HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

5 MAY 2021

The legally binding text is the original French opinion version

upadacitinib

RINVOQ 15 mg prolonged-release tablets

New indication

Key points

Favourable opinion for reimbursement in the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The French Rheumatology Society (SFR) published guidelines on the management of patients with axial spondyloarthritis - axSpA (radiographic and non-radiographic - nr-axSpA) in 2018.

The objectives of treatment are to control symptoms (inflammation, pain and spinal stiffness) and prevent structural damage in order to preserve or improve the functional capacities, autonomy, social participation and quality of life of patients and obtain clinical remission or, failing this, a low level of disease activity.

The first-line medicinal treatment of axSpA is based on the use of NSAIDs (prescription on demand, adapted to the patient and the evolution of symptoms, up to the maximum dose) as a symptomatic treatment. In the event of failure or an inadequate effect of an NSAID used at the maximum tolerated dose, a switch of NSAID can be performed.

Adjuvant therapies such as analgesics can be combined with the NSAIDs for residual pain but systemic or local corticosteroid therapy is not justified in axial forms. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (e.g., methotrexate, leflunomide, sulfasalazine) only appear to be effective in forms with peripheral joint involvement refractory to symptomatic treatment. Their efficacy in purely axial forms has not been demonstrated.

As second-line treatment, biologic therapies (bDMARDs) should be considered in patients with active disease despite NSAIDs. However, in the absence of inflammation demonstrated by laboratory tests or MRI, these biologic therapies are not indicated in nr-axSpA. A total of five TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and two IL-17A inhibitors (ixekizumab, secukinumab) have an MA in active nr-axSpA in the event of failure, inadequate response, intolerance or contraindication to NSAIDs.

According to the guidelines published by the French Radiology Society (SFR), TNF inhibitors are preferred as first-line treatment given current experience; however the lack of direct comparative data between them means that it is not possible to determine a hierarchy. In the event of loss of response, primary inefficacy or intolerance to a first TNF inhibitor, a rotation to a second TNF inhibitor or a switch to an IL-17A inhibitor are alternatives deemed to be beneficial. Given its new mechanism of action, as a selective and reversible Janus kinase (JAK 1 and JAK 1/3) inhibitor, upadacitinib is a new treatment option.

It should be noted that the updated American College of Rheumatology (ACR) guidelines published in 2019 preferentially recommend rotation to a second TNF inhibitor in the event of loss of response and favour the use of secukinumab or ixekizumab in the event of primary inefficacy, intolerance or contraindication to a first TNF inhibitor, despite the low level of evidence of the guidelines.

Role in the therapeutic strategy:

RINVOQ (upadacitinib), the first JAK inhibitor and the first oral treatment available in this indication, is a new therapeutic option in the treatment of ankylosing spondylitis in patients who have responded inadequately to conventional therapy although its role is difficult to determine compared to the available alternatives (TNF inhibitor and IL17 inhibitor).

The Committee highlights that the decision to prescribe RINVOQ (upadacitinib) should take into consideration:

- **uncertainties in terms of efficacy related to the absence of comparative data versus TNF inhibitors in second and later-line therapy (patients without prior bDMARD treatment) and the absence of third and later-line data (patients in whom a bDMARD has failed),**
- **the more limited experience in terms of safety compared to the available alternatives,**
- **the administration methods and patient preferences (oral versus subcutaneous or intravenous route)**

Hence, the Committee recommends that:

- **in second-line treatment (patients in whom NSAIDs have failed and with no prior bDMARD treatment), TNF inhibitors should be favoured given the absence of direct comparison and the greater experience in terms of tolerance and efficacy.**
- **in third and later-line treatment (patients in whom a bDMARD has failed), in the event of failure of a TNF inhibitor and if a change of therapeutic target is envisaged, IL17 inhibitors**

should be favoured in the absence of data at present relative to the efficacy of RINVOQ (upadacitinib) in this population, in contrast with IL17 inhibitors.

◗ Special recommendations

The Committee 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

◗ Ankylosing spondylitis is a chronic disease which, in its severe form with an inadequate response or intolerance to NSAIDs, is painful and affects spinal mobility and functional capacities.

◗ The proprietary medicinal product RINVOQ (upadacitinib) is a symptomatic disease-modifying treatment.

◗ The efficacy/adverse effects ratio of RINVOQ (upadacitinib) has not been adequately established on the basis of currently available data given the absence of comparison with TNF inhibitors, the absence of data in third and later-line treatment (i.e., in patients in whom biologic therapy has failed) and uncertainties in terms of safety.

◗ There are therapeutic alternatives in this indication represented, in particular, by TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and IL17 inhibitors (secukinumab and ixekizumab), see paragraph 06 of the present opinion.

◗ RINVOQ (upadacitinib) is a new therapeutic option in the treatment of ankylosing spondylitis in patients who have responded inadequately to conventional therapy although its role is difficult to determine compared to the available alternatives (TNF inhibitor and IL17 inhibitor). (see section 08 of this opinion).

◗ **Public health impact**

Considering:

- the seriousness of active ankylosing spondylitis and its impact on the functional capacities of patients, in particular in those in whom NSAIDs have failed,
- its prevalence,
- the medical need partially met by TNF inhibitors and IL17 inhibitors (secukinumab and ixekizumab).
- the partial response to the identified medical need due to demonstration of the superiority of upadacitinib compared to placebo in terms of ASAS 40 responder rate (primary endpoint considered to be relevant) and on disease activity, reduction of inflammation in the spine, achievement of partial remissions and spinal functional capacity (ranked secondary endpoints) in a phase 2/3 controlled, randomised double-blind study conducted in 187 adult patients with ankylosing spondylitis without any prior biologic therapy who have responded inadequately to NSAIDs.

- the lack of demonstrated additional impact on the care and/or life pathway, in the absence of comparative data versus TNF inhibitors and data in patients in whom biologic therapies have failed,
- the lack of demonstrated impact on the organisation of care (hospitalisation, etc.)

RINVOQ (upadacitinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RINVOQ (upadacitinib) is low 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 new indication and at the MA dosages.

- **Recommended reimbursement rate: 15%**

Clinical Added Value

Considering:

- **demonstration of the superiority of upadacitinib 15 mg compared to placebo in terms of ASAS 40 responder rate (primary endpoint considered to be relevant) and on disease activity, reduction of inflammation in the spine, achievement of partial remissions and spinal functional capacity (ranked secondary endpoints) in the SELECT-AXIS 1 double-blind study conducted in 187 adult patients with ankylosing spondylitis who have responded inadequately to NSAIDs,**
- **the absence of demonstration of its superiority compared to placebo in terms of quality of life,**
- **the lack of data:**
  - **compared to TNF inhibitors, whereas this comparison would have been possible,**
  - **in patients in whom biologic therapy has failed (i.e. in third and later-line treatment),**
- **and concerns in terms of long-term safety, particularly with respect to infectious risks and potential cardiovascular and carcinogenic risks,**

the Transparency Committee considers that RINVOQ (upadacitinib) provides no clinical added value (CAV V) in the care pathway for active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.