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Our reference
2024030788

Date 29 August 2024
Subject Amendment of the List 2 conditions for inclisiran (Leqvio®) and bempedoic acid (Nilemdo®)

Dear Ms Agema,

In its letter of 17 April 2023, the National Health Care Institute advised your predecessor on the amendment of the further conditions for the medicinal products evolocumab (Repatha®) and alirocumab (Praluent®). Part of the amendment to the further conditions involved dropping the requirement of mandatory ezetimibe use for patients with documented intolerance. The National Health Care Institute now recommends that you also drop this requirement for two other lipid-lowering medicinal products, inclisiran (Leqvio®) and bempedoic acid (Nilemdo®).

Guideline for lipid-lowering therapy
The guideline issued by the Dutch College of General Practitioners (NHG) recommends starting primarily with a statin as lipid-lowering therapy. If the result is insufficient, ezetimibe can be added. Adding a PCSK9 inhibitor may be considered if LDL cholesterol target values are not achieved with the combination therapy of a statin and ezetimibe[1].

Previous amendment to the conditions for evolocumab and alirocumab
A Dutch study has shown that about 7% of patients who may be eligible for treatment with a PCSK9 inhibitor, including alirocumab and evolocumab, are intolerant to ezetimibe (i.e. 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 deemed this to be sufficient grounds for dropping the requirement of mandatory ezetimibe use for patients with documented intolerance who use a PCSK9 inhibitor. These patients should however have tried ezetimibe for a sufficiently long period first.[2]

Current conditions for inclisiran and bempedoic acid

[1] Cardiovascular risk management | NHG guidelines

[2] GVS advisory report on extending the List 2 conditions for evolocumab (Repatha®) and alirocumab (Praluent®) for excessive cholesterol levels | Advisory report | National Health Care Institute

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Inclisiran and bempedoic acid – like evolocumab and alirocumab – are lipid-lowering medicines. Inclisiran lowers the LDL cholesterol level by preventing the translation of proprotein convertase subtilisine/kexine type 9 (PCSK9) messenger RNA into PCSK9. Bempedoic acid works by inhibiting the enzyme adenosine triphosphate citrate lyase (ACL) in the liver.

Adding inclisiran may be considered for certain patients if LDL cholesterol target values are not achieved with the combination therapy of a statin and ezetimibe.[3] Adding bempedoic acid may be considered for patients who are not eligible for a PCSK9 inhibitor where LDL cholesterol target values are not achieved with the combination therapy of a statin and ezetimibe.[4] List 2 conditions apply for both medicinal products.

Amendment to the conditions for inclisiran and bempedoic acid
The National Health Care Institute has received signals from the field that the issues regarding the mandatory use of ezetimibe with alirocumab and evolocumab also apply to inclisiran and bempedoic acid. After discussions with the Association of Dutch Healthcare Insurers, the National Health Care Institute therefore recommends dropping the requirement of mandatory ezetimibe use for patients with documented intolerance who use inclisiran or bempedoic acid. These patients should however have tried ezetimibe for a sufficiently long period first. The National Health Care Institute would like to emphasise here that ezetimibe can therefore be used at the licensed daily dose of 10 mg or at a dose of 0 mg in the event of intolerance. A dose reduction to 5 mg per day is not recommended.

The National Health Care Institute recommends amending points 1 and 2 of the reimbursement conditions as follows:

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

1. *in combination with both a statin and ezetimibe* ***at the maximum tolerable dosage****, or*
2. *in combination with only ezetimibe* ***at the maximum tolerable dosage*** *in the event of documented statin intolerance: statin-associated muscle pain for at least three different statins has been determined 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. *heterozygous familial hypercholesterolaemia patients,*
2. *patients who have experienced a cardiovascular event* and *have had a recurring cardiovascular event,*
3. *patients with diabetes mellitus type 2 who have* also *experienced a cardiovascular event, or*

[3] GVS advisory report on inclisiran (Leqvio®) for treating hypercholesterolaemia | Advisory report | National Health Care Institute

[4] GVS advisory report on bempedoic acid (Nilemdo®) for treating 2 fat metabolism disorders | Advisory report | National Health Care Institute

4. *patients who have experienced a cardiovascular event and have an actual statin intolerance that has been established and documented.*

<u>Condition for bempedoic acid</u>:
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 **at the maximum tolerable dosage**, or*
2. *in combination with only ezetimibe **at the maximum tolerable dosage** in the event of documented statin intolerance: statin-associated muscle pain for at least three different statins has been determined 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

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