



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

10 February 2022  
EMA/PRAC/68283/2022

## PRAC List of questions

To be addressed by the marketing authorisation holder(s) for Xeljanz, Cibinqo, Olumiant, Rinvoq and Jyseleca

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Janus Kinase inhibitors (JAKi)

Xeljanz (tofacitinib) EMEA/H-A20/1517/C/004214/0048

Cibinqo (abrocitinib) EMEA/H-A20/1517/C/005452/0003

Olumiant (baricitinib) EMEA/H-A20/1517/C/004085/0032

Rinvoq (upadacitinib) EMEA/H-A20/1517/C/004760/0017

Jyseleca (filgotinib) EMEA/H-A20/1517/C/005113/0014

Marketing authorisation holder(s): Pfizer Europe MA EEIG, Eli Lilly Nederland B.V., AbbVie Deutschland GmbH & Co. KG, Galapagos N.V.

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# 1. Background

Janus Kinase inhibitors are a group of oral immunomodulatory disease-modifying anti-rheumatic drugs (DMARDs). The following JAK inhibitors are centrally authorised products indicated for the treatment of inflammatory disorders in the European Union:

- Xeljanz (tofacitinib) is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and juvenile idiopathic arthritis.
- Olumiant (baricitinib) is indicated for the treatment of rheumatoid arthritis and atopic dermatitis.
- Rinvoq (upadacitinib) is indicated for the treatment rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis.
- Jyseleca (filgotinib) is indicated for the treatment of rheumatoid arthritis and ulcerative colitis.
- Cibinqo (abrocitinib) is indicated for the treatment of atopic dermatitis.

The ORAL surveillance study (Ytterberg et al, 2022<sup>1</sup>) was a Phase 3b/4 randomised, parallel arm, open-label study that evaluated the safety of tofacitinib at two doses (5 mg and 10 mg BID) versus TNF-alpha inhibitors. This study was a post marketing commitment to assess the risk of cardiovascular events in subjects 50 years of age and older with at least one cardiovascular risk factor with moderately or severely active rheumatoid arthritis (RA). Final results of the completed ORAL surveillance study showed a higher incidence of major adverse cardiovascular events (MACE) (nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes), malignancies, venous thromboembolisms (VTEs), all-cause mortality, and serious infections, in patients treated with tofacitinib as compared to TNF-alpha inhibitors.

No randomised controlled studies have been conducted with the other JAK inhibitors to evaluate these safety concerns. For baricitinib, preliminary data from an observational study (I4V-MC-B023 (B023)) is available, including data from several healthcare databases of patients with RA. The preliminary results indicate an increased rate of MACE and VTE for baricitinib compared to TNF-alpha inhibitors in patients with RA.

In view of the seriousness of the emerging data, as well as the comparable mode of action of these five JAK inhibitors, a safety review on MACE, VTE, serious infections, malignancies, and mortality should be performed for the JAK inhibitors authorised in inflammatory diseases. The impact of these serious events on the benefit/risk balance in all authorised indications should correspondingly be assessed.

The marketing authorisation holders (MAHs) are requested to address the following questions for their respective product(s):

## 2. Questions

### Q1 Exposure (all MAHs)

All MAHs are requested to provide an overview of the marketing status and exposure in European Union (EU) Member States, Liechtenstein, Iceland, and Norway, and worldwide of their respective product(s) for each of the approved indications. This should include data from ongoing and completed clinical trials and all post-marketing sources. In addition, the exposure data from post-marketing

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<sup>1</sup> Ytterberg SR, Bhatt DL, Mikuls TR, Koch GC, Fleischmann R, Rivas JL, Germino R, Menon S, Sun Y, Wang C, Shapiro AB, Kanik KS, Connel CA (2022). Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. The New England Journal of Medicine 386 (4): 316-326

sources in EU, Liechtenstein, Iceland and Norway should be stratified per indication, country and dosing regimen used.

