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To the Minister of Health, Welfare and Sport
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*2023013549*

Date 17 April 2023
Subject GVS advice for PCSK9 inhibitors

**National Health Care Institute**
Care
Medicinal Products

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**Our reference**
2023013549

Dear Mr Kuipers,

In the letter dated 17 September 2022 [CIBG-22-04456], you requested the Health Care Institute to issue an opinion on the adjustment of the further conditions of the medicinal products evolocumab (Repatha®) and alirocumab (Praluent®) in response to a request from the marketing authorisation holder of these medicines.

**Current position in the Medicine Reimbursement System (GVS)**
Evolocumab and alirocumab are currently included in List 1A, together with the medicinal product inclisiran (Leqvio®). There are conditions attached to the reimbursement of evolocumab and alirocumab (and also inclisiran):

Condition:
*In patients with hypercholesterolemia (familial and non-familial) and sufficiently high risk, if a maximum tolerable statin in combination with ezetimibe does not reach the treatment objective in accordance with the guidelines accepted in the Netherlands by the relevant physicians associations, evolocumab can be used as follows:*

1. *in combination with both a statin and ezetimibe; or*
2. *in combination with ezetimibe alone in cases of documented statin intolerance: statin-associated muscle pain has been determined for at least three different statins according to the flow chart and criteria described by EAS/ESC consensus (European Heart Journal 2015; 36: 1012-1022).*

*Patients at sufficiently high risk are defined as one of the following groups:*

1. *Patients with heterozygous familial hypercholesterolemia;*
2. *Patients who have experienced a cardiovascular event and have had a recurring cardiovascular event;*
3. *Patients with type 2 diabetes mellitus who have experienced a cardiovascular event;*
4. *Patients who have experienced a cardiovascular event and genuine statin intolerance that has been established and documented.*
5. ***Also, only for evolocumab:** Patients with homozygous familial hypercholesterolemia who are not LDL-receptor negative;*

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**Request for reassessment of the condition for List 2**
Both the Dutch multidisciplinary cardiovascular risk management guideline (CVRM, 2019) and the NHG (Dutch College of General Practitioners) Standard Cardiovascular risk management derived from it (2019)[1] and the latest European dyslipidaemia guidelines recommend PCSK9 antibodies for all very high-risk patients with established cardiovascular disease (CVD). This use is broader than what is stated in the current reimbursement conditions for evolocumab and alirocumab. The proposed expansion of the reimbursement conditions covers patients with a single experienced cardiovascular event without type 2 diabetes mellitus or established intolerance to statins, plus patients with a very high cardiovascular risk who have not experienced a cardiovascular event. These are for instance patients with stable angina pectoris (heart pain due to a temporary oxygen deficit), symptomatic aortic atherosclerosis (arterial calcification of an aortic aneurysm), aortic aneurysm (abnormal dilatation of the aorta), intermittent claudication, coronary or peripheral revascularisation (restoration of the blood supply).

The marketing authorisation holders have submitted a dossier as justification for expanding the population at risk to include all patients at very high risk of cardiovascular disease (update to the List 2 conditions). The dossier does not suggest a different position in the treatment algorithm for evolocumab and alirocumab. However, with the nuance that if treatment with ezetimibe proves to be inadequate for the patient and they are eligible for evolocumab or alirocumab, a patient does not necessarily have to use ezetimibe e.g. in cases of intolerance.

**Claim by the marketing authorisation holder**
The marketing authorisation holders claim that the PCSK9 inhibitors evolocumab and alirocumab, when added to the maximum tolerable oral lipid-lowering therapy in patients at very high cardiovascular risk due to previously diagnosed cardiovascular disease (CVD) who do not reach the LDL-C target value as per the current CVRM guideline with the maximum tolerable oral lipid-lowering therapy, have added therapeutic value compared with the maximum tolerable oral lipid-lowering therapy alone.

**Assessment**
The application to extend the reimbursement conditions of evolocumab and alirocumab was discussed at a meeting of the Scientific Advisory Council (Dutch: WAR).

The following were considered:

*Therapeutic value*
The efficacy of the PCSK9 inhibitors evolocumab and alirocumab on cardiovascular outcome measures and mortality in patients with very high cardiovascular risk due to previously diagnosed CVD has been investigated in two large randomised, double-blind, placebo-controlled phase 3 trials (FOURIER and ODYSSEY OUTCOMES) involving a total of about 45,000 patients. This involved adding PCSK9 inhibitors to treatment with a statin, with or without ezetimibe. The results show that both evolocumab and alirocumab have clinically relevant effects on

[1] NHG-Standaard Cardiovasculair risicomanagement (version 4.0) 2019

preventing cardiovascular events. The studies do not show an effect of evolocumab on reducing the risk of mortality regardless of cause, probably because the studies' follow-up durations are too short as yet. Alirocumab does have a statistically significant effect on reducing the risk of mortality regardless of cause, but it is uncertain whether this effect is clinically relevant.

Neither evolocumab nor alirocumab is likely to have a clinically relevant effect on the incidence of serious adverse effects. The number of patients discontinuing treatment because of such adverse effects was very low (<4%) in both studies. Long-term data from the FOURIER open-label extension study show that evolocumab can also be used safely over a long period (>5 years). This long-term data also suggests that PCSK9 inhibitors should be used as soon as possible when the combination of a statin and/or ezetimibe is not enough to meet LDL-C targets.

