HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
23 MARCH 2022

The legally binding text is the original French opinion version

risankizumab
SKYRIZI 75 mg and 150 mg solution for injection in pre-filled syringe
SKYRIZI 150 mg solution for injection in pre-filled pen

New indication

Key points

Favourable opinion for reimbursement, in the treatment, alone or in combination with methotrexate (MTX), of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

According to the guidelines of the French Rheumatology Society (SFR), updated in 2022, the objective of treatment is to obtain clinical remission or, failing this, a low level of disease activity, in order to improve quality of life, control symptoms and inflammation, prevent structural damage, and preserve or restore the functional capacities, autonomy and socioprofessional integration of patients.

Nonsteroidal anti-inflammatories (NSAIDs) (up to the maximum authorised dose) are the reference first-line treatment. Analgesics can be used for residual pain, in conjunction with the other therapies. Local corticosteroid injections may be considered, particularly in the event of a single location.

As first-line DMARD therapy, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (methotrexate, leflunomide, sulfasalazine) should be considered in the event of peripheral arthritis refractory to symptomatic treatment. Conventional DMARDs have not demonstrated efficacy on axial manifestations or in the event of isolated enthesitis or dactylitis.

As second-line DMARD therapy, in the event of inadequate response, contraindication or intolerance to csDMARDs, biologic disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic therapies (tsDMARDs) may be considered.

The bDMARDs currently available include TNF inhibitors and interleukin inhibitors, i.e.:

- five TNF inhibitors: adalimumab, etanercept, infliximab, golimumab and certolizumab pegol, which have an MA in PA in the event of failure of at least one DMARD,
- an interleukins 12 and 23 inhibitor, which has an MA in PA in the event of failure of non-biologic disease-modifying anti-rheumatic drugs: ustekinumab (STELARA),
- two interleukin 17 inhibitors, secukinumab (COSENTYX) and ixekizumab (TALTZ), which have an MA in the event of failure of DMARDs (biologic or otherwise),
- an interleukin 23 inhibitor, which has an MA in PA in the event of failure of at least one DMARD: guselkumab (TREMFYA).

TNF inhibitors and interleukin inhibitors (anti-IL12/23, anti-IL23 and anti-IL17) have identical marketing authorisations from the second line of treatment; however the Committee recommended that the latter be used preferentially in the event of failure of TNF inhibitors (i.e. as third or later-line therapy).

It should be noted that the latest version of the EULAR guidelines no longer establish a hierarchy between these treatments. However, they indicate a reassuring and well-known long-term safety profile of TNF inhibitors, some uncertainties with respect to the safety of IL17 inhibitors and an efficacy that appears to be lower on joint destruction with IL12/23 inhibitors. The SFR guidelines specify that TNF inhibitors and IL17 inhibitors should be favoured as first-line treatments in certain cases (TNF inhibitors should be favoured in the event of IBD or uveitis, whereas IL17 inhibitors should be favoured in the event of associated skin involvement).

In addition, two Janus Kinase (JAK) inhibitors (belonging to the tsDMARD class) - XELJANZ (tofacitinib) and RINVOQ (upadacitinib) - are also available in the event of failure of at least one conventional DMARD (i.e. from the second line). Like interleukin inhibitors, the Committee considered that TNF inhibitors should be favoured at this stage of the disease given the absence of comparative studies. Therefore JAK inhibitors primarily have a role following the failure of at least one TNF inhibitor (i.e. as third-line therapy). At this stage in the care pathway, the Committee also specified that their role compared to the other available treatments (interleukin inhibitors) could not be specified. The EULAR guidelines indicate that in patients having responded inadequately to at least one conventional disease-modifying therapy and at least one biologic therapy, or in whom the use of a biologic therapy is not appropriate, a JAK inhibitor may be considered.

Finally, it should be noted that in patients with non-severe, not very active forms, having responded inadequately to at least one csDMARD and in whom neither bDMARDs nor JAK inhibitors are appropriate, apremilast (OTEZLA), a PDE4 inhibitor, may be considered.

Role of the medicinal product in the care pathway

SKYRIZI (risankizumab), an IL23 inhibitor, is a second or later-line disease-modifying treatment for active psoriatic arthritis in adults following the failure of first-line treatment with a conventional DMARD.

