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National Health Care Institute
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2023048704

Our reference
2023048704

Date 13 December 2023
Re: Package advice evinacumab (Evkeeza®)

Dear Mr Kuipers,

National Health Care Institute advises you about the assessment of evinacumab (Evkeeza®) for the treatment of homozygous familial hypercholesterolaemia (HoFH).

This advice was prompted by the inclusion of evinacumab in the lock procedure for expensive medicinal products for the medical treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia.

Registered indication:
Evinacumab is indicated as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH).

The marketing authorisation holder is requesting reimbursement for patients aged 12 years and older with HoFH who, despite optimal use of lipid-lowering treatments, do not achieve sufficient LDL-C reduction.

Package advice
The National Health Care Institute has determined that evinacumab, for patients aged 12 years and older with HoFH who do not achieve sufficient LDL-C reduction despite optimal use of lipid-lowering treatments, meets the established medical science and medical practice and has a therapeutic equal value to lomitapide (Lojuxta®). The National Health Care Institute therefore advises you to include evinacumab in the basic health care package for the stated indication, provided that the price negotiations successfully deliver a net price for a treatment with evinacumab that does not exceed that of the treatment with lomitapide. We would like to point out that the Insured Package Advisory Committee (ACP) has advised the National Health Care Institute in general terms that the price for a treatment should be reduced when several medicinal products are available for the same indication.

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We explain the preparation of this package advice below.

General:
At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums. We consider this both in the scientific sense and in terms of public support. We also review the aspects of efficiency and transparency.

The National Health Care Institute has assessed evinacumab on the basis of the four package criteria: [1]effectiveness[2], cost-effectiveness[3], necessity [4]and feasibility[5]. The National Health Care Institute is advised by the Scientific Advisory Board (WAR) for the review of data according to established medical science and medical practice, the budget impact and cost-effectiveness. We also consulted stakeholders during the assessment process.

Comprehensive weighting of package criteria
Established medical science and medical practice
Homozygous familial hypercholesterolaemia (HoFH) is a very rare genetic condition characterized by an extremely high *low-density* lipoprotein cholesterol (LDL-C) plasma level. The disorder is usually caused by a *loss-of-function* (LoF) mutation in the gene that encodes for the *low-density* lipoprotein receptor (LDLR) that normally removes the LDL-C from the circulation.

The prevalence of HoFH is estimated to be approximately 1:300,000.
Patients with HoFH are basically all treated from, or in close consultation with, one of the three Dutch centres of expertise: Amsterdam University Medical Center, Erasmus MC and the Radboud Medical Center. Because of the national tracking of patients with centralised HoFH treatment, we have a good understanding of the number of patients. The population of adolescent and adult HoFH patients in the Netherlands is estimated to be approximately 50 patients.

The severity of HoFH is determined by the atherosclerosis that develops due to the exceptionally high LDL-C levels. Without adequate treatment, it leads to cardiovascular morbidity before the age of twenty, and death before the age of thirty. HoFH patients often develop severe and progressive atherosclerosis and cardiovascular disease, such as acute coronary syndrome, myocardial infarction and aortic stenosis, in childhood, leading to premature death. Heart infarcts before the age of twenty occur in HoFH patients.

The primary objective of treatment is to prevent mortality and cardiovascular morbidity. A surrogate marker for this crucial outcome measure is reduction of the

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Beoordeling Stand van de Wetenschap en Praktijk (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[4] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something.

[5] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic health care package. It is therefore mainly a test of a number of implementation aspects such as health care organisation, support, ethical and legal aspects, budget impact and so on.

LDL-C level. In HoFH patients, reduction of LDL-C level is associated with the prevention of death and cardiovascular disease, as in patients without genetic predisposition.

Patients in the Netherlands are treated according to the consensus statement of the *European Atherosclerosis Society* (2023). When the target LDL level is not achieved with a high dosage of statins combined with ezetimib and *subtilisin/kexin type 9 inhibitor (*PCSK9), treatment with lomitapide, evinacumab and/or LDL apheresis is indicated. According to the Dyslipidaemia working group of the Dutch Association of Vascular Medicine Specialists (NVIVG), evinacumab has a place in the treatment algorithm alongside lomitapide and LDL apheresis. The National Health Care Institute concluded in 2015 that lomitapide has an added value compared to LDL apheresis. That is why lomitapide is used as a comparative treatment.

