the choices for modelling mortality, bariatric surgery or BMI classes). These points all made the outcomes of the model highly uncertain. In addition, it is unclear which subpopulations the medicinal product is most and least cost-effective in.

The National Health Care Institute cannot therefore provide a methodologically reliable estimate of cost-effectiveness, nor can it give an indication of the price reduction required to get close to an acceptable cost-effectiveness. The cost-effectiveness model should in any event be validated using Dutch models that have already been published; that is currently not present in the analysis.