Zorginstituut Nederland

Evolocumab (Repatha®) for the treatment of hypercholeresterolaemia

Package advice of the *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 18 January 2018

Zorginstituut Nederland issued package advice on the medicinal product evolocumab (Repatha®), whereby they came to the following conclusion.

In a letter dated 11 September 2017 (CIBG-17-05102), the predecessor of the current Minister of Health, Welfare and Sport (WVS) asked Zorginstituut Nederland (ZIN) to issue advice on amending the specific conditions for evolocumab (Repatha®) in response to recent results of clinical research with this medicinal product.

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

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):
Condition**s:**
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 objective according to the guidelines accepted by the professional group in the Netherlands, 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: this is defined as 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).

Patients who are at sufficiently high risk are defined as one of the following groups:
1. Patients with homozygous familial hypercholesterolaemia who are not LDL receptor-negative;
2. Patients with heterozygous familial hypercholesterolaemia;
3. Patients who have suffered a cardiovascular event and a recurrent cardiovascular event;
4. Patients with type 2 diabetes mellitus and who have suffered a cardiovascular event;
5. Patients who have suffered a cardiovascular event and with a documented history of statin-intolerance.

Application for re-assessment of a List 2 condition
The marketing authorisation holder has submitted a dossier to substantiate broadening the risk population to include non-familial hypercholesterolemia for which the reimbursement of evolocumab applies (alteration in List 2 conditions). The dossier 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. However, with the nuance that, if treatment with statin/ezetimibe proves inadequate for the patient, and

the patient is eligible for evolocumab, ceasing treatment with ezetimibe and/or statin should be possible if prompted by adverse effects of ezetimibe or statin.

Marketing authorisation holder's claim
Based on the results of new studies, particularly the FOURIER study, the marketing authorisation holder claims that the addition of evolocumab has demonstrable therapeutic added value in comparison with placebo, if the combination of the maximum tolerated statin + ezetimibe achieves insufficient effects for patients (adults) with non-familial hypercholesterolemia who have suffered at least one cardiovascular event (CVE).

Grounds
The application to extend the reimbursement condition of evolocumab was discussed during a meeting of the Scientific Advisory Board (WAR) on 30 October 2017. They found as follows.

The treatment of hypercholesterolemia is described in the Dutch multidisciplinary guidelines on Cardiovascular risk-management (CRVM, revised version, 2011) and the relevant derivative NHG Standard Cardiovascular Risk-Management. The revised guidelines on Cardiovascular Risk-Management are expected in the spring of 2018.

The FOURIER study, on which the request to alter the reimbursement condition is based, is an extremely large placebo-controlled study with ca. 25,000 patients. It examined the effect of evolocumab, added to treatment with a statin and, if necessary, ezetimibe, on reducing the morbidity and/or mortality of patients with a peripheral arterial disorder, a myocardial infarction or a stroke in their anamnesis and an increased risk of cardiovascular disease. In this study, a number of marginal comments can be made, e.g., regarding the degree to which this population is representative of the Dutch situation, in view of the background treatment in the study. Furthermore, another comment is that the study was overpowered and has a relatively short follow-up duration, as a result of which only limited data are available on safety and effectiveness during long-term use.

Prompted in part by the marginal comments relating to the FOURIER study, the Zorginstituut feels it appropriate to carry out the re-assessment only as and when that the revised guidelines on CRVM are available, so that any revised treatment goals – e.g. in relation to reducing the LDL-cholesterol – can also be taken into account.

Zorginstituut Nederland's advice
The Zorginstituut advises the Minister of WVS not to alter the reimbursement condition for evolocumab (Repatha®) for the time being; the current List 2 condition can remain unchanged. As soon as the update of the Multidisciplinary Guidelines on CVRM are available, we will resume establishing our advice on the application to alter the specific conditions.

For further information, please contact: JBoer@zinl.nl; warcg@zinl.nl