HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
06 APRIL 2022

The legally binding text is the original French opinion version

evolocumab
REPATHA 140 mg solution for injection in pre-filled pen

New indications

Key points

Favourable opinion for reimbursement in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia (HFHe), inadequately controlled (LDL-c > 1.30 g/L) by a maximum tolerated oral therapy, as an adjunct to diet, and:
- in combination with an optimised lipid-lowering therapy;
- or as monotherapy in the event of contraindication or known intolerance to both statins and ezetimibe.

Favourable opinion for reimbursement in paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia (HFHo) in combination with other lipid-lowering therapies.

Unfavourable opinion for reimbursement in the other clinical situations of the MA, in particular in the event of non-optimised lipid-lowering therapy.

What therapeutic improvement?

No clinical added value in the therapeutic strategy in of patients with HFHe.

Therapeutic improvement in the management of patients with HFHo.

Role in the care pathway?

Heterozygous familial hypercholesterolaemia in paediatric patients aged 10 years and over
Paediatric patients with HFHe with extremely high LDL-c levels should receive lipid-lowering therapy as soon as possible.
In other cases, if lifestyle and dietary measures have not been sufficient, statins are recommended as first-line therapy and are generally initiated from the age of 8 years. They should be started at the lowest recommended dose, which should be increased based on the patient's response and tolerance to treatment.
In the event of failure of treatment with a statin at the maximum tolerated dose, combination with ezetimibe is recommended. In accordance with the guidelines, LDL-apheresis may be used in patients far from the cholesterol level goals (LDL-c >3 g/L) despite optimised lipid-lowering therapy. However, it should be noted that LDL-apheresis is very rarely practised in France.

Role of REPATHA (evolocumab) in the care pathway:
REPATHA (evolocumab) should be used as **third-line treatment** as an adjunct to lifestyle and dietary measures and in combination with an optimised oral lipid-lowering therapy*, or as monotherapy only in the event of contraindication or known intolerance to both statins and ezetimibe in children and adolescents aged 10 years and over with HFHe diagnosed in accordance with Wiegman's criteria, inadequately controlled (LDL-c > 1.30 g/L) by a maximum tolerated oral lipid-lowering therapy.

REPATHA (evolocumab) has no role in the other clinical situations of the MA, in particular in combination with non-optimised lipid-lowering therapy.

Homozygous familial hypercholesterolaemia in paediatric patients aged 10 to 11 years
The early identification of these children and their rapid management in a specialised centre is crucial.
The management of HFHo is based on the combination of lifestyle and dietary measures, early lipid-lowering therapy and lipoprotein apheresis if available.
Statins are recommended as first-line treatment. In the event of failure of treatment with a statin at the maximum tolerated dose, combination with ezetimibe is recommended.
In addition, LDL-apheresis is also recommended in HFHo patients.

Role of REPATHA (evolocumab) in the care pathway:
REPATHA (evolocumab) should be used as **third-line treatment** as an adjunct to lifestyle and dietary measures and in combination with an optimised oral lipid-lowering therapy*.

* As a reminder, optimised lipid-lowering therapy is defined as:
- a statin at the maximum tolerated dose in combination with ezetimibe in the absence of contraindications or known intolerance to statins and ezetimibe;
- a statin at the maximum tolerated dose alone in the event of contraindication or intolerance to ezetimibe;
- ezetimibe in the event of contraindication or known intolerance to statins.

Special recommendations

The Committee recommends that exception drug status be extended to this indication.

The Committee warns that there is a risk of misuse in populations not eligible for treatment, including, in particular, patients not receiving an optimised treatment where this is possible.

The Committee will pay particularly close attention to the real conditions of use of REPATHA (evolocumab) at its next assessments.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

Heterozygous familial hypercholesterolaemia in paediatric patients aged 10 years and over

◗ The cardiovascular diseases promoted by heterozygous familial hypercholesterolaemia can cause serious complications and be life-threatening for the patient.

◗ The proprietary medicinal product REPATHA (evolocumab) is a preventive medicinal product.

◗ The efficacy/adverse effects ratio is high in children and adolescents aged 10 years and over with HFHe, inadequately controlled by a maximum tolerated oral therapy: in combination with an optimised lipid-lowering therapy or as monotherapy in the event of contraindication or known intolerance to both statins and ezetimibe.

◗ There are therapeutic alternatives (see section 05 Clinically relevant comparators).

◗ REPATHA (evolocumab) should be used as third-line treatment as an adjunct to lifestyle and dietary measures and in combination with an optimised oral lipid-lowering therapy, or as monotherapy only in the event of contraindication or known intolerance to both statins and ezetimibe in children and adolescents aged 10 years and over with HFHe diagnosed in accordance with Wiegman's criteria, inadequately controlled (LDL-c > 1.30 g/L) by a maximum tolerated oral lipid-lowering therapy.

