HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New indications
Mars 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

KINERET (anakinra), immunosuppressant

High clinical benefit in Still's disease in children and adults, but no demonstrated clinical added value in the therapeutic strategy

Main points

- KINERET now has a MA in adults and children aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids.
- Its role is well established in the management of these two rare diseases, since it had been used off-label in their treatment for a number of years.
- Its efficacy has been demonstrated versus placebo in children with SJIA after failure of corticosteroid therapy.
- In adults, the data available are of poor methodological quality; no difference between KINERET versus disease-modifying drugs has been demonstrated.
- No data are available concerning other biologic therapies.

Pre-existing indications*

KINERET already has a MA in the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndromes (see SPC for further details).

Therapeutic strategy

- In children
  The treatment of SJIA is based on NSAIDs, corticosteroid therapy and biologic agents, in particular inflammatory cytokine antagonists such as interleukins 1 and 6 (anakinra, canakinumab and tocilizumab), depending on the severity of the disease. The most widely used first-line treatment is systemic corticosteroid therapy. In certain cases, anti-IL-1 biologic therapy may be discussed before systemic corticosteroid therapy, following the opinion of a reference or expert centre. The use of anakinra as first-line therapy corresponds, in particular, to exceptional and/or threatening clinical situations (expert opinion). In patients having received systemic corticosteroid therapy, in the absence of a clinical response after 1 to 2 weeks of corticosteroid therapy or corticosteroid dependence during dose reduction or major adverse reaction, anti-IL-1 or anti-IL-6 biologic therapy may be envisaged. No studies are available having compared biologic agents targeting IL-1 or IL-6 in SJIA, which means that they cannot be ranked in any order in its management.
- In adults
  High-dose systemic corticosteroid therapy remains the first-line treatment. In systemic forms, the use of an anti-IL-1 biologic therapy with a MA (canakinumab or anakinra) or anti-IL6 (off-label) is justified due to their superior efficacy to methotrexate. Methotrexate retains a role in forms predominantly affecting the joints or with few symptoms. Biologic agents targeting TNF have an efficacy - and, above all, a therapeutic maintenance rate - inferior to IL-1 and IL-6 inhibitors. They retain a role in chronic articular forms.
  Anti-IL-1 agents (preferentially anakinra) can be introduced:

* This summary does not concern these indications.

- in patients with an inadequate response to corticosteroid therapy and relapsing when corticosteroid doses are rapidly reduced,
- in corticosteroid-naive patients, concomitantly with corticosteroid therapy or possibly alone, following multidisciplinary team discussion at the reference centre.

- **Role of the medicinal product in the therapeutic strategy**
  The role of KINERET is primarily as a second-line treatment following an inadequate response, intolerance or dependence on systemic corticosteroid therapy. However, its first-line use can be discussed before systemic corticosteroid therapy, particularly in exceptional emergency situations, following the opinion of a reference or expert centre. Regardless of the indication concerned, given the rare but serious identified risk of systemic reactions following injection, including anaphylactic reactions with anakinra, but also with other biologic disease-modifying drugs, the first subcutaneous injection of this medicinal product must be given in an appropriate healthcare structure.

Clinical data

- The evaluation of the efficacy and safety of anakinra in Still's disease in adults and children is based on bibliographic data, including observational studies. Only two randomised, controlled clinical trials on small populations conducted versus placebo (24 children) and versus disease-modifying drugs (22 adults) enable assessment of the effect size of anakinra in this rare disease.
  In children, after 1 month of treatment, the superiority of anakinra (2 mg/kg/d SC, 100 mg maximum) was demonstrated versus placebo in terms of modified ACRPedi30 response (primary endpoint): 8/12 with anakinra versus 1/12 with placebo, p =0.003.
  In adults, at week 8, the superiority of anakinra compared to DMARDs was not demonstrated in terms of achievement of clinical remission (primary endpoint): 7/12 patients receiving anakinra as monotherapy or in combination were in remission versus 5/10 in the DMARD group, a difference that is not statistically significant.
- There are no new safety data to report, apart from the risk of occurrence of macrophage activation syndrome. However long-term safety data are limited.

Prescription requirements

- Exception drug
- Medicinal product subject to initial annual hospital prescription
- Medicinal product subject to prescription limited to certain health professionals: rheumatology, internal medicine, paediatrics, dermatology specialists.

Benefit of the medicinal product

- The actual clinical benefit* of KINERET is high.
- KINERET does not provide clinical added value (CAV V) in the treatment strategy for AOSD and SJIA.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 06 February 2019 (CT-17195) available at **www.has-sante.fr**

* 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".