Evolocumab (Repatha®) for the treatment of adults with primary hypercholesterolaemia

Summary of recommendations by National Health Care Institute dated 23 January 2019.

National Health Care Institute carried out a re-assessment of the medicinal product Evolocumab (Repatha®), whereby they came to the following conclusion.

In a letter dated 11 September 2017, the former Minister of VWS asked National Health Care Institute for a substantive assessment (reassessment) of the pharmaceutical product evolocumab (Repatha) regarding an adjustment in the List 2 condition in response to recent results of clinical research (reference CIBG-17-05102). On 18 January 2018 National Health Care Institute informed the Minister that it would prefer to postpone its assessment until the amended (draft) multidisciplinary guidelines on Cardiovascular Risk Management (CRVM) were available. On 12 March 2018 the Minister asked National Health Care Institute to continue its assessment, making use of the most recent (draft) guidelines and information after consulting experts (reference CIBG-18-05974). National Health Care Institute has completed its assessment. Their considerations are to be found in the Medicine Reimbursement System (GVS) report that was sent to the Minister.

On 21 December 2018 the manufacturer, Amgen, asked the Minister and the National Health Care Institute to postpone the final assessment of evolocumab, to allow consultation to take place with interested parties. However, we see no reason for this, as sufficient time was allowed for input from other parties during the assessment procedures in which our Scientific Advisory Board (WAR) carefully weighed up the scientific arguments of interested parties.

Background

Evolocumab is a cholesterol-lowering product, belonging to the class of PCSK9 antibodies. It is available as a pre-filled syringe with 140 mg evolocumab in 1 ml solution for subcutaneous injection.

Registered indication

Evolocumab (Repatha®) is indicated for hypercholesterolaemia. It is registered for the following indications:

Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as adjuvant to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C-goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.

Adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia:

- in combination with other lipid-lowering therapies.

Adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disorder) to reduce cardiovascular risk by

lowering LDL-C levels:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies, or
- alone or in combination with other lipid-lowering treatments in patients who are statin-intolerant or for whom a statin is contraindicated.

Current place in the Medicine Reimbursement System (GVS)
Evolocumab is currently included on List 1A, together with the medicinal product alirocumab (Praluent®), which also belongs to the class of PCSK9 antibodies. Conditions have been attached to the reimbursement of evolocumab (and of alirocumab), whereby reimbursement is limited to very high-risk groups of patients.

Application for reassessment of the List 2 condition
The marketing authorisation holder has submitted a dossier, based on the results of new studies, to substantiate broadening the risk population to include non-familial hypercholesterolemia for which evolocumab will be reimbursed (alteration in List 2 condition). The file does not suggest a different position for evolocumab in the treatment algorithm for secondary prevention. This remains unaltered: after failure on maximum tolerated statin in combination with ezetimibe.

Marketing authorisation holder's claim
Based on the results of new studies, in particular the FOURIER study, the marketing authorisation holder claims the following extension in the current List 2 condition (the extension, in bolt letters, in comparison with the current condition):

Condition: For patients with hypercholesterolemia (familial and non-familial) and sufficiently high risk, if maximum tolerated oral lipid-lowering therapy (statin, ezetimibe) does not achieve the treatment objective in accordance with the guidelines that have been accepted by the professional group concerned in the Netherlands, evolocumab can be used as follows:

1. in combination with maximum tolerated oral lipid-lowering therapy, i.e. statin and/or ezetimibe
2. in combination with ezetimibe alone, in the event of documented statin-intolerance: statin-associated myalgia for at least three different statins, established based on the flow diagram and the criteria described by the EAS/ESC consensus (European Heart Journal 2015; 36: 1012-1022).

3. in combination with only a statin, if ezetimibe is unsuitable for the patient on medical grounds, e.g. due to a contraindication and/or unintended effect of ezetimibe

4. as monotherapy in the event of a combination of points 2 and 3 above.

