HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

10 MARCH 2021

The legally binding text is the original French opinion version

filgotinib

JYSELECA 100 and 200 mg film-coated tablets

First assessment

Key points

Favourable opinion for reimbursement only for the treatment of moderate to severe active rheumatoid arthritis in women who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Unfavourable opinion for reimbursement in men with moderate to severe active rheumatoid arthritis.

What therapeutic improvement?

No clinical added value in the therapeutic strategy in women.

Role in the care pathway?

According to French and European guidelines, the treatment of rheumatoid arthritis (RA) is based on the early prescription (early administration is crucial to the success of treatment) of a disease-modifying anti-rheumatic drug (DMARD) in order to induce clinical and biologic remission. Pending the efficacy of DMARD treatment, corticosteroid therapy may be proposed, respecting a low cumulative dose, if possible for a maximum period of 6 months. Corticosteroid therapy should be reduced as quickly as possible.

Close monitoring and frequent treatment adjustments (every 1 to 3 months) are necessary until the objective is reached. This is what is termed "tight control" of the disease, with a dynamic treatment strategy and a clearly defined goal. In the absence of any improvement within 3 months following the start of treatment or if the therapeutic objective is not achieved in 6 months, the treatment must be adjusted.

In first-line treatment, methotrexate (MTX) is the reference conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) for rheumatoid arthritis. Initiation of treatment at a dose of 10 to 15 mg/week orally is recommended, with rapid escalation of doses (for example dose escalation of 5 mg every 1 to 4 weeks), up to an optimised dose of around 0.3 mg/kg/week (i.e. between 15 and 25 mg/week, depending on the clinical context and tolerance to treatment).

In the event of a contraindication or intolerance to MTX, leflunomide or sulfasalazine can be used, since they have demonstrated their symptomatic and structural efficacy.

The Transparency Committee considered that, although it has an MA in patients not previously treated with MTX, the prescription of a biologic therapy (in combination with MTX or as monotherapy), of whatever type, is not justified for first-line treatment. The only exceptional situation in which the first-line prescription of a biologic could be considered would be in the event of contraindication to all csDMARDs.

In second or later-line therapy, in patients who have responded inadequately or who are intolerant to methotrexate, treatment should be optimised as follows:

- In the absence of factors for a poor prognosis, a combination of synthetic disease-modifying anti-rheumatic drugs (MTX/sulfasalazine/hydroxychloroquine) or a rotation for another synthetic disease-modifying anti-rheumatic drug (leflunomide, sulfasalazine) may be proposed. It should be noted that the non-inferiority of MTX, sulfasalazine and hydroxychloroquine triple therapy has been demonstrated compared to the combination of biologic TNF inhibitor (etanercept) + MTX as short-term treatment (48 weeks),

- In the event of failure (or contraindication), targeted therapy should be considered. The target therapies that can be considered in this situation are:

o targeted biologic therapies (biologics or bDMARDs) represented by TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), interleukin 6 receptor antagonists (tocilizumab and sarilumab), T lymphocyte co-stimulation modulator (abatacept), or rituximab in certain circumstances only,

o as well as targeted synthetic therapies (tsDMARDs) represented by JAK inhibitors (baricitinib and tofacitinib), although the Committee recommends their use following the failure of a biologic therapy (third or later line),

- In the presence of factors for a poor prognosis (particularly structural involvement), the addition of a targeted therapy to MTX may be proposed.

It should be noted that the optimisation strategy depends on the presence or otherwise of the following factors for a poor prognosis or response: presence of early erosions, presence of rheumatoid factor and anti-citrullinated protein antibodies (particularly in the event of high levels ≥ 3N), persistence of

moderate to strong disease activity despite csDMARD treatment (with a high level of sedimentation rate and/or C-reactive protein or a high number of swollen joints), and failure of ≥ 2 csDMARDs.

The use of targeted therapy should be preferentially implemented in combination with MTX. However, if it is necessary to use targeted therapy as monotherapy, it seems logical to favour an IL6 inhibitor or a JAK inhibitor given their demonstrated superiority as monotherapy compared to MTX alone. In the event of failure of a first targeted therapy, rotation to another targeted therapy is justified if the disease activity so requires. Hence, patients in whom a first TNF inhibitor has failed may receive a second TNF inhibitor or a targeted therapy based on another action mechanism.

It is not currently possible to establish a preferential hierarchy within the targeted therapies in view of the absence of comparative efficacy and/or safety data and given the absence of predictive factors for treatment response to guide the clinician's choice. However, it should be noted that, according to the SFR guidelines, bDMARDs can be preferred as second-line therapy given the greater experience with their use and long-term safety data from registries.

In its previous assessments, the Committee recommended that the three chemical agents targeting janus kinases, baricitinib (OLUMIANT), tofacitinib (XELJANZ) and upadacitinib (RINVOQ), should preferably be used as third or later-line treatment (i.e., after the failure of at least one biologic therapy) given the greater experience with biologic therapies.

