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Date 26 September 2019
Subject Extension of further conditions for GLP-1ra by reducing the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2

Dear Mr Bruins,

In your letter of August 2019 (CIBG-19-08625) you asked the National Health Care Institute to extend the further conditions for the glucagon-like peptide 1 receptor agonists (GLP-1ra). The application for further extension was submitted by the Rondetafel Diabeteszorg (Diabetes Care Round Table), concerning a reduction in the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2. *The application was prompted by recent changes made to the treatment guidelines for type 2 diabetes mellitus in primary and secondary care by the Dutch College of General Practitioners and the Dutch Internists Association respectively.* Since your request concerns an adjustment to the existing reimbursement condition for GLP-1ra, we will respond to this in the form of a letter report, supplemented by a budget impact analysis (enclosed as a separate document).

Current situation
GLP-1ra are registered for the regulation of blood glucose levels in adults with type 2 diabetes mellitus, in combination with oral hypoglycaemic medicinal products and/or basal insulin, if these do not provide adequate glycaemic control in conjunction with diet and exercise. Six GLP-1ra are currently registered in the Netherlands, namely dulaglutide (Trulicity®), exenatide (Byetta® and Bydureon®), liraglutide (Victoza®), lixisenatide (Lyxumia®) and semaglutide (Ozempic®). Based on previous assessments by the National Health Care Institute, these GLP-1ra have been placed on List 1A (cluster 0A10BXAP V) of the Medicines Reimbursement System (GVS). With regard to reimbursement, conditions 58 and 85 from List 2 currently apply:

1. *only for insured persons with type 2 diabetes mellitus and a BMI ≥ 35 kg/m² whose blood glucose values cannot be adequately regulated with the combination of metformin and a sulphonylurea derivative at the maximum tolerable dosages, and who do not use insulin;*

2. *as an addition to metformin and basal insulin (NPH insulin/long-acting insulin analogue) in an insured person with type 2 diabetes mellitus and a BMI ≥ 30kg/m^2 whose blood glucose values are insufficiently regulated after ≥3 months of treatment with optimally titrated basal insulin in combination with metformin (whether or not with a sulphonylurea derivative) at a maximum tolerable dosage.*

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Extension of further conditions
The application for further extension concerned a reduction in the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2 in the 1st condition. This was prompted by recent changes (concerning GLP-1ra) to the treatment guidelines for type 2 diabetes mellitus *in primary and secondary care by the Dutch College of General Practitioners and the Dutch Internists Association respectively.* The revised guidelines (2018) state that GLP-1ra has a place in the treatment of selected cases where it is vital to avoid hypoglycaemia (for example, in case of professional drivers) and/or the patient has a BMI of ≥30 kg/m^2. The treatment guideline and the considerations for extending the further conditions are specified in detail in Annex 1.

Conclusion regarding therapeutic assessment
Based on the place of GLP-1ra in the revised treatment guidelines for type 2 diabetes mellitus and on the supporting scientific evidence, reducing the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2 is in line with the 1st further condition (and thus with an extension of the further conditions) concerning the state of science and practice.

Conclusion regarding the budget impact analysis
The extension of the List 2 conditions for GLP-1ra will be accompanied by additional costs estimated at €13.5 million in the third year following adjustment of the List 2 conditions, if the costs of GLP-1ra alone are included, and €8.2 million if basal insulin substitution is also taken into account. This estimate only includes the costs of the medicinal products. From the broader care perspective, including the cost of lancets and hypodermic needles for basal insulin, the budget impact is estimated at €7.5 million in the third year following an adjustment to the List 2 conditions, if basal insulin substitution is taken into account.

Advice from National Health Care Institute
GLP-1ra are already included in List 1A of the Medicine Reimbursement System (cluster 0A10BXAP V). We recommend extending the List 2 conditions for GLP-1ra by reducing the BMI cut-off value in the 1st condition from 35 kg/m^2 to 30 kg/m^2. This extension to the further conditions involves additional costs.