The new reimbursement claim covers all patients with previously diagnosed CVD. The definition of CVD drawn up by the profession is broader than the type of patients included in the studies. Patients with stable angina pectoris or an aortic aneurysm were for example not included in the FOURIER or ODYSSEY OUTCOMES studies, but are included in the definition of patients with CVD according to the CVRM guideline. Because atherosclerosis is a major cause of these conditions, it is plausible that PCSK9 inhibitors are also effective in these patients. This is because PCSK9 inhibitors lower the risk of atherosclerosis by lowering LDL-C levels.

A Dutch study has shown that about 7% of patients who may be eligible for treatment with a PCSK9 inhibitor are intolerant to ezetimibe (i.e. there are insurmountable side effects). A review by the National Health Care Institute has also shown that there are signs that ezetimibe is being used at dosages that are too low (or being prescribed but not taken) in order to comply with the current reimbursement conditions of the PCSK9 inhibitors. The National Health Care Institute considers this sufficient reason to drop the requirement for mandatory use of ezetimibe in patients with documented intolerance. Patients should then have tried ezetimibe for a sufficiently long time first.

*Budget impact analysis*
Taking 8,047 to 11,467 additional patients into account who can be treated with a PCSK9 inhibitor (evolocumab or alirocumab) plus market penetration of 96% in the third year, extending the List 2 conditions of evolocumab and alirocumab to all patients at very high cardiovascular risk due to previously diagnosed CVD will be accompanied by additional costs against the pharmacy budget of €42.4 million to €60.4 million in the third year after the extension. Assuming the list prices, the cost per patient per year is €5,266. Because the prices of the PCSK9 inhibitors have already been negotiated confidentially, the actual additional cost will be lower than currently calculated.

*Cost-effectiveness*
There is a great deal of uncertainty surrounding the magnitude of the effect on cardiovascular mortality and this has a large effect on the results of the cost-effectiveness model. This was examined during the scientific weighting by varying the hazard ratio for cardiovascular mortality in the model. When the hazard ratio turned out to be much more favourable (i.e. at the lower end of the 95% confidence interval), the ICER falls to €48,653/QALY. When it turns out to be much less favourable (i.e. at the upper end of the 95% confidence interval), the

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ICER rises to €150,257/QALY.

Although these uncertainties do therefore play a role, the National Health Care Institute considers the ICER of €69,026 per QALY as reported by the marketing authorisation holders to be the most realistic estimate of cost-effectiveness at present. When the medical costs in years of life gained are also included, the ICER is about €74,817 per QALY. At a reference value of €20,000 per QALY, the PCSK9 inhibitors are not cost-effective compared to placebo. Assuming the deterministic ICER of €69,026/QALY, the price of the PCSK9 inhibitors would have to come down by over 65% for them to be cost-effective. These calculations were based on the list prices of the medicinal products.

**Advice**

Based on the above, the National Health Care Institute recommends that you amend the List 2 conditions for evolocumab (Repatha®) and alirocumab (Praluent®) as stated below, subject to the condition that a price reduction is achieved. The Package Advisory Committee (Dutch: ACP) believes that a reduction of significantly more than 65% is indicated in social terms because:

- there are still uncertainties about the effectiveness (cost-effectiveness),
- it involves extending the reimbursement conditions of medicinal products that are already reimbursed and for which it is likely that any investments made have already been largely recovered.

It is also recommended that the professional group should follow the prescribing policy closely in practice, paying specific attention to use in the elderly and in patients with comorbidities, as well as to the discontinuation criteria. The National Health Care Institute will continue to monitor the use of PCSK9 inhibitors in the coming years.

Conditions for evolocumab

***Evolocumab*** *may be used as follows, exclusively for insured persons with hypercholesterolemia (familial or non-familial) who are at sufficiently high risk when the maximum tolerable oral lipid-lowering therapy comprising a statin plus ezetimibe does not achieve the LDL-C target value in line with the prevailing cardiovascular risk management (CVRM) guideline:*

1. *In combination with both a statin and the maximum tolerable dose of ezetimibe*
2. *in combination with the maximum tolerable dose of ezetimibe alone in cases of documented statin intolerance: statin-associated muscle pain has been determined for at least three different statins according to the flow chart and criteria described by the EAS/ESC consensus (European Heart Journal 2015; 36: 1012-1022).*

*Hypercholesterolemia patients at sufficiently high risk are defined as one of the following groups:*

1. *Patients with homozygous familial hypercholesterolemia who are not LDL-receptor negative;*
2. *Patients with heterozygous familial hypercholesterolemia*
3. *Patients at very high cardiovascular risk due to established cardiovascular disease, as defined in the current CVRM guideline.*

Conditions for alirocumab

***Alirocumab*** *may be used as follows, exclusively for insured persons with hypercholesterolemia (familial or non-familial) who are at sufficiently high risk*

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*where the maximum tolerable oral lipid-lowering therapy comprising a statin plus ezetimibe does not achieve the LDL-C target value in line with the prevailing cardiovascular risk management (CVRM) guideline:*

1. *In combination with both a statin and the maximum tolerable dose of ezetimibe*
2. *in combination with the maximum tolerable dose of ezetimibe alone in cases of documented statin intolerance: statin-associated muscle pain has been determined for at least three different statins according to the flow chart and criteria described by the EAS/ESC consensus (European Heart Journal 2015; 36: 1012-1022).*

*Hypercholesterolemia patients at sufficiently high risk are defined as one of the following groups:*

1. *Patients with heterozygous familial hypercholesterolemia*
2. *Patients at very high cardiovascular risk due to established cardiovascular disease, as defined in the current CVRM guideline.*

Yours sincerely,

Sjaak Wijma
*Chair of the Executive Board*