The beneficial and adverse effects of evinacumab for the registered indication were investigated in 65 patients in a randomised, double-blind, placebo-controlled phase three study, the ELIPSE-HoFH study. In addition to placebo or evinacumab, patients in this study also received optimal lipid-lowering therapy. At 25 weeks, LDL-C levels in the evinacumab group decreased by 47.1% from baseline. In the placebo group, LDL-C levels increased by 1.9% from baseline. The placebo-corrected mean change from baseline in LDL-C value was -49.0% (95% CI: -65.0% to – 33.1%; p<0.001). Treatment with evinacumab results in statistically significant and clinically relevant reductions in LDL-C as a surrogate for the decrease of mortality and cardiovascular disease.
The effectiveness of lomitapide was studied in a single-arm, open-label, multicentre phase III study (UP1002). After 26 weeks, lomitapide had reduced LDL-C rates by an average of 40% (95% CI -51.9 to -28.2, p<0.001) from the baseline.

A naive indirect comparison may suggest that the reduction percentage of evinacumab is approximately equivalent to that of lomitapide.

The effect of evinacumab compared to lomitapide on the incidence of severe adverse effects and the incidence of discontinuations due to adverse effects is very uncertain due to the naive indirect comparison. The point estimations suggest a decrease in the risk of severe adverse effects and discontinuation due to adverse effects compared to lomitapide, but due to the very broad 95% confidence intervals, this effect is very uncertain. However, evinacumab has a more favourable side effects profile with respect to gastrointestinal and hepatic side effects, which are characteristic of lomitapide treatment. The long-term safety profile of evinacumab is unknown.

All in all, the National Health Care Institute concludes that evinacumab for homozygous familial hypercholesterolaemia does meet the established medical science and medical practice and has a therapeutic equal value to lomitapide.

Budget impact analysis (BIA)
The National Health Care Institute estimates that 31 patients aged 12 years and older with HoFH, who do not achieve sufficient LDL-C reduction despite optimal use of lipid-lowering treatments, will be treated with evinacumab in the third year after inclusion in the basic health care package. The cost of one vial of

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evinacumab is €7000. The annual treatment costs per patient are €364,000. The macro costs of including evinacumab in the basic health care package thus amounts to approximately €10 to €12 million per year. The BIA estimates the costs of the comparative treatment, lomitapide, at € 316,214.10 per year (based on the list price). Taking into account substitution, the use of evinacumab in the treatment of HoFH will result in additional costs of approximately €4.0 to 4.3 million per year. The National Health Care Institute notes that lomitapide is reimbursed through the GVS and evinacumab is an intramural product.

Cost-effectiveness
Due to the equal therapeutic value of evinacumab compared to standard of care, the National Health Care Institute did not perform a cost-effectiveness analysis.

Appropriateness
Appropriate use arrangements should be made to ensure the appropriate use monitoring and tracking of evinacumab. This will establish arrangements on, among other things, start and stop criteria and an indication committee.

Package advice
The National Health Care Institute has determined that evinacumab, for patients aged 12 years and older with HoFH who do not achieve sufficient LDL-C reduction despite optimal use of lipid-lowering treatments, meets the established medical science and medical practice and has a therapeutic equal value to lomitapide. The National Health Care Institute therefore advises you to include evinacumab in the basic health care package for this indication with the following conditions:

- The net price for evinacumab treatment following successful price negotiations should not exceed the net price of lomitapide treatment. We would like to point out that the Insured Package Advisory Committee (ACP) has advised the National Health Care Institute in general terms that the price for a treatment should be reduced when several medicinal products are available for the same indication.
- Appropriate use agreements must be made.

In practice, including at equal prices, the inclusion of evinacumab will be associated with additional costs from the pharmaceutical budget due to the (expected) broader use of the product for HoFH patients, compared to lomitapide. Lastly, the National Health Care Institute concludes that the Ministry of Health, Welfare and Sport has agreed a confidential price arrangement with regard to the price of lomitapide. In this context, the marketing authorisation holder has indicated that it is open to confidential negotiations on the price of evinacumab.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Annexes:
FT report
BIA