New conditions for GLP-1ra

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

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Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Annex 1: Assessment of extension of further conditions by amending the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2

Annex 1

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Assessment of extension of further conditions for GLP-1ra by reducing the BMI cut-off value from 35 kg/m² to 30 kg/m²

Type 2 diabetes mellitus[1]
Type 2 diabetes mellitus is a chronic disorder characterised by insulin deficiency. The result is an excessively high blood glucose level. The disease is caused by insufficient insulin secretion by β cells in the pancreas and by insulin resistance in liver, muscle, and adipose tissue. Insulin resistance is often associated with elevated blood pressure, overweight, elevated triglyceride levels, and decreased HDL cholesterol levels. Type 2 diabetes mellitus patients run an increased risk of microvascular complications, such as damage to the eyes, kidneys and nerves (diabetic foot), macrovascular complications (cardiovascular disorders) and mortality.

Treatment guideline for type 2 diabetes mellitus[1, 2]
In 2018, partially revised treatment guidelines for type 2 diabetes mellitus in primary and secondary care were issued by the Dutch College of General Practitioners and the Dutch Internists Association respectively. The key change to the guidelines concerns an adjustment to the medical management roadmap, in which substances such as glucagon-like peptide 1 receptor agonists (GLP-1ra) have been given a place.

Treatment options[1, 2]
The treatment of type 2 diabetes mellitus focuses on preventing and treating microvascular and macrovascular symptoms and complications by regulating blood glucose levels, blood pressure, and lipid levels, plus caring for foot problems and treating any potential comorbidities. In addition, lifestyle recommendations are discussed with the patient, such as not smoking, adopting a healthy diet, weight control, getting sufficient exercise, and having the patient come in for regular check-ups.

Various medicinal products are available for regulating blood glucose levels, including GLP-1ra. The treatment objective is to achieve a target value for haemoglobin A1c (HbA1c) in the blood, while allowing for the patient's age and factors such as comorbidity, complications, feasibility and motivation. The treatment consists of four steps, in accordance with the Dutch College of General Practitioners' standard. Treatment commences with oral hypoglycaemic medicinal products, namely metformin (step 1). If this fails to achieve sufficient results, a sulphonylurea derivative is added (step 2). The next step preferably involves the addition of insulin therapy, initially involving long-acting (or intermediate-acting) insulin (basal insulin) once daily (step 3), followed by the addition of short-acting insulin (bolus insulin) (step 4). In consultations between the practitioner and the patient, a GLP-1ra or dipeptidyl-peptidase-4 inhibitor (DPP-4r) could be considered as an alternative to insulin in steps 3 and 4.

The goal of the reimbursement application is to extend the 1st further condition, in which GLP-1ra serves as an alternative to basal insulin (step 3). According to the revised guidelines, GLP-1ra can be considered as an alternative to insulin in patients with an HbA1c level of <15 mmol/mol above the individual target value where it is vital to avoid hypoglycaemia (for example, in the case of professional drivers) and/or the patient has a BMI of ≥30 kg/m^2. However, the Dutch College of General Practitioners notes that dipeptidyl-peptidase-4 inhibitors (DPP-4r) are preferable to GLP1 agonists in patients with a BMI of 30–35 kg/m². This is due to the fact that DPP-4r have a more convenient formulation (oral versus

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subcutaneous for GLP-1ra) and to the high cost of GLP-1ra. In patients with a BMI of ≥ 35 kg/m², GLP1 agonists are preferred (over DPP-4r), due to their desirable effects on weight.

GLP-1ra must be used in combination with metformin and a sulphonylurea derivative. Unlike insulin use, no self monitoring is required in this instance. The contraindications are a history of pancreatitis, or pancreatic or thyroid malignancies, or a greatly increased risk of these disorders. In addition, caution should be exercised when prescribing GLP-1ra for patients with a known history of gastroparesis, hepatic insufficiency, renal failure (eGFR <30 ml / min/1.73 m^2) or heart failure. After six months, a minimum reduction of 5 mmol/mol in the HbA1c level must be achieved – with no weight gain – before further treatment with GLP-1ra can be permitted. If this is not achieved then the treatment should be terminated and once-daily insulin treatment should be initiated.

