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2022035409

Date 15 February 2023
Subject GVS advice icosapent-ethyl (Vazkepa®)

This is a revision of the previously sent letter on the 16th of September 2022, in which the composite endpoint was incorrectly noted. The composite endpoint has been corrected in both the letter to the minister as well as the pharmacotherapeutic assessment report.

Dear Mr Kuipers,

In this letter, the National Health Care Institute advises you on icosapent-ethyl (Vazkepa®) for reducing the risk of cardiovascular events in adult statin-treated patients with high cardiovascular risk with elevated triglycerides and diagnosed cardiovascular disease or diabetes with at least one cardiovascular risk factor.

The reason for this advisory report is your request of 30 March 2022 (CIBG-22-03602) for a substantive review to determine whether icosapent-ethyl is interchangeable with another medicinal product included in the Medicine Reimbursement System (GVS).

Icosapent-ethyl can be placed on List 1B. For the complete registered indication, icosapent-ethyl has an added value compared to the standard treatment. As far as cost effectiveness is concerned, there is a large difference between the 'primary prevention' and 'secondary prevention' subgroups. Therefore, the National Health Care Institute recommends that icosapent-ethyl should only be reimbursed for 'secondary prevention'; i.e. statin-treated patients with high cardiovascular risk with elevated triglycerides and a diagnosed cardiovascular disease. Since icosapent-ethyl is not cost effective with the current price for the treatment of these patients, the National Health Care Institute recommends negotiating a 30% discount.

In this letter, I explain our findings and final conclusion.

General

At your request, the National Health Care Institute assesses whether new care should be part of the basic health insurance package from the perspective of the basic health care package paid from joint premiums. To be able to make a recommendation, the National Health Care Institute has assessed icosapent-ethyl

on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. We consider these 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 is advised in its package reviews by two independent committees:

- the Scientific Advisory Board (WAR) for the review of data according to the established medical science and medical practice, and to determine the cost-effectiveness; and
- the Insured Package Advisory Committee (ACP) for the social deliberations.

We also consulted stakeholders during the assessment process.

Comprehensive weighting of package criteria

Established medical science and medical practice

The efficacy of icosapent-ethyl was investigated in a multicentre randomized double-blind and placebo-controlled phase 3 study (the REDUCE-IT study) with a median follow-up duration of 4.9 years.
The primary endpoint was a compound endpoint consisting of five components, namely cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, and unstable angina pectoris. The secondary endpoint also consists of compound components, namely cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. Icosapent-ethyl resulted in statistically significant and clinically relevant reduction of the primary endpoint by 24.8% compared to placebo and 26.5% for the secondary endpoint.

The effectiveness of icosapent-ethyl has also been investigated in the primary and secondary prevention groups through subgroup analysis. The results of the subgroup analysis suggest that icosapent-ethyl is less effective in the primary prevention group than the secondary prevention group. However, this difference is not statistically significant. In addition, the effect of icosapent-ethyl in both subgroups remains clinically relevant.

An important criticism of the registration study is the use of mineral oil as placebo, because it is unlikely to be completely inert and therefore may have negative effects on cardiovascular outcomes. The negative impact of mineral oil explains about 0.3 to 3% of cardiovascular events in the placebo group. Taking into account this overestimation, the effect of icosapent-ethyl is statistically significant and clinically relevant for the time being.

Icosapent-ethyl meets the criteria of established medical science and medical practice for reducing the risk of cardiovascular events in adult statin-treated patients with high cardiovascular risk with elevated triglycerides (at least 1.7 and at most 5.6 mmol/l) and diagnosed cardiovascular disease or diabetes with at least one cardiovascular risk factor. The National Health Care Institute concludes, on the basis of the data, that the medicinal product has an added value compared to the usual care.

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[1] *Real-world package management 3* (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] *Established medical science and medical practice assessment: updated version* (2015). National Health Care Institute,
Diemen. Via www.zorginstituutnederland.nl.

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

Budget impact analysis
The purchase price of a bottle with 120 capsules containing 998 mg per capsule is €200. The costs per patient per year of icosapent-ethyl are €2,433.33. Icosapent-ethyl's inclusion in List 1B of the GVS will be accompanied by additional costs charged to the pharmaceutical budget of €36.8 million for the full registered indication (€12.6 million primary prevention group and €24.2 million secondary prevention group) in the third year after inclusion in the package.

Cost-effectiveness
The cost-effectiveness analysis is of sufficient methodological quality.
The marketing authorisation holder reports a deterministic ICER of €20,524 per increased QALY for icosapent-ethyl compared to the standard treatment. This does not take into account the negative treatment effect of the placebo added to the statin. In addition, the marketing authorisation holder assumes that the effect will be retained for 20 years.
The National Health Care Institute believes (a) that the possible negative effect of placebo added to the statin is uncertain in size and (b) that when taking into account treatment waning (reduction in effect after treatment is stopped), a period of 10 years would have been better in the base case analysis. The National Health Care Institute finds it more plausible to apply an ICER range based on both treatment waning (after 10 years) and the possible negative treatment effect of the placebo added to statin (1.5% - 3%).

The ICER range for the entire population ranges from €34,528 (at a 1.5% reduction in the treatment effect) to €38,003 per increased QALY (at a 3% decrease in the treatment effect). Within this range, the product is not cost effective. Based on the lower limit, the price reduction should be approximately 45% to get the ICER below the reference value of €20,000. Based on the upper limit of the range, the price reduction should be approximately 50%.

Within the total population, two subgroups can be distinguished: a primary prevention group and a secondary prevention group.
For the primary prevention group, the burden of disease is 0.35 and the reference value is €20,000/QALY. The ICER range for this group is €133,222 - €165,191 per increased QALY. Based on the lower limit, the price reduction should be approximately 85% to get the ICER below the reference value of €20,000. At the upper limit, the price discount should be 90%.
For the secondary prevention group, the burden of disease is 0.40 and the reference value is €20,000/QALY. The ICER range for this group is €25,533 - €27,884. Based on the lower limit, the price reduction should be approximately 25% to get the ICER below the reference value of €20,000. At the upper limit, the price discount should be 30%.

Final conclusion
Icosapent-ethyl can be placed on List 1B. For the complete registered indication, icosapent-ethyl has an added value compared to the standard treatment. As far as cost effectiveness is concerned, there is a large difference between the 'primary prevention' and 'secondary prevention' subgroups. Therefore, the National Health Care Institute recommends that icosapent-ethyl should only be reimbursed for 'secondary prevention'; i.e. statin-treated patients with high cardiovascular risk with elevated triglycerides and a diagnosed cardiovascular

disease. Since icosapent-ethyl with the current price for the treatment of these patients is not cost effective, the National Health Care Institute recommends negotiating a 30% discount.

If the application of icosapent-ethyl is included in the package after successful price negotiations, the National Health Care Institute recommends the following reimbursement condition:

Condition for icosapent-ethyl
Only for an insured person with diagnosed cardiovascular disease
- that is treated with statin,
- with high cardiovascular risk,
- with elevated triglycerides (at least 1.7 and at most 5.6 mmol/l).

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

National Health Care Institute
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16 September 2022

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