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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

REPATHA (evolocumab), anti-PCSK9

Minor clinical added value in uncontrolled homozygous familial hypercholesterolaemia
Insufficient clinical benefit in heterozygous familial or non-familial hypercholesterolaemia and primary mixed dyslipidaemia

Main points

- REPATHA has Marketing Authorisation in primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia and homozygous familial hypercholesterolaemia in combination with statins (except in case of intolerance or contraindication to statins).
- In homozygous familial hypercholesterolaemia, the efficacy of REPATHA, in combination with other lipid-lowering agents, has been demonstrated only in terms of reduction of biological parameters (LDL-C). The efficacy in terms of morbidity and mortality has not been demonstrated.
- In primary hypercholesterolaemia and mixed dyslipidaemia, there are therapeutic alternatives that have demonstrated their efficacy in terms of morbidity and mortality. In this context, the efficacy of evolocumab was demonstrated only in one biological criteria (reduction of LDL-C levels) in studies in which the majority of patients were not treated at the maximum tolerated dose of statins and for whom the level of cardiovascular risk was not systematically considered.
- There remain uncertainties as to its adherence and its safety, especially on neurocognitive functions, the risk of diabetes and liver safety.

Therapeutic use

Hypercholesterolaemia and mixed dyslipidaemia
In the majority of patients with hypercholesterolaemia for whom lifestyle changes are not sufficient, therapeutic needs are covered by use of statins currently available and that have demonstrated a benefit in morbidity and mortality (prevention of cardiovascular events and death due to all causes).
In uncontrolled patients despite regular use of an appropriate dosage of statins, cholesterol-lowering combinations can be proposed: statin + ezetimibe or statin + cholestyramine.
In dyslipidaemic patients and patients in whom statin treatment is poorly tolerated, the prescriber currently has the choice of three medicinal products: fibrates, cholestyramine, ezetimibe.

Role of the medicinal product in the therapeutic strategy

Given the lack of demonstration on morbidity and mortality and uncertainties about safety and adherence, the role of REPATHA in the therapeutic cannot be established.

Homozygous familial hypercholesterolaemia
The prognosis is a direct function of the patient's age, LDL-C levels and permanent exposure since birth to excess LDL-C.
The goal of treatment is to reduce LDL-C levels to prevent the occurrence of cardiovascular events.
Treatment is based on the prescription of lipid-lowering agents. Statins are recommended as first-line treatment and may be combined with ezetimibe or cholestyramine if the goals are not met. Apheresis of LDL-C particles may also be suggested. Medicinal treatment must be combined with lifestyle and dietary measures.

Role of the medicinal product in the therapeutic strategy

In adults and adolescents age 12 and older with homozygous familial hypercholesterolaemia uncontrolled by available lipid-lowering agents, REPATHA may be offered in addition to a diet low in fat and in combination with existing lipid-lowering treatments at maximum doses, with or without low density lipoprotein (LDL) apheresis.

Clinical data

- The efficacy of evolocumab was evaluated only in the reduction of a biological criteria, LDL-C. To date, there is no data justifying the efficacy of evolocumab in terms of morbidity and mortality. In all of these studies, patients at high cardiovascular risk represented 43.5 to 46% of included patients, without stratification for the majority of these studies. A post-hoc analysis of patients at high CV risk from 4 phase III clinical studies (1401/3433, i.e. 41% of patients included) was carried out by the company; they showed consistent results with those observed in the general population (reduced LDL-C levels between 61 and 72%).
- In most of these studies, evolocumab was administered in combination with statins; patients may or may not have achieved LDL-C target. Thus, LDL-C levels at inclusion were relatively low (about 105 mg/dl) which makes the prescription of REPATHA questionable in the patients included in these studies. The inclusion criteria related to the LDL-C threshold in the studies were very different from one study to another.
- Few patients over 75 years of age were included in the studies (<4%); thus, the efficacy and safety of evolocumab cannot be established in this population.
- There are still uncertainties in terms of tolerance, especially with regard to:
  - the impact of the significant reduction of LDL-C levels and obtaining very low LDL-C levels on neurocognitive functions (study under way) and the risk of diabetes,
  - the development of antibodies.
- There are also still uncertainties in terms of patient adherence with this treatment in the form of SC injection given the current lipid-lowering treatments all available orally.
- Considering the mode of action of this medicinal product (monoclonal antibody), its method of administration (SC) and the uncertainties in terms of adherence, its actual use cannot be determined at date.

Special prescribing conditions

- Exception drug status
- Medicine for initial annual prescription reserved for specialists in cardiology, endocrinology, diabetes and metabolic disorders or internal medicine. Unrestricted renewal.

Benefit of the medicinal product

- The actual benefit of REPATHA is substantial in homozygous hypercholesterolaemia. It is insufficient to justify its reimbursement by National Health Insurance in primary hypercholesterolaemia (heterozygous familial and non-familial) hypercholesterolaemia or mixed dyslipidaemia
- The addition of REPATHA to an optimal lipid-lowering therapy, used at maximum doses, whether or not combined with apheresis, in adult patients with uncontrolled homozygous familial hypercholesterolaemia (HoFH), provides a minor improvement in actual benefit (CAV IV).
- Does not recommend inclusion on the list of reimbursable products for supply by pharmacists and for hospital use in primary hypercholesterolaemia and mixed dyslipidaemia.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use in homozygous hypercholesterolaemia.

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This document was created on the basis of the Transparency Committee Opinion of 16 December 2015 (CT-14598) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".