Public health impact

Considering:

- heterozygous familial hypercholesterolaemia and its long-term consequences on the high risk of cardiovascular diseases and/or death,
- its prevalence,
- the identified partially met medical need,
- the lack of response to the identified need, due to the lack of demonstrated impact on morbidity and mortality but in view of a demonstration versus placebo only on a biological endpoint (LDL-c reduction),
- the lack of any demonstrated impact on quality of life and the organisation of care, REPATHA (evolocumab) is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of REPATHA (evolocumab) is:

- **substantial in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia, inadequately controlled (LDL-c > 1.30 g/L) by a maximum tolerated oral therapy, as an adjunct to diet, and:**
  - **in combination with an optimised lipid-lowering therapy, or;**
  - **as monotherapy in the event of contraindication or known intolerance to both statins and ezetimibe;**
- **insufficient in the other clinical situations of the MA, in particular in the event of non-optimised lipid-lowering therapy.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia, inadequately controlled (LDL-c > 1.30 g/L) by a maximum tolerated oral therapy and at the MA dosages, as an adjunct to diet, and in combination with an optimised lipid-lowering therapy or as monotherapy in the event of contraindication or known intolerance to both statins and ezetimibe.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other clinical situations of the MA, in particular in the event of non-optimised lipid-lowering therapy.

Homozygous familial hypercholesterolaemia in paediatric patients aged 10 to 11 years

◗ Homozygous familial hypercholesterolaemia is a very rare and severe disease that can be life-threatening to patients due to its cardiovascular consequences.

◗ The proprietary medicinal product REPATHA (evolocumab) is a preventive medicinal product.

◗ The efficacy/adverse effects ratio of evolocumab is high in this paediatric indication extension to children aged 10 to 11 years.

◗ There are therapeutic alternatives (see section 05 Clinically relevant comparators).

◗ **REPATHA (evolocumab) should be used as third-line treatment as an adjunct to lifestyle and dietary measures and in combination with an optimised oral lipid-lowering therapy.**

Public health impact

Considering:

- the seriousness of the cardiovascular diseases promoted by HFHo,
- the rarity of the disease,
- the identified inadequately met medical need,
- the additional partial response to the medical need due to the additional impact on morbidity and mortality, quality of life and the organisation of care, which remains to be demonstrated in view of the slow progressing nature of the disease,
  however, it should be noted that the superiority of evolocumab has been demonstrated in adolescents aged 12 years and more and adults on a biological endpoint,
- the lack of any demonstrated impact on quality of life and the organisation of care,

REPATHA (evolocumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of REPATHA (evolocumab) is substantial in paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia (HFHo) in combination with other lipid-lowering therapies.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication and at the marketing authorisation dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Heterozygous familial hypercholesterolaemia in paediatric patients aged 10 years and over

Considering:
- demonstration of the superiority of REPATHA (evolocumab), in terms of the reduction in biological parameters (reductions in LDL-c levels at 24 weeks, the primary endpoint) in a comparative randomised study, with a moderate effect size compared to placebo,
- the lack of data enabling confirmation of treatment optimisation in the population included in this study, making it impossible to rule out over-estimation of the effect,
- the absence of data relative to a potential effect of evolocumab on morbidity and mortality in children and adolescents aged 10 years and over,
- uncertainties in terms of medium and long-term safety, in particular due to the short duration of the studies,

the Committee considers that REPATHA (evolocumab) provides no clinical added value (CAV V) in the treatment of paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia, inadequately controlled (LDL-c > 1.30 g/L) by a maximum tolerated oral therapy, as an adjunct to diet, and:
- **in combination with an optimised lipid-lowering therapy;**
- **or as monotherapy in the event of contraindication or known intolerance to both statins and ezetimibe.**

<u>In the other populations of the "heterozygous familial hypercholesterolaemia" indication:</u>
Not applicable.

Homozygous familial hypercholesterolaemia in paediatric patients aged 10 to 11 years

Considering:
- the known efficacy profile of evolocumab in paediatric patients aged 12 years and over, with demonstration of its efficacy in terms of reduction in biological parameters (reduction in LDL-c levels) versus placebo,
- the safety profile in this paediatric population, which is consistent with the known profile for the medicinal product in adults and adolescents aged 12 years and over in this indication and acceptable,
- the need to have access to effective, well tolerated alternatives, to be initiated as soon as possible in this severe disease, which presents early and rapid progression,

but in view of:
- the lack of any demonstrated effect of evolocumab on morbidity and mortality in children and adolescents aged 10 years and over,
- uncertainties in terms of the medium and long-term safety in this population,

the Committee considers that REPATHA (evolocumab) provides a minor clinical added value (CAV IV) in the treatment of paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia (HFHo) in combination with other lipid-lowering therapies.