As with the other interleukin inhibitors, considering:
- the absence of direct comparative data versus TNF inhibitors,
- experience of around 15 years with these medicinal products (marketing authorisation for etanercept dating back to 2003),
- demonstration of their efficacy on joint destruction,
the Committee considers that, in the event of failure of conventional DMARD therapy (i.e. as second-line treatment), TNF inhibitors should be favoured first. Therefore SKYRIZI (risankizumab) primarily has a role following the failure of at least one TNF inhibitor (i.e. as third and later-line therapy).

In the absence of direct comparison between risankizumab and the other treatment options available following the failure of at least one TNF inhibitor (interleukin inhibitors and JAK inhibitors), its role compared to these medicinal products cannot be specified.

Special recommendations

Given the rare but serious potential risk of systemic reactions following injection, including anaphylactic reactions with subcutaneous risankizumab but also with other biologic disease-modifying drugs, the Transparency Committee recommends that the first subcutaneous injection of this drug be given in an appropriate care structure.

The Committee also highlights that it is important to manage cardiovascular risk factors given the increased cardiovascular risk in chronic inflammatory arthritis.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Psoriatic arthritis is a chronic disease, which can be serious and disabling in certain forms.

◗ The proprietary medicinal product SKYRIZI (risankizumab) is a symptomatic disease-modifying treatment.

◗ Considering:
- the demonstrated superiority of risankizumab compared to placebo on the ACR 20 response (primary endpoint representing a modest objective), with a moderate effect size,
- the superiority of risankizumab versus placebo for achievement of minimal disease activity, for the resolution of enthesitis and dactylitis or for functional capacities and quality of life in the KEEPsAKE-2 study (ranked secondary endpoints), and despite improvements considered to be modest;
- the absence of demonstration of a structural effect versus placebo in the KEEPsAKE-1 study (ranked secondary endpoint) and the absence of data relative to this endpoint in the KEEPsAKE-2 study;
- the absence of direct comparison with an active treatment, in particular a TNF inhibitor, despite this being feasible;
- a safety profile consistent with the known profile in plaque psoriasis, marked primarily by infections, but also given a specific risk of frequent increases in transaminases in patients treated for psoriatic arthritis, and long-term immunogenic and carcinogenic risks that have not been evaluated,

the efficacy/adverse effects ratio of SKYRIZI (risankizumab) is moderate.
Additional efficacy data versus an active comparator, in particular a TNF inhibitor, and long-term safety data are required to assess the benefit of SKYRIZI (risankizumab) in psoriatic arthritis.

◗ There are medicinal alternatives, in particular TNF inhibitors, which have demonstrated an efficacy on joint destruction in psoriatic arthritis, in some cases with around 15 years of experience of their use. (See section 05 of this opinion)

◗ The Committee considers that in the event of failure of a conventional DMARD therapy (i.e. as second-line treatment), TNF inhibitors should be favoured first considering experience with these medicinal products in terms of efficacy and safety. Therefore, as with other interleukin inhibitors, SKYRIZI (risankizumab) primarily has a role following the failure of at least one TNF inhibitor (i.e. as third and later-line therapy).

Public health impact

Considering:

- the seriousness of the disease and its disabling nature in severe forms,
- the low prevalence of forms with previous failure (inadequate response, intolerance or contraindication) to one or more disease-modifying treatments,
- the partially met medical need due to failures and intolerance to available treatments and resistance phenomena,
- the absence of any demonstrated additional impact on morbidity or on quality of life compared to the available medicinal products due to a lack of direct comparative data versus these medicinal products, in particular TNF inhibitors, but also the partial response to the identified partially met need treatment due to resistance phenomena and/or the safety associated with these medicinal products,
- the lack of expected additional impact on the patient's care and/or life pathway,

SKYRIZI (risankizumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of SKYRIZI (risankizumab) is moderate 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 indication and at the marketing authorisation dosages.

- **Recommended reimbursement rate: 30%**

Clinical Added Value

In the absence of direct comparative data versus the other biologic medicinal products available in the treatment of psoriatic arthritis, the Transparency Committee considers that SKYRIZI (risankizumab) provides no clinical added value (CAV V) in the care pathway for the treatment of active psoriatic arthritis in adults who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).