OPINION ON MEDICINAL PRODUCTS

upadacitinib
RINVOQ 15 mg,
sustained-release tablet
New indication

Adopted by the Transparency Committee on 9 November 2022

SUMMARY

The legally binding text is the original French opinion version

- **Non-radiographic axial spondylarthritis**
- **Sectors: Community and Hospital**

Key points

Approval of reimbursement for the treatment of active non-radiographic axial spondylarthritis with objective signs of inflammation among adults responding poorly to non-steroidal anti-inflammatory drugs (NSAIDs).

Therapeutic improvement?

No therapeutic improvement for the treatment of active non-radiographic axial spondylarthritis with objective signs of inflammation among adults responding poorly to non-steroidal anti-inflammatory drugs (NSAIDs).

Role in therapeutic strategy?

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

The first-line drug treatment of axSpA is based on the use of NSAIDs (prescription on demand, tailored to the patient and symptom progression, up to the maximum dose) as a symptomatic treatment. In the event of failure to respond or poor response to an NSAID used at the maximum tolerated dose, the NSAID may be replaced with multiple trials if needed. Adjunctive treatments such as analgesics may be associated with NSAIDs for residual pain, but systemic or local corticosteroid therapy is not justified for axial forms. Synthetic conventional basic treatments (csDMARD) (e.g. methotrexate, leflunomide, sulfasalazine) only appear to be effective for forms with symptomatic treatment-refractory peripheral joint involvement. There is no evidence of their efficacy in solely axial forms, and they are not indicated for these forms.

As a second-line approach, targeted treatments including (bDMARD) and ts(DMARD) biological treatments must be envisaged for patients whose disease is active despite the use of NSAIDs. However, in the absence of inflammation found in pathology samples and MRI investigation, these biomedicines are not indicated for nr-axSpA. There are 7 bDMARDs: 5 TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), 2 IL-17A inhibitors (ixekizumab, secukinumab). At the present time, upadacitinib is the only tsDMARD to have been granted a marketing authorisation as a second-line approach for active nr-axSpA.

According to the recommendations published by the French Society of Rheumatology, TNF inhibitors are preferred as a first-line approach given the greater follow-up with this class; however, it is not possible to establish a ranking in view of the lack of a direct comparison between these agents. In the event of loss of response, primary inefficacy or intolerance to a first TNF inhibitor, replacing with a second TNF inhibitor or switching to an IL-17A inhibitor or a JAK inhibitor are deemed to be beneficial alternatives.

Role of the medicinal product

RINVOQ (upadacitinib) in the treatment of active non-radiographic axial spondylarthritis with objective signs of inflammation among adults responding poorly to NSAIDs is ranked as a third-line and subsequent approach, after failure to respond to TNF inhibitors and/or IL17A inhibitors, considering:

- the lack of comparison to TNF inhibitors even though it was feasible, meaning that the medicinal product cannot be ranked with respect to TNF inhibitors after failure to respond to NSAIDs,
- the identified therapeutic need among patients considering effects in respect of therapeutic failure, poor response, contraindications and intolerance to TNF and IL17A inhibitors,
- the exploratory nature of the analyses conducted in the subgroup of patients previously treated with a bDMARD (small sample size, 95%CI including 0),
- uncertainties in terms of long-term safety of JAK inhibitors.

Thus, the Committee recommends that:

- as a second-line treatment (patients failing to respond to NSAIDs who are bDMARD treatment-naive), preference must be given to TNF inhibitors considering the greater follow-up in terms of safety and efficacy.

- as a third-line and subsequent approach (patients failing to respond to a bDMARD), in the event of failure to respond to a TNF inhibitor or if a change of therapeutic target is envisaged, preference must be given to IL17 inhibitors.

Moreover, as per the PRAC (EMA) recommendations following the reassessment of JAK inhibitors, it is recommended to prescribe them for their marketing authorisation indications only if no suitable therapeutic alternative is available for patients over 65 years of age, current and former smokers, and in the event of increased risk of major cardiovascular disorders and cancer. They must also be used with caution in the event of pre-existing risk factors of other forms of venous thromboembolism. Upadacitinib is contraindicated during pregnancy.

Committee's conclusions

Clinical Benefit

- Non-radiographic axial spondylarthritis is a chronic disease which, in its severe form with poor response or intolerance to NSAIDs, is painful, and affects spinal mobility and functional capacities.
- The proprietary medicinal product RINVOQ (upadacitinib) is a symptomatic medicinal product.
- The efficacy/adverse effect ratio of RINVOQ (upadacitinib) is modest, considering the effect size versus placebo and the concerning safety profile of the JAK inhibitor class.
- Therapeutic alternatives are available in the form of TNF inhibitors (adalimumab, certolizumab pegol, etanercept and golimumab) and IL17 inhibitors (secukinumab and ixekizumab).
- For the treatment of patients with active non-radiographic axial spondylarthritis with objective signs of inflammation responding poorly to NSAIDs, RINVOQ (upadacitinib) is a third-line and subsequent treatment. In addition, as per the PRAC (EMA) recommendations following the re-assessment of JAK inhibitors, it is recommended to prescribe them for their marketing authorisation indications only if no suitable therapeutic alternative is available for patients over 65 years of age, current and former smokers, and in the event of increased risk of major cardiovascular disorders and cancer. They must also be used with caution in the event of pre-existing risk factors of other forms of venous thromboembolism.

- **Public health benefit**

Considering:

- the impact of non-radiographic axial spondylarthritis on quality of life and functional capacities among patients, especially among patients failing to respond to NSAIDs, and its prevalence,
- the medical need partially met by TNF inhibitors and IL17A inhibitors;
- the partial response to the identified medical need, considering:
  - the evidence of the superiority of upadacitinib versus placebo in terms of disease activity, functional capacities and quality of life, but with a modest effect size,
  - the lack of evidence of an impact on the delivery of care, despite an orally administered form, compared to other biotherapies administered by injection,

RINVOQ (upadacitinib) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems the actual clinical benefit of RINVOQ (upadacitinib) to be moderate in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for the marketing authorisation indication and at the marketing authorisation dosages.

Recommended reimbursement rate: 30%

Clinical Added Value

Considering:

- the demonstrated clinical benefit versus placebo in the *SELECT-AXIS 2 Trial 2* study in terms of ASAS40 responder rate (primary outcome measure) and on the majority of ranked secondary outcome measures particularly in respect of quality of life at week 14,

but,

- the lack of comparison to TNF inhibitors even though it was feasible,

the Transparency Committee deems that RINVOQ (upadacitinib) provides no clinical added value (CAV V) in the therapeutic strategy, for patients with active non-radiographic spondylarthritis with objective signs of inflammation and responding poorly to non-steroidal anti-inflammatory drugs (NSAIDs).