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Our reference
2020018412

Date 29 May 2020
Subject GVS assessment of oral semaglutide (Rybelsus®)

Dear Mr van Rijn,

In your letter of 9 March 2020 (CIBG-20-0120), you requested Zorginstituut Nederland to assess, using the parallel procedure CBG-ZIN, whether oral semaglutide (Rybelsus®) is interchangeable with a product that is included in the medication reimbursement system (GVS).
In the Parallel Procedure CBG-ZIN pilot, the reimbursement process was started while the registration process had not yet been completed. Medicinal products that go through these parallel procedures, rather than the current sequential procedures, will become available to the patient more quickly. The EMA registration of oral semaglutide (Rybelsus®) was published on the EMA website on 27 May 2020. This is normally the time when a reimbursement dossier can be submitted. Due to the parallel procedure, the Zorginstituut can now rule on the reimbursement immediately after registration.
The Zorginstituut has since completed its assessment. The considerations are included in the GVS report attached to this letter, with the pharmaco-therapeutic report and the budget impact analysis.

The manufacturer is asking for inclusion on List 1B of the Health Insurance Regulation.

Semaglutide belongs to the pharmaco-therapeutic group of GLP-1 (glucagon-like peptide-1) receptor agonists. The product is already available as an injection fluid (Ozempic®). This assessment is related to the first oral formulation of a GLP-1 receptor agonist (Rybelsus®). The product is available in 3 mg, 7 mg, and 14 mg tablets.
Semaglutide (Rybelsus®) is indicated for 'for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise
• *as monotherapy when metformin is considered* inappropriate *due to intolerance or contraindications*
• *in combination with other medicinal products for the treatment of diabetes'*.

The starting dose of semaglutide is 3 mg once a day. After one month, the dosage should be increased to a maintenance dose of 7 mg once a day. After at least one month, the dosage can be increased to the maximum recommended dose of 14 mg once a day.

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Assessment of interchangeability
Rybelsus® (oral semaglutide) is not interchangeable with Ozempic® (subcutaneous semaglutide) and the other subcutaneous GLP-1 receptor agonists included in the GVS, due to a difference in the route of administration. On the basis of the criteria for interchangeability, semaglutide (Rybelsus®) is also not interchangeable with the other oral blood glucose reducing medicinal products included in the GVS and registered for use in diabetes mellitus type 2.
Based on the above, semaglutide (Rybelsus®) cannot be placed on List 1A. Next, the Zorginstituut assessed whether Rybelsus® is eligible for inclusion on List 1B.

Therapeutic value
In the pharmaco-therapeutic report, semaglutide (Rybelsus®) was compared to subcutaneous semaglutide or another subcutaneous GLP-1 receptor agonist. The Zorginstituut has been advised by its Scientific Advisory Board (WAR). Zorginstituut Nederland has come to the final conclusion that oral semaglutide has a therapeutically equal value compared to subcutaneous semaglutide or another subcutaneous GLP-1 receptor agonist. This applies to a defined (more limited) population within the registered indication, namely the reimbursement conditions as set out below. This corresponds with the reimbursement conditions for the subcutaneous GLP-1 receptor agonists.

Budget impact analysis
Taking into account assumptions about the number of patients eligible for oral semaglutide (Rybelsus®) and the market penetration, inclusion of Rybelsus® on List 1B will be accompanied by additional costs of €24.9 million, charged to the pharmaceutical budget in the third year after inclusion in the basic insured package when only the costs of Rybelsus® are taken into account. However, taking into account the substitution of subcutaneous semaglutide or another subcutaneous GLP-1 receptor agonist, the inclusion will result in cost savings for the benefit of the pharmaceutical budget. These savings are estimated at €35.9K in the third year after inclusion in the basic insured package.

There is some uncertainty about the number of patients who will start on Rybelsus®. In addition, the preference for Rybelsus® over subcutaneous semaglutide or another subcutaneous GLP-1 receptor agonist will vary per individual patient, making it difficult to properly estimate the number of patients who will prefer the oral administration of Rybelsus®. The budget impact analysis provides a broad estimate of the number of new patients who will start on Rybelsus®. In practice, the number of patients may differ. There is also uncertainty about the percentage of patients that will switch from the current diabetes medication to Rybelsus®.

This product has been exempted from pharmaco-economic analysis.

Advice on inclusion in the GVS
On the basis of the criteria for interchangeability, oral semaglutide (Rybelsus®) is not eligible for inclusion on List 1A. Zorginstituut Nederland advices including

semaglutide (Rybelsus®) on List 1B and List 2 of the Health Insurance Regulation and imposing the conditions stated below. This corresponds with the reimbursement conditions for the subcutaneous GLP receptor agonists. Inclusion on List 1B is accompanied by savings of €35.9K.

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Conditions for oral semaglutide

1. Exclusively for insured persons with diabetes mellitus type 2 and a body mass index (BMI) ≥ 30 kg/m² whose blood glucose values cannot be adequately regulated with the combination of metformin and a sulfonylurea derivative in the maximum tolerable dosages and who does not use insulin, or
2. as an addition to metformin and basal insulin (NPH insulin/long acting analogue insulin) in an insured person with type 2 diabetes mellitus and a BMI ≥ 30 kg/m^2 whose blood glucose values are insufficiently controlled after ≥ 3 months of treatment with optimal titrated basal insulin in combination with metformin (whether or not with a sulfonylurea derivative) in a maximum tolerable dosage.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board