HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

19 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 psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ (upadacitinib) may be used as monotherapy or in combination with methotrexate.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

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.

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 for arthritis and enthesitis.

As first-line 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. They have not demonstrated efficacy on isolated axial or enthesitic manifestations.

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

The biologic therapies currently available include TNF inhibitors (adalimumab, etanercept, infliximab and certolizumab pegol) and interleukin inhibitors (an IL12/23 inhibitor, ustekinumab, two IL17 inhibitors, secukinumab and ixekizumab, and, recently, an IL23 inhibitor, guselkumab). TNF inhibitors and interleukin inhibitors have identical MAs from the second line of treatment, but the Committee recommends that interleukin inhibitors be used preferentially in the event of failure of TNF inhibitors (i.e., as third and later-line treatment).

In addition, another JAK inhibitor (tsDMARD), tofacitinib (XELJANZ), also has an MA in the event of failure of at least one conventional DMARD (i.e., from the second line). Given the absence of clinical studies having directly compared tofacitinib with TNFα antagonists, the latter should be favoured as second-line disease-modifying therapy. In the absence of data versus interleukin inhibitors, the role of JAK inhibitors cannot be specified compared to these medicinal products.

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 RINVOQ (upadacitinib) in the care pathway:
Given the absence of demonstrated superiority of upadacitinib 15 mg compared to adalimumab (TNF inhibitor) and the greater experience in terms of efficacy and safety with this family of drugs, the Committee considers that in the event of failure of a conventional disease-modifying drug (i.e., in second-line therapy), TNF inhibitors should be favoured first. RINVOQ (upadacitinib) 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 upadacitinib 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

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

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

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

◗ Its efficacy/adverse effects ratio is high in the short term. However, concerns persist in terms of its long-term safety, particularly with respect to infectious risks and potential cardiovascular and thromboembolic risks.

◗ There are medicinal alternatives, in particular TNF inhibitors, which have demonstrated an efficacy on joint destruction in psoriatic arthritis, in some cases with 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 disease-modifying drug, TNF inhibitors should be favoured first considering experience with these medicinal products in terms of efficacy and safety. As is the case with tofacitinib, RINVOQ (upadacitinib) primarily has a role following the failure of at least one TNF inhibitor (see section 08 of this opinion).

Public health impact

Considering:

- the seriousness of the disease and its disabling nature in severe forms,
- the small population of patients responding inadequately to prior disease-modifying treatments,
- the medical need partially met by TNF inhibitors, interleukin inhibitors, a PDE4 inhibitor and another JAK inhibitor, but the persistence of a need to have access to alternatives due to inadequate response and intolerance to the available medicinal products and resistance phenomena,
- the partial response to the identified medical need due to demonstration of the superiority of upadacitinib compared to placebo for the proportion of ACR20 responders, on quality of life and disease activity in second and third or later-line treatment, as well as its structural efficacy compared to placebo and its non-inferiority compared to adalimumab in terms of proportion of ACR20 responders in second-line treatment,
- the possible impact on the organisation of care (reduction in need for nursing care, hospitalisations required to administer certain biologic therapies and use of medical transport),

RINVOQ 15 mg (upadacitinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RINVOQ 15 mg (upadacitinib) prolonged-release tablets 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:

- **demonstration of the superiority of upadacitinib 15 mg compared to placebo in terms of ACR20 responders at W12 (primary endpoint), quality of life, functional capacity and achievement of minimal disease activity (ranked secondary endpoints) in patients having responded inadequately to a conventional disease-modifying therapy and with no prior TNF inhibitor therapy, i.e., as second-line disease-modifying therapy (SELECT-PsA1 study) as well as in patients in whom at least one TNF inhibitor has failed, i.e., in third and later-line therapy (SELECT-PsA2 study),**
- **demonstration of an efficacy on joint destruction compared to placebo only as second-line treatment (SELECT-PsA1 study),**
- **demonstration of the non-inferiority of upadacitinib 15 mg compared to adalimumab 40 mg (TNF inhibitor), in terms of ACR20 response rate at W12, in patients with no prior biologic treatment, i.e., as second-line disease-modifying treatment (SELECT-PsA1 study) without demonstration of superiority,**
- **the absence of direct comparison with the available alternatives in third or later-line therapy despite this comparison being possible,**
- **concerns in terms of long-term safety, particularly with respect to infectious risks and potential cardiovascular risks,**

the Transparency Committee considers that RINVOQ (upadacitinib) provides no clinical added value (CAV V) in the care pathway for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).