HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

18 NOVEMBER 2020

The legally binding text is the original French opinion version

anakinra

KINERET 100 mg/0.67 ml solution for injection in pre-filled syringe

New indication

Key points

Favourable opinion for reimbursement in the treatment of Familial Mediterranean Fever (FMF) only when colchicine is ineffective, poorly tolerated or contraindicated.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

According to the treatment guidelines, in the absence of curative treatment, management is based on symptomatic treatment of disease flares and their prevention, the aim being to prevent complications, particularly related to amyloidosis, and preserve patients' quality of life.

The treatment of Familial Mediterranean Fever (FMF) is based exclusively on symptomatic treatment. Inflammatory flares require rest and justify time off work or school throughout the duration of symptoms. Treatment of inflammatory flares involves analgesics, antipyretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroid therapy for as short a time as possible.

Concerning maintenance therapies, apart from anakinra (anti-IL1) another two proprietary medicinal products currently have an MA in FMF: colchicine and canakinumab (ILARIS, anti-IL1).

According to the French national diagnostic and care protocol (PNDS) produced in 2013 as well as the 2016 European Alliance of Associations for Rheumatology (EULAR) guidelines, colchicine is effective in the prevention of flares and amyloidosis. It is recommended as first-line treatment and should be taken daily for life. However, its use is contraindicated in the event of severe renal or hepatic impairment.

In the rare patients (3 to 5%) not responding or resistant to colchicine, biologic therapies, and in particular anti-IL1 inhibitors (canakinumab and anakinra) should be envisaged. These should be given in combination with colchicine wherever possible in order to reduce the risk of amyloidosis (except in the event of intolerance or contraindication to this drug). In the absence of comparative data, anakinra and canakinumab are options that can be used at the same stage in the strategy.

According to the PNDS, the effects of the other treatments proposed in the literature are controversial and they cannot be recommended (corticosteroids, interferon alpha, thalidomide, TNF alpha inhibitors, etc.).

Role of the medicinal product in the care pathway

KINERET (anakinra) is a second-line treatment, in the same way as ILARIS (canakinumab), to be reserved for patients with Familial Mediterranean Fever (FMF) only when colchicine is ineffective, poorly tolerated or contraindicated, considering:

- well-established use in clinical practice in these patients and recognition of this use by the national and European guidelines and by experts,
- and its documented efficacy in the literature despite the low level of evidence of the available data, the clinical study conducted by Ben-Zvi et al. in 2017 and numerous observational studies.

In accordance with the Ben-Zvi et al. 2017 study and the SPC, the Committee recommends that anakinra (KINERET) be used in combination with colchicine wherever possible, since this is the only treatment to have demonstrated efficacy against the development of amyloidosis.

The attention of physicians is drawn to the fact that, in patients demonstrating no clinical improvement, the benefit of continued treatment with KINERET (anakinra) should be reassessed.

Special recommendations

The Committee recommends:

- that the decision to initiate treatment with KINERET (anakinra) be taken after a documented proposal resulting from a treatment review meeting with a reference centre with expertise in the treatment of FMF, and
- that the first subcutaneous injection of this medicinal product be administered in an appropriate healthcare setting given the rare but serious identified risk of systemic reactions to the injection, including anaphylactic reactions with anakinra (as well as with other biologic DMARDs).

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Familial Mediterranean Fever (FMF) is a rare auto-inflammatory disease that can be incapacitating, lead to a marked deterioration in quality of life and be life-threatening in the event of development of amyloidosis.

◗ KINERET (anakinra) is a symptomatic treatment.

◗ Its efficacy/adverse effects ratio is high in FMF patients in whom colchicine is ineffective, poorly tolerated or contraindicated in view of its use in clinical practice reported by experts and data from the literature, particularly the Ben-Zvi *et al.* 2017 study and observational studies, despite their low level of evidence.

◗ There is only one therapeutic alternative with an MA in the treatment of FMF patients in whom colchicine is ineffective, poorly tolerated or contraindicated: the proprietary medicinal product ILARIS (canakinumab).

◗ KINERET (anakinra) is a second-line treatment, in the same way as the proprietary medicinal product ILARIS (canakinumab), to be reserved for patients in whom colchicine is ineffective, poorly tolerated or contraindicated. (see section 08 of the present opinion)

Public health impact

Considering:

- the seriousness of the disease, related to the deterioration in quality of life and the risk of development of amyloidosis, which can be life-threatening,
- its rarity,
- the medical need partially met by colchicine and by the proprietary medicinal product ILARIS (canakinumab) in colchicine-resistant patients,
- the suggested impact of KINERET (anakinra) on the number of flares supported by data in the literature and off-label use in clinical practice,
- the absence of robust demonstration of a favourable impact on quality of life and the absence of data on the prevention of secondary amyloidosis (a major complication),
- the lack of any demonstrated impact on the organisation of care (hospitalisation, AEs, etc.) and of daily SC injections in comparison with monthly SC injections of ILARIS (canakinumab),
- the partial response to the identified medical need in the rare patients who are colchicine-resistant, in the same way as ILARIS (canakinumab),

KINERET (anakinra) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of KINERET (anakinra) is substantial in the treatment of FMF patients in whom colchicine is ineffective, poorly tolerated or contraindicated.

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 treatment of FMF patients in whom colchicine is ineffective, poorly tolerated or contraindicated and at the MA dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **the superiority compared to placebo in the institutional clinical study conducted by Ben-Zvi *et al.* in 2017 in terms of the mean number of flares per month (first primary endpoint) and observational data suggesting its clinical benefit,**

but considering:

- **the methodological limitations of the clinical study and the low level of evidence of observational data,**
- **the absence of comparative data with ILARIS (canakinumab), the only clinically relevant comparator in colchicine-resistant patients,**
- **the absence of demonstration of the prevention of secondary amyloidosis, a major complication that is liable to life-threatening, and**
- **the daily character of subcutaneous injections of anakinra compared to the monthly injections of canakinumab,**

KINERET (anakinra) provides no clinical added value (CAV V) in the care pathway for the treatment of FMF in patients in whom colchicine is ineffective, poorly tolerated or contraindicated.