Role of the medicinal product in the care pathway

In accordance with its MA, JYSELECA (filgotinib), a targeted synthetic therapy inhibiting janus kinases, could be used following the failure of one or more DMARDs, either as second-line treatment (following the failure of a conventional DMARD such as MTX) or as third-line treatment (failure of a biologic) or later-line treatment (failure of several conventional DMARDs and/or biologics). JYSELECA (filgotinib) may be used as monotherapy or in combination with methotrexate (MTX).

However, the Transparency Committee:

- recommends that, in women, as is the case for OLUMIANT (baricitinib), XELJANZ (tofacitinib) and RINVOQ (upadacitinib), JYSELECA (filgotinib) should preferably be used as third or later-line therapy (i.e. following the failure of at least one biologic therapy) given concerns in terms of safety, particularly long-term, related to the new action mechanism of action and the greater experience in terms of efficacy and safety of biologics. In these patients, the Committee considers that combination with MTX should be favoured and that monotherapy should be reserved for situations of intolerance to MTX or when continued treatment with MTX is inappropriate.
- considers that, in men, JYSELECA (filgotinib) has no role in the care pathway for the treatment of active to moderate rheumatoid arthritis due to a potential and possibly irreversible risk on spermatogenesis, not identified with the other JAK inhibitors. This opinion is returned pending the results of ongoing clinical studies assessing the effect of filgotinib on spermatogenesis.

Special recommendations

The Committee highlights the importance of managing cardiovascular risk factors in patients with rheumatoid arthritis.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Rheumatoid arthritis is a serious, chronic debilitating condition that can lead to a marked deterioration in quality of life.

◗ The proprietary medicinal product JYSELECA (filgotinib) is a symptomatic disease-modifying treatment. Filgotinib has also demonstrated its efficacy in terms of preventing joint damage.

◗ Its efficacy/adverse effects ratio is moderate in women due to concerns in terms of its long-term safety, particularly with respect to the identified infectious risk and potential cardiovascular, thromboembolic and carcinogenic risks.
In men, its efficacy/adverse effects ratio has not been adequately established given the potential risk on spermatogenesis and fertility, pending the results of additional studies currently underway to assess this risk.

◗ There are numerous medicinal alternatives (see section 05 of this opinion).

◗ In women with moderate to severe active rheumatoid arthritis this is a second or later-line treatment (following the failure of one or more DMARDs). In these patients, the Committee nonetheless recommends that JYSELECA (filgotinib) preferably be used as third or later-line therapy (i.e. following the failure of at least one biologic therapy).
In men, JYSELECA (filgotinib) has no role in the care pathway pending the results of ongoing clinical studies assessing the effect of filgotinib on spermatogenesis.

Public health impact

Considering:

- the seriousness and prevalence of rheumatoid arthritis,
- the medical need to have access to alternatives given treatment resistance phenomena and/or the safety of the medicinal products currently available,
- the response to the identified medical need in women due to the expected impact on morbidity and quality of life of patients with moderate to severe active RA,
- the lack of response to the identified medical need in men due to safety concerns associated with a potential effect of filgotinib on spermatogenesis and male fertility,
- the expected impact on the organisation of care compared to biologics administered by injection (reduction in need for nursing care, hospitalisations required to administer certain biologic therapies and use of medical transport),

JYSELECA (filgotinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of JYSELECA (filgotinib) is:

- **substantial only for the treatment of moderate to severe active rheumatoid arthritis in women who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs),**
- **insufficient to justify public funding cover in men pending the results of ongoing clinical studies assessing the effect of filgotinib on spermatogenesis.**

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 only in the indication "Treatment of moderate to severe active rheumatoid arthritis in women who have responded inadequately to, or who are intolerant to one or more disease-modifying

anti-rheumatic drugs (DMARDs). JYSELECA (filgotinib) may be used as monotherapy or in combination with methotrexate (MTX)" and at the MA dosages.

The Committee issues an unfavourable 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 "Treatment of moderate to severe active rheumatoid arthritis in men who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). JYSELECA (filgotinib) may be used as monotherapy or in combination with methotrexate (MTX)" and at the MA dosages.

- **Recommended reimbursement rate: 65% (only in women)**

Clinical Added Value

In women:

Considering:

- **the non-inferiority of JYSELECA (filgotinib) in combination with methotrexate (MTX) compared to adalimumab (HUMIRA) in combination with MTX as second-line therapy, i.e. following the failure of MTX, in terms of obtaining low disease activity (DAS28 score ≤ 3.2),**
- **the absence of comparison with available third-line alternatives (in particular, other TNF inhibitors, IL6 inhibitors, abatacept and rituximab),**
- **and uncertainties in terms of long-term safety, particularly with respect to the identified infectious risk and potential cardiovascular, thromboembolic and carcinogenic risks,**

the Transparency Committee considers that JYSELECA (filgotinib) provides no clinical added value (CAV V) in the care pathway for moderate to severe active rheumatoid arthritis in women who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

The care pathway for the second and later-line treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) includes the clinically relevant comparators indicated in part 5 of the present opinion.

In men:

Not applicable