TRANSPARENCY COMMITTEE OPINION SUMMARY

REPATHA (evolocumab), anti-PCSK9

High clinical benefit in uncontrolled primary hypercholesterolaemia or mixed dyslipidaemia with established atherosclerotic cardiovascular disease, and in uncontrolled heterozygous familial hypercholesterolaemia, requiring apheresis, but no clinical benefit demonstrated in the therapeutic strategy

Insufficient clinical benefit to justify reimbursement in other populations

Main points

- REPATHA has MA in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, homozygous familial hypercholesterolaemia and established atherosclerotic cardiovascular disease.
- In primary hypercholesterolaemia or mixed dyslipidaemia, its efficacy in combination with a statin has been demonstrated in terms of reduction in LDL-c levels and reduction in the number of cardiovascular events compared to a statin alone. There are uncertainties as to the extent of the effect and the transposability of the results observed.
- In severe heterozygous familial hypercholesterolaemia requiring LDL-apheresis treatment, its efficacy in combination with a lipid-lowering therapy has been demonstrated on the reduction in LDL-c level and the reduction in the use of LDL-apheresis compared to LDL-apheresis combined with a lipid-lowering therapy.
- No benefit has been demonstrated on cardiovascular mortality, overall mortality and quality of life.

Pre-existing indications*

- REPATHA has MA in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies treatments.

Therapeutic strategy

Primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia

- The objective of the treatment is to reduce LDL-c levels in order to prevent the occurrence of cardiovascular events. Treatment is guided by targeted LDL-c levels which are different according to the patient's cardiovascular risk. It is based on the prescription of lipid-lowering therapy along with lifestyle and dietary measures. Statins are recommended in first line and can, if targets are not reached at a suitable dose, be combined with ezetimibe or as a last resort cholestyramine.
- In patients with dyslipidaemia in whom statin treatment is poorly tolerated, the choice is made between fibrates, cholestyramine and ezetimibe.
- In secondary prevention, the treatment is based on the use of statins. Despite the range of lipid-lowering therapies available, certain patients can remain uncontrolled. LDL-apheresis can also be envisaged in patients with heterozygous familial hypercholesterolaemia with high LDL-c levels despite optimised oral treatment.
- **Role of the medicinal product in the therapeutic strategy**

* This summary does not cover this indication.

REPATHA is a 3rd intention treatment which must be reserved, in addition to lifestyle and dietary measures and in combination with optimised lipid-lowering therapy for:

- adult patients at very high cardiovascular risk, with primary hypercholesterolaemia or mixed dyslipidaemia, with a history of myocardial infarction, non-haemorrhagic stroke and/or symptomatic peripheral arterial disease (secondary prevention) and uncontrolled (LDL-c ≥ 0.7 g/L) despite optimised treatment including at least one statin at maximum tolerated dose;
- adults with heterozygous familial hypercholesterolaemia, insufficiently controlled with optimised treatment, requiring LDL-apheresis treatment.

In other situations, in light of the lack of clinical data, REPATHA does not have a role in the therapeutic strategy.

Clinical data

- Two studies were conducted in patients at very high cardiovascular risk with clinically established atherosclerotic cardiovascular disease (FOURIER study), and in patients with heterozygous familial hypercholesterolaemia treated with LDL-apheresis (REPATHA APHERESIS study).
- In the randomised, double-blind FOURIER study conducted in 27,564 patients with clinically established atherosclerotic cardiovascular disease, the benefit of adding REPATHA to a statin treatment was demonstrated compared to statin treatment alone, on the reduction in occurrence of a first cardiovascular event combining cardiovascular deaths, myocardial infarctus and strokes (clinically-relevant endpoint): 5.92% versus 7.35%, therefore an absolute difference of 1.43%; 95%CI [0.73; 0.88]; p<0.0001. These results mainly came from a reduction in the risk of occurrence of myocardial infarction. The absolute difference observed was however low and no difference concerning cardiovascular mortality and overall mortality was observed.
  There are uncertainties as to the quantity of the effect and the transposability of the results observed, with respect to the small percentage of patients treated at maximum statin doses (29%).
- In the randomised, open-label REPATHA APHERESIS study conducted in 39 patients requiring regular apheresis (every two weeks or every week) due to an LDL-c level of between 100 and 190 mg/dL, after 4 weeks' treatment, a significantly higher number of patients treated with evolocumab and optimised lipid-lowering therapy (statin ± ezetimibe) did not require conditional apheresis in weeks 5 or 6 compared to the patients treated with LDL-apheresis and optimised lipid-lowering therapy (statin ± ezetimibe): 84.2% versus 10.0%, therefore an absolute difference of 74.2% (95%CI [44.6; 86.8]; p<0.0001). The small number of patients included in this study and the short follow-up (26 weeks), with an endpoint measured in week 6, limits the transposability of the results. A third of the patients included in this study were not treated with a statin but with LDL-apheresis alone due to intolerance to statins.
- The impact on mortality (cardiovascular and overall) and on quality of life was not demonstrated.
  Few patients over the age of 75 were included in the studies (5% to 10%); thus the efficacy and tolerance of evolocumab cannot be determined in this population.

Special prescription requirements

- Initial annual prescription by cardiology, endocrinology, diabetes and metabolic diseases or internal medicine specialists.
- Unrestricted repeat prescription.
- Exception drug

Benefit of the medicinal product

- The actual clinical benefit* of REPATHA is high only in combination with optimised lipid-lowering therapy in:
  - adult patients at very high cardiovascular risk, with primary hypercholesterolaemia or mixed dyslipidaemia, with established atherosclerotic cardiovascular disease confirmed by a history of myocardial infarction, non-haemorrhagic stroke and/or symptomatic peripheral artery disease (secondary prevention) and uncontrolled (LDL-c ≥ 0.7 g/L) despite optimised treatment including at least one statin at maximum tolerated dose;
  - adults with heterozygous familial hypercholesterolaemia, insufficiently controlled with optimised treatment, requiring LDL-apheresis treatment.
- It is insufficient to justify reimbursement by public funding in the other populations for the "primary hypercholesterolaemia and mixed dyslipidaemia" and "established atherosclerotic cardiovascular disease" indications.
- Adjuvant REPATHA treatment with optimised lipid-lowering therapy does not provide clinical added value ** (CAV V) in the treatment of populations eligible for reimbursement.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment only in combination with optimised lipid-lowering therapy in the populations eligible for reimbursement.

HAUTE AUTORITÉ DE SANTÉ

This document was drafted on the basis of the Transparency Committee opinion dated 05 September 2018 (CT-16427) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"