HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

18 NOVEMBER 2020

The legally binding text is the original French opinion version

canakinumab

ILARIS 150 mg powder for solution for injection and solution for injection

New indication

Key points

Favourable opinion for reimbursement in the treatment of adult-onset Still's disease (AOSD) in patients who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

A French national diagnostic and care protocol (PNDS) was produced by reference centres for adult-onset Still's disease (AOSD) in 2018. According to this protocol, the treatment of AOSD has several objectives: “control of the symptoms of AOSD and achievement of clinical and laboratory remission (absence of signs of the disease), the prevention of erosive joint involvement, the prevention of systemic complications of chronic inflammation and of treatment-associated adverse effects”.

Symptomatic treatments include analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid infiltrations and non-medicinal treatments (putting ice on the joints, relaxation, sophrology or hypnosis for chronic pain).

As regards DMARDs, only two IL1 inhibitors - anakinra and canakinumab - have an MA in this indication. Despite the absence of an MA, several treatments are proposed off-label according to the PNDS, in particular methotrexate, tocilizumab (IL6 inhibitor) or TNF inhibitors.

According to the care pathway established by the PNDS, in the event of failure or a partial response to NSAIDs and systemic corticosteroids, the second-line treatment should be discussed at a multidisciplinary team (MDT) meeting. The guidelines recommend the use of biologic therapy with an IL1 inhibitor (anakinra or canakinumab) or even an IL6 inhibitor (tocilizumab) due to their superior efficacy to methotrexate. Methotrexate nonetheless retains a role in forms predominantly affecting the joints or with few symptoms. Targeting the inflammasome pathway, and hence the IL1 pathway appears to be more specific to AOSD, in fact, and should therefore be favoured. It should be noted that these biologic therapies can be used as monotherapy or in combination with methotrexate.

In the event of resistance to second-line treatment, a switch to the other IL1 inhibitor is proposed, and in the event of primary failure, tocilizumab should be introduced directly.

Finally, in the event of failure or a partial response to this third-line treatment, the initiation of a TNF inhibitor may be proposed at an MDT meeting, although the efficacy and, especially, the therapeutic maintenance rate of the latter are inferior to those of IL1 and IL6 inhibitors.

The safety of ciclosporin limits its value but it may nonetheless be useful in some complex or refractory situations.

In all cases, in the event of prolonged remission (> 6 months), a reduction in DMARDs may be attempted, either by reducing the doses (methotrexate or IV biologic therapy), or by increasing the interval between injections (subcutaneous biologic therapies).

Role of the medicinal product in the care pathway

In the treatment of adult-onset Still's disease (AOSD), ILARIS (canakinumab) is a second-line treatment, in the same way as KINERET (anakinra), to be used in patients who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids, considering:

- its efficacy established in paediatric patients with systemic juvenile idiopathic arthritis (SJIA) and the clinical continuum with AOSD, and
- the well-established use of ILARIS (canakinumab) in patients with AOSD, supported by expert recommendations and numerous observational data available in the literature.

Considering the specificities of the disease in terms of its rarity and seriousness, as well as the low level of evidence of the available data, the Committee recommends that the decision to prescribe ILARIS (canakinumab) should be taken at a multidisciplinary team meeting in reference and expert centres belonging to the rare auto-immune and auto-inflammatory diseases network (FAI²R).

The Committee recommends that ILARIS (canakinumab) be used in accordance with the strategy established in the context of the PNDS, particularly in terms of the recommended dose (150 mg / month SC).

Special recommendations

The Committee recommends:

- that the decision to prescribe ILARIS (canakinumab) be taken at a multidisciplinary team (MDT) meeting in reference and expert centres belonging to the FAI²R network given the specificities of the disease and low level of evidence of the available data,

- that ILARIS (canakinumab) be used in accordance with the strategy established in the context of the PNDS, particularly in terms of the recommended dose (150 mg / month SC), and

- that the first subcutaneous injection of this medicinal product be administered in an appropriate healthcare setting given the rare but serious risk of systemic reactions to the injection, including anaphylactic reactions with canakinumab (as well as with other biologic DMARDs).

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Adult-onset Still's disease (AOSD) is a rare, serious, chronic debilitating condition that can lead to a marked deterioration in quality of life.

◗ This is a symptomatic treatment.

◗ Its efficacy/adverse effects ratio is high in patients with AOSD in the event of an inadequate response to NSAIDs and systemic corticosteroids, in view of its use in clinical practice reported by experts and supported by the observational studies available in the literature despite their low level of evidence.

◗ There are therapeutic alternatives in the management of AOSD in patients who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. However, with the exception of ILARIS (canakinumab), only the proprietary medicinal product KINERET (anakinra) has an MA in this indication.

◗ ILARIS (canakinumab) is a second-line treatment, in the same way as the proprietary medicinal product KINERET (anakinra), to be reserved for use in patients who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (see section 08 of this opinion).

Public health impact

Considering:

- the seriousness of the disease, in terms of the deterioration in patients' quality of life, in particular,
- its rarity,
- the medical need partially met by the proprietary medicinal product KINERET (anakinra) in patients who have not responded to or are intolerant to NSAIDs and corticosteroids, as well as by the off-label use of biologic therapies and/or conventional DMARDs,
- the absence of superiority of ILARIS versus placebo in a phase 2 study conducted on a very limited number of patients lower than the number of subjects scheduled in the protocol, which may explain a lack of power of the study, and taking into account the observational data available and experience of its use in young adults and children in SJIA,
- the absence of a robust demonstration of an impact on quality of life,
- the lack of any demonstrated impact on the organisation of care (hospitalisation, AEs, etc.) despite its convenience of use (monthly SC injections) compared to anakinra (daily SC injections),
- the partial response to the identified medical need in patients who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids,

ILARIS (canakinumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ILARIS (canakinumab) is substantial in the new MA indication.

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 marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **the methodological weakness of the available efficacy data (institutional clinical study not having demonstrated a difference versus placebo in a small patient sample and observational studies without a control group with a low level of evidence), not enabling assessment of its effect size,**
- **the absence of data versus KINERET (anakinra), the only clinically relevant comparator with an MA in this indication, not enabling it to be assessed in comparison with the latter,**

and despite:

- **the well-established use of ILARIS (canakinumab) in patients with AOSD, supported by expert recommendations and numerous observational data available in the literature,**
- **and its convenience of use as monthly SC injections compared to daily SC injections for anakinra,**

ILARIS (canakinumab) provides no clinical added value (CAV V) in the treatment of adult-onset Still's disease (AOSD) in patients who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.