HAUTE AUTORITÉ DE SANTÉ

ASSESSING HEALTH TECHNOLOGIES

OPINION ON MEDICINAL PRODUCTS

evinacumab

EVKEEZA 150 mg/ml,

dilutable solution for perfusion

First assessment

Adopted by the Transparency Committee on 19 October 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for EVKEEZA (evinacumab) for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia as an adjunct to diet and other therapies that reduce low-density lipoprotein cholesterol (LDL-c).

Therapeutic improvement?

A therapeutic advance in the management strategy for adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia.

Role in therapeutic strategy?

The management of homozygous familial hypercholesterolaemia (HoFH) is based on a combination of dietary and hygiene measures, several hypolipidaemic treatments, initiated as early as possible, and lipoprotein apheresis, if available.

Statins are recommended as a first-line treatment. In the event of failure of statin therapy at the maximum tolerated dose, combination with ezetimibe or cholestyramine is recommended. However, it should be noted that due to very poor digestive tolerance, cholestyramine is now hardly ever used. In addition, LDL apheresis is also recommended for HoFH patients.

As a third-line treatment, a PCSK9 inhibitor (evolocumab) is recommended in combination with the aforementioned treatments.

For adults not controlled by the available hypolipidaemic drugs, LOJUXTA (lomitapide) may be proposed as an adjunct to a low-fat diet and in combination with other well-conducted hypolipidaemic treatments at maximum dose, with or without low-density lipoprotein (LDL) apheresis.

Note that an optimised first-line hypolipidaemic treatment is defined as:

- statin at maximum tolerated dose in combination with ezetimibe if there is no known contraindication or intolerance to statins and ezetimibe;
- or statin at maximum tolerated dose, alone in the event of contraindication or intolerance to ezetimibe;
- or ezetimibe alone in the event of contraindication or known intolerance to statins.

Role of EVKEEZA (evinacumab) in the therapeutic strategy:

For adolescents and adults with homozygous familial hypercholesterolemia not controlled by available hypolipidaemic drugs at the maximum tolerated dose, EVKEEZA (evinacumab) is a last-line treatment, in addition to a low-fat diet and in **combination with optimised oral hypolipidaemic treatment, including at least one statin, ezetimibe and a PCSK9 inhibitor (evolocumab), with or without LDL apheresis**.

Special recommendations

The Committee recommends exception drug status.

Committee's conclusions

Clinical Benefit

- Homozygous familial hypercholesterolaemia is a very rare and severe disease, characterised by the presence of extravascular cholesterol deposits, high LDL levels (>3.30 g/L) and cardio-vascular diseases, from childhood onwards. Such diseases are favoured by these dyslipidae-mias and can be prematurely life threatening due to complications.
- The proprietary medicinal product EVKEEZA (evinacumab) is a curative medicinal product.
- The efficacy of EVKEEZA (evinacumab), in combination with other hypolipidaemic drugs (statins + other hypolipidaemic drugs +/- LDL-apheresis), has only been demonstrated in terms of the reduction of biological parameters (LDL-c). Efficacy in terms of morbidity and mortality has not been demonstrated to date. Uncertainties remain, given the duration of follow-up and the size of the populations in the clinical trials, particularly in terms of safety. However, the efficacy/adverse effect ratio is significant.
- LOJUXTA (lomitapide) is an alternative for adults only, which is not widely used in France and which has known serious adverse effects – particularly hepatic.
- It is a last-line treatment that should be reserved for adult patients and adolescents over 12 years of age with uncontrolled HoFH, in addition to a low-fat diet and in combination with an optimised oral hypolipidaemic treatment, including at least one statin, ezetimibe and a PCSK9 inhibitor (evolocumab), with or without LDL apheresis.

Public health benefit

Considering:

- the severity of cardiovascular disease promoted by HoFH,
- the rarity of this disease with a current prevalence of about 1 case/300,000,
- the medical need for effective and well-tolerated medicines in children, adolescents and adults with HoFH,
- the partial response of EVKEEZA (evinacumab) to the medical need, due to:
  - the demonstrated impact of EVKEEZA (evinacumab) on LDL-c reduction (biological outcome measure) but in the absence of comparative data and a demonstrated impact on morbidity,
  - the lack of evidence of EVKEEZA (evincumab) having an impact on quality of life and the delivery of care,

EVKEEZA (evinacumab) is not likely to have a public health benefit.

Considering all of these elements, the Committee deems that the actual clinical benefit of EVKEEZA (evinacumab) is SUBSTANTIAL in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and at the marketing authorisation dosages.

Clinical Added Value

Considering:

- the evidence of the superior efficacy of EVKEEZA (evinacumab) versus placebo in reducing LDL-c (biological outcome measure) in patients with homozygous familial hypercholesterolemia not controlled by other hypolipidaemic drugs, in a randomised, double-blind, multicentre study (ELIPSE HoFH study);
- the substantial effect size demonstrated (difference of -49.0%, 95% CI [-65.0; -33.1]; p<0.0001), in a relatively elderly population (mean age 41 years) with a median LDL-c level at inclusion of 2.0 g/l and a predominant history of coronary heart disease;
- the insufficiently met medical need for effective and well-tolerated drugs enabling a reduction in recourse to LDL-apheresis, in patients who have not been controlled despite receiving optimized hypolipidemic treatment, notably those with a bi-allelic mutation in the LDLR gene, and lacking functional LDLR receptors;
- its acceptable safety profile to date,

But in the light of:

- uncertainties about the safety profile due to a new mechanism of action and limited experience (safety data < 2 years);
- the lack of data on clinically relevant morbidity and mortality outcome measures;
- the lack of direct comparison with other hypolipidaemic drugs in this indication;
- the lack of robust quality-of-life data,

the Transparency Committee considers that EVKEEZA (evinacumab) provides minor clinical added value (CAV IV) in the management strategy for adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia, as an adjunct to diet and other LDL-c cholesterol-lowering therapies.