HAUTE AUTORITÉ DE SANTÉ

CARDIOLOGY
New indication
July 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

PRALUENT (alirocumab), anti-PCSK9

High clinical benefit for the secondary prevention of recent acute coronary syndrome for uncontrolled patients despite optimised hypolipidaemic treatment but no demonstrated clinical added value in the therapeutic strategy

Insufficient clinical benefit to justify reimbursement for other populations for secondary prevention of established atherosclerotic cardiovascular disease

Main points

- PRALUENT has now been granted a marketing authorisation for the secondary prevention of established atherosclerotic cardiovascular disease.
- Evidence has been obtained of its efficacy in combination with a statin in terms of reduction of the number of cardiovascular events compared to a statin alone in a selected population. There are uncertainties as to the effect size and the transposability of the results observed.
- No benefit has been demonstrated on mortality (coronary, cardiovascular or overall mortality) and quality of life.
- Failing a direct comparison of PRALUENT to ezetimibe for secondary prevention, the respective role of one in relation to the other has yet to be determined.
- Uncertainties remain in terms of safety, particularly on the long-term effects of continuing alirocumab treatment in the presence of anti-alirocumab antibodies.

Pre-existing indications*

PRALUENT has been granted a marketing authorisation for adults presenting with primary hypercholesterolaemia (familial heterozygous and non-familial) or mixed dyslipidaemia, alongside dietary measures:

- in combination with a statin alone or a statin with other hypolipidaemic therapies for patients unable to meet their LDL-C target, treated with statins at the maximum tolerated dose or,
- alone or in combination with other hypolipidaemic therapies for statin-intolerant patients, or patients for whom statins are contraindicated.

Therapeutic strategy

The first-line management of total blood cholesterol in patients with previous history of atherosclerotic cardiovascular disease is based on the implementation of lifestyle and dietary measures (reducing fat consumption, exercise), the management of other cardiovascular risk factors (smoking, high blood pressure, diabetes, etc.) and the early initiation of high-intensity statin treatment, unless contraindicated, after the acute coronary syndrome (ACS) event, regardless of the patient's LDL-c level. If the LDL-c target is not met with the maximum tolerated statin dose, it is recommended to combine ezetimibe with a statin. In the event of failure to meet the target LDL-c despite combining a statin at the maximum tolerated dose +/- ezetimibe, PCSK9 inhibitors may be proposed in addition to the hypolipidaemic treatment (second- or third-line). U.S. guidelines recommend PCSK9 inhibitors as secondary prevention for persistently uncontrolled patients (LDL-c level > 70 mg/dl) despite

* This summary does not cover this indication.

receiving hypolipidaemic treatment including a statin at the maximum tolerated dose and ezetimibe (third-line treatment).

- **Role of the proprietary medicinal product in the therapeutic strategy**
  Failing a comparison to ezetimibe, PRALUENT should be used as a third-line treatment alongside lifestyle and dietary measures and in combination with optimised hypolipidaemic treatment (statin + ezetimibe) only for adult patients with previous history of recent ACS (secondary prevention) and who are uncontrolled (LDL-c ≥ 0.7 g/L) despite receiving optimised hypolipidaemic treatment including at least a statin at the maximum tolerated dose.
  Few patients over the age of 75 were included in the ODYSSEY OUTCOMES study (5%); it is not possible to determine the role of alirocumab in this population.
  The Committee also notes the short follow-up period available, limited to 2.8 years.
  In other situations, in light of the lack of clinical data, PRALUENT does not have a role in the therapeutic strategy.

Clinical data

- The assessment of PRALUENT is based on the findings of a comparative double-blind randomised superiority phase III trial versus placebo (ODYSSEY OUTCOMES), conducted on 18,924 adults with a recent history of ACS and uncontrolled lipid levels despite receiving stable high-intensity stain (atorvastatin or rosuvastatin) treatment at the maximum tolerated dose with or without other hypolipidaemic treatments. The primary endpoint was the incidence of the first major cardiovascular event based on the combined endpoint (coronary-related deaths, non-fatal myocardial infarction [MI], fatal and non-fatal ischaemic stroke and hospitalisation due to unstable angina), assessed by an independent committee. Seven endpoints were then tested according to a ranked procedure. The doses of alirocumab were adjusted (doses of 75 mg or 150 mg of alirocumab or switch to a placebo) to achieve a target LDL-c level between 30 and 50 mg/dl during the treatment phase.
- After a median follow-up period of 33 months, the benefit of adding PRALUENT was demonstrated versus placebo on the primary endpoint: 9.5% versus 11.1%, therefore an absolute difference of 1.6% (HR=0.85; CI95.02% [0.78; 0.93]; p=0.0003). These findings mainly stemmed from a reduction in the risk of non-fatal MI.
  This study also demonstrated a significantly greater reduction when treated with alirocumab versus placebo in the first 4 ranked secondary morbi-mortality endpoints.
  However, the absolute difference observed on the various endpoints was slight, and no difference concerning coronary mortality, cardiovascular mortality and mortality, whatever the cause, was observed.
- The safety profile of PRALUENT was similar overall to that already known.
- There are uncertainties as to the effect size and the transposability of the findings observed, in view of the small number of patients treated at maximum statin doses (27%) and the small number of patients treated with the statin + ezetimibe combination (3%).
  The impact on quality of life and care organisation has not been demonstrated to date.
  The median study duration is 2.8 years. This period is short compared to those of studies assessing oral hypolipidaemic therapies (statins, ezetimibe). As such, uncertainties remain in terms of safety, particularly on the long-term effects of continuing alirocumab treatment in the presence of anti-alirocumab antibodies.

Specific prescribing conditions

- 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 PRALUENT is high only in combination with optimised hypolipidaemic treatment for adult patients with atherosclerotic cardiovascular disease established by previous history of recent ACS (secondary prevention) and who are uncontrolled (LDL-c ≥ 0.7 g/L) despite receiving optimised hypolipidaemic treatment including at least a statin at the maximum tolerated dose.
  It is insufficient to justify public funding cover in other populations for the “established atherosclerotic cardiovascular disease” indication
- PRALUENT provides no clinical added value** (CAV V) in the management of patients suffering eligible for reimbursement.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment only in combination with optimised hypolipidaemic treatment in the populations eligible for reimbursement.

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

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