Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

Ministry of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

2022024275

National Health Care Institute
Care
Medicinal products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms J.M. van der Waal
T +31 (0)6 120 017 28

Our reference
2022024275

Date 5 July 2022
Subject Medicine Reimbursement System advisory report on bempedoic acid (Nilemdo®)

Dear Mr Kuipers,

In this letter, the National Health Care Institute is advising you about bempedoic acid (Nilemdo®) for use in adults with primary hypercholesterolaemia or mixed dyslipidaemia.

The reason for this advisory report is your request of 5 January 2022 (CIBG-21-03111) to assess whether bempedoic acid is interchangeable with another medicinal product included in the Medicine Reimbursement System (GVS).

Bempedoic acid can be placed on List 1B and it has added therapeutic value compared to the standard treatment. However, this added therapeutic value is based on surrogate endpoints; there are no results for hard endpoints. In addition, there are uncertainties about the cost-effectiveness. Based on the calculated disease burden of the study populations, two different reference values should apply. There are signals from the physicians' association that the disease burden is the same in both populations. The National Health Care Institute recommends a price reduction of 50%. It may be possible to renegotiate in the future if long-term data shows that effects are achieved at hard endpoints.

I would like to explain our findings and final conclusion below.

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 bempedoic acid against 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

[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

public support. We also assess 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 established medical science and medical practice and to determine cost-effectiveness; and
- the Insured Package Advisory Committee (ACP) for the appraisal.

We also consulted stakeholders during the assessment process.

Bempedoic acid (Nilemdo®)

Partly based on a statement by the physicians' association, reimbursement is being requested for an indication that is narrower than the registered indication. This refers to adults with non-familial hypercholesterolaemia or mixed dyslipidaemia with a high or very high cardiovascular risk who do not achieve the LDL cholesterol treatment goals through diet and maximum possible dosages of statins and ezetimibe, including patients who are statin-intolerant, or for whom a statin is contraindicated, and who are not eligible for treatment with a PCSK9 inhibitor.

The marketing authorisation holder claims there is a place for bempedoic acid after other available cholesterol-lowering medicinal products were insufficiently effective and where the patient is not eligible for treatment with a PCSK9 inhibitor.

Comprehensive weighting of package criteria

Established medical science and medical practice

The effectiveness of bempedoic acid was studied in four multi-centre, randomised, double-blind, placebo-controlled studies with over 3,500 adult patients with hypercholesterolaemia or mixed dyslipidaemia. The primary endpoint for the effectiveness in all phase-three studies was the average percentage reduction of the initial LDL cholesterol value compared to a placebo. Patients with hypercholesterolaemia were divided into two groups:

1) Patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolaemia or both, treated with the maximum tolerated level of statins;
2) Patients with statin intolerance.

Bempedoic acid gives a statistically significant effect in terms of lowering LDL cholesterol. In statin-tolerant patients, LDL was decreased by 12.7% (versus a 0.4% increase in the placebo group) after 52 weeks of treatment with bempedoic acid. In statin-intolerant patients, LDL was decreased by 22.2% after 24 weeks of treatment with bempedoic acid (versus a 1.8% decrease in the placebo group). There is uncertainty because LDL cholesterol is a surrogate outcome measure for lowering death and cardiovascular disease and because patients were not optimally dosed with statins and ezetimibe. Additionally, it is unclear whether the statin-intolerant patients had indeed been proved to be statin-intolerant. Nevertheless, the National Health Care Institute concludes that the effect on lowering death and cardiovascular diseases is possibly clinically relevant. Bempedoic acid is in line with established medical science and medical practice for use on adults with non-familial hypercholesterolaemia or mixed dyslipidaemia with a high or very high cardiovascular risk who do not achieve the LDL cholesterol treatment goals through diet and the maximum possible dosages of statins and ezetimibe and who are not eligible for treatment with a PCSK9 inhibitor.

Budget impact analysis
Inclusion of bempedoic acid (Nilemdo®) on List 1B of the GVS for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia will be accompanied by additional costs charged to the pharmaceutical budget of €46 million in the third year after inclusion in the package.

Cost-effectiveness
The National Health Care Institute concludes that the cost-effectiveness analysis of bempedoic acid in the studied patient population is of sufficiently high methodological quality.
For the statin-intolerant population, usual care is ezetimibe. Given the burden of disease of 0.31, the National Health Care Institute uses a reference value of €20,000 per QALY as a threshold for the cost-effectiveness. A deterministic ICER of €12,437 per QALY has been reported for bempedoic acid combined with ezetimibe compared to placebo combined with ezetimibe. The probability that bempedoic acid in combination with ezetimibe is cost-effective compared to placebo in combination with ezetimibe for the statin-intolerant population at a reference value of €20,000 per QALY is approximately 73%.
For the statin-tolerant population, usual care consists of a statin in combination with ezetimibe. Given the burden of disease of 0.42, the National Health Care Institute uses a reference value of €50,000 per QALY as a threshold for the cost-effectiveness. A deterministic ICER of €46,342 per QALY has been reported by the marketing authorisation holder for bempedoic acid combined with a statin + ezetimibe compared to a placebo combined with a statin + ezetimibe. The probability that bempedoic acid in combination with ezetimibe is cost-effective compared to a placebo in combination with a statin + ezetimibe for the statin-tolerant population at a reference value of €50,000 per QALY is approximately 50%.
At a price discount of 50%, the probability of cost-effectiveness at a reference value of €20,000 per QALY for the statin-intolerant population increases to 95%, and the probability of cost-effectiveness at a reference value of €50,000 per QALY for the statin-tolerant population increases to 78%.

Final conclusion
Bempedoic acid can be placed on List 1B and it has added therapeutic value compared to usual care. However, this added therapeutic value is based on surrogate endpoints; there are no results for hard endpoints. In addition, there are uncertainties about the cost-effectiveness. Based on the calculated disease burden of the study populations, two different reference values should apply. There are signals from the physicians' association that the disease burden is the same in both populations. The National Health Care Institute recommends a price discount of 50%. It may be possible to renegotiate in the future if long-term data shows that effects are achieved at hard endpoints.

If the application of bempedoic acid (Nilemdo®) is included in the package after successful price negotiations, the National Health Care Institute recommends the following reimbursement conditions:

Conditions for bempedoic acid

Bempedoic acid can be used as follows, exclusively for an insured person with non-familial hypercholesterolaemia or mixed dyslipidaemia and high or very high cardiovascular risk, if a maximum tolerable statin dosage combined with ezetimibe does not achieve the treatment objective in accordance with the guidelines accepted in the Netherlands by the relevant physicians' associations; and the patient is not eligible for treatment with a PCSK9 inhibitor:

1 In combination with both a statin and ezetimibe as a daily dose or;
2 In combination with ezetimibe alone as a daily dose 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).

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

National Health Care Institute
Care
Medicinal products

Date
5 July 2022

Our reference
2022024275