Patients with sufficient high risk are defined as one of the following groups:
a) Homozygous familial hypercholesterolaemic patients (HoFH) who are not LOL-receptor-negative;
b) Heterozygous familial hypercholesterolaemic patients (HeFH);
c) Non-familial hypercholesterolaemic patients who have suffered at least one cardiovascular event (secondary prevention) **plus at least 1 severe risk factor for developing another cardiovascular event**.

ALTERNATIVE (in the new claim):

c) Non-familial hypercholesterolaemic patients who have suffered at least one cardiovascular event (secondary prevention) **plus at least 1 severe risk factor for developing another cardiovascular event: statin intolerance, DM type 2, relapsed CVE, recent MI or stroke (<6 months), smoking, age 65 years, or multiple vascular disease.'**

National Health Care Institute considerations
After consulting stakeholders, and having been advised by our Scientific Advisory Board (WAR), the National Health Care Institute finds as follows.

Based on the new data, there is no reason to amend the List 2 condition for evolocumab in the direction of a population with non-familial hypercholesterolaemia and who have suffered at least one cardiovascular event (secondary prevention), nor is there sufficient evidence for extending the current condition in the direction of a number of additional risk factors based on the FOURIER study:

- The population in the FOURIER study does not preclude the use of ezetimibe for the population that, according to the draft CVRM guidelines, is eligible in the Netherlands for treatment with evolocumab. The manufacturer's claim also focusses on this population: a population optimally treated with a statin to which ezetimibe has first been added. Only 5% were treated with ezetimibe in the FOURIER study. When pre-treatment is not optimal, evolocumab should not be considered.
- A clinically relevant effect on firm endpoints was not achieved in the most important study (FOURIER) due to the study's short follow-up duration. Partly because the risk of cardiovascular mortality increases during the course of the first 2 years, expectations of a clinically relevant effect on cardiovascular morbidity and mortality are uncertain.
- Publications on additional risk factors on which evolocumab is expected to have an extra-large effect do suggest a trend towards a bigger effect on certain sub-groups (MI < 2 years, ≥ 2 MIs; multiple vascular disease), but this has not yet been sufficiently established and proven to be able to include these factors in the reimbursement conditions.
- There is no reason, with evidence, for a specific description for excluding ezetimibe in the conditions, as suggested in the manufacturer's revised claim, analogous to statin-intolerance. In the event that ezetimibe is not suitable on medical grounds, good medical action is required, to which the doctor responds and if necessary, adjusts the treatment.

Advice
Based on the above considerations, the National Health Care Institute advises the Minister against altering the List 2 condition. Reimbursement according to the current conditions can continue (List 2 Rzv, no. 106):

For patients with hypercholesterolemia (familial and non-familial) and sufficiently high risk, if a maximum tolerated statin in combination with ezetimibe does not achieve the treatment goal in accordance with the guidelines that have been accepted in the Netherlands by the professional group concerned, evolocumab can be used as follows:

1. in combination with both a statin and ezetimibe or:
2. in combination with ezetimibe alone, in the event of documented statin-

intolerance: statin-associated myalgia for at least three different statins, established based on the flow diagram and criteria described by the EAS/ESC consensus (Eur. Heart J 2015; 36: 1012-1022).

Patients with sufficient high risk are defined as one of the following groups:
1. Homozygous familial hypercholesterolaemic patients who are not LDL-receptor-negative;
2. Heterozygous familial hypercholesterolaemic patients;
3. Patients who have suffered a cardiovascular event (CVE) and one relapsed CVE;
4. Patients with diabetes mellitus type 2 and who have suffered a CVE;
5. Patients who have suffered a CVE and whose statin-intolerance has been established and documented.

Future developments
Naturally, the National Health Care Institute is willing to re-consider the amendments in the List 2 condition for evolocumab if scientific publications result from supplementary research data not yet assessed by National Health Care Institute.

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The original text of this excerpt from advice of National Health Care Institute was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of National Health Care Institute's advice.
Furthermore, National Health Care Institute points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.