Desirable and undesirable effects of GLP-1ra
Some recent studies, including a meta-analysis, show that after approximately 26 weeks of treatment, GLP-1ra are just as effective in reducing HbA1c levels as basal insulin. They lead to weight loss (0.5-5.5 kg on average), and involve a lower risk of non-severe symptomatic hypoglycaemia than basal insulin.[3, 4] These studies were largely performed in type 2 diabetes mellitus patients with a BMI of ≥30 kg/m^2. There is no evidence that baseline BMI has any effect on the degree of reduction in HbA1c levels or on the level of weight reduction that can be achieved with this medicinal product. This conclusion was reached back in 2009, in the review of exenatide[5]. It is also supported by more recent studies of liraglutide involving cut-off BMI values of <30, 30-35, and> 35 kg/m^2[6, 7]. The observed reduction in HbA1c levels associated with GLP-1ra indicates a positive effect on cardiovascular complications. This is supported by a meta-analysis showing a reduction in non-fatal stroke, non-fatal myocardial infarction, mortality associated with cardiovascular disease, in addition to total mortality from some GLP-1ra (lixisenatide, liraglutide and semaglutide) compared to placebo over a period of 2.1 to 3.8 years[8]. The most common undesirable effects (i.e. gastrointestinal side effects and skin reactions) have been discussed in previous assessments by the National Health Care Institute. They are listed in the GLP-1ra summary of product characteristics. There are still no details concerning the occurrence of long-term side effects such as gallstones, retinopathy, thyroid and pancreatic carcinoma.

Considerations regarding determination of placement
GLP-1ra have a place in the treatment of type 2 diabetes mellitus in selected cases. This concerns patients with an HbA1c level <15 mmol/mol above the individual target value, if hypoglycaemia causes problems in relation to work and/or efforts to achieve weight reduction at a BMI ≥30 kg/m^2 are a key consideration. In the past, a BMI cut-off value of 35 kg/m^2 was selected when establishing the 1st condition for GLP-1ra (in 2009). At the time, there was little evidence to indicate that GLP-1ra – unlike insulin – had any positive effects on hard outcomes (i.e. microvascular and macrovascular complications)[5]. It is now clear that GLP-1ra have no adverse effects on cardiovascular disease (see above).

As yet, there is no solid burden of proof to support a BMI cut-off value above which GLP-1ra have an added value compared to once-daily basal insulin. However, in addition to the above-mentioned new evidence concerning the effectiveness of GLP-1ra and their consequent place in treatment, there are some considerations that support a reduction of the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2 in the 1st further condition. This is the National Institute for Health and Care Excellence's (NICE) recommendation. The Institute was consulted when the 1st condition was being formulated (in 2009), at which time it indicated a BMI cut-off value of 35 kg/m^2. In addition, it now also recommends the use of GLP-1ra in

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patients with a BMI of less than 35kg/m^2[9]. In addition, the majority of studies into the effects of GLP-1ra were performed in patients with a BMI of ≥30 kg/m^2[3]. For this reason, the 2nd further condition for GLP-1ra (which was drawn up in 2016) already has a BMI cut-off value of 30 kg/m^2[10]. Furthermore, as mentioned above, there is no evidence that the baseline BMI (<30, 30-35 and >35 kg/m^2) has any effect on the degree of reduction in HbA1c levels or on the extent of weight reduction due to GLP-1ra[7, 6]. Finally, individuals with a BMI of 30 kg/m^2 and above are obese, as such they exhibit a high BMI-related mortality level and burden of disease[11]. The guideline advises individuals in this situation to lose weight, as it has been shown that a weight reduction of 5 percent leads to improved insulin sensitivity in adipose tissue, liver, and muscle tissue and to improved β-cell function[12]. Furthermore, improving the risk profile for cardiovascular disease can deliver health gains[13]. The use of GLP-1ra is in line with this effort to achieve weight reduction as they have a weight-reducing effect, albeit a relatively small one (average weight advantage 3.7 kg[3]). However, according to the type 2 diabetes mellitus working group, this is still clinically relevant.[2]

Conclusion
Based on the place of GLP-1ra in the revised treatment guidelines for type 2 diabetes mellitus and on the supporting scientific evidence, reducing the BMI cut-off value from 35 kg/m^2 to 30 kg/m^2 is in line with the 1st further condition (and thus with an extension of the further conditions) concerning the state of science and practice.

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