#### Q2 Request for safety data (all MAHs)

All MAHs are requested to submit and discuss data for their respective product(s) regarding MACE, myocardial infarction (MI), malignancy, VTE (such as DVT/PE), serious infections, and all-cause mortality per indication from completed and ongoing clinical trials (including pooled clinical trial databases), (long-term) extension studies, and observational studies stratified by dose.

This analysis should include a comparison between the event rates (including exposure adjusted event rates) observed during JAK inhibitor exposure and active comparators, where applicable. Data should be presented in a tabular overview, accompanied by incidence rates (IR), hazard ratio (HR)s or other appropriate measures of frequency.

The MAHs should take into account any prior discussion on presentation of safety data from other ongoing procedures.

#### Q3 Extrapolation of clinical safety data and class effects (all MAHs)

a) Although differences in the specificity of the approved JAK inhibitors have been demonstrated in cell-free and in vitro cellular assays, the in vivo and therapeutic studies have not necessarily replicated this specificity. More recent studies have found that at therapeutic drug exposures, drug concentrations attain levels in which the in vitro specificity of inhibitors would not be expected. This may contribute to similarity in efficacy and safety profiles among JAK inhibitors. The MAHs should perform a thorough literature search addressing potential class effects, provide relevant in-house data, and provide an overall discussion on these aspects.

b) The MAHs should also discuss whether the safety outcomes of the ORAL surveillance study including MACE [particularly MI], VTE, serious infections, malignancies, and mortality as observed in patients with RA can be considered class effects of JAK inhibitors, across all indications in inflammatory diseases.

#### Q4 Further risk minimisation measures (RMMs) (all MAHs)

The MAHs should discuss possible risk factors for each safety concern namely MACE, malignancy, VTE (DVT/PE), serious infections, and all-cause mortality, taking into account the different patient populations for which the respective JAK inhibitor is approved, available safety data, and the appropriateness to extrapolate results from the ORAL surveillance study. Based on that, the MAHs should discuss the need for changes to the product information (in addition to potential amendments of the indication – see Q5) which may improve the benefit-risk balance of the respective JAK inhibitor. This may include safety information on the risks observed, the patient populations at particular risk and actions to prevent the risks. The relevant recommendations already included in the product information for Xeljanz should be taken into account.

##### Q4.1 MAH Xeljanz

The product information for Xeljanz (sections 4.4, 4.8, 5.1 of the SmPC) should be updated to reflect the final results of the ORAL surveillance study on MACE, VTE, serious infections, malignancies and mortality, taking into account discussions already held in the context of other ongoing procedures.

#### Q5 Benefit Risk balance in approved indications (all MAHs)

Considering the totality of data and the increased risk for serious safety outcomes namely MACE, VTE, malignancy, serious infections and all-cause mortality with tofacitinib as compared with TNF-alpha inhibitors from the ORAL surveillance study, as well as all other available data for the individual active

substances on these risks from all sources, the MAHs should discuss how these data impact the benefit/risk balance of their respective JAK inhibitor for each of the approved indications. The discussions above on extrapolation of the ORAL surveillance study to other indications for tofacitinib, or the other JAK inhibitors (Q3), as well as further risk minimization measures (Q4), should be taken into account, as applicable.

For their respective JAK inhibitors, the MAHs should provide an in-depth discussion for each indication separately, including:

- a) For all indications, except atopic dermatitis, the MAHs should provide available efficacy data for their respective JAK inhibitor in patients previously treated with TNF alpha inhibitors, or for the atopic dermatitis indication, in patients previously treated with systemic therapy. Furthermore, the MAHs should discuss for each indication, whether there are patients for whom it would not be appropriate to initiate TNF alpha inhibitor (all except atopic dermatitis) or systemic (atopic dermatitis) therapy but who would still benefit from treatment with their respective JAK inhibitor.
- b) Based on the above, discuss if/how the wording of the respective indications should be restricted. A separate assessment should be done for the atopic dermatitis indication in adolescents 12 years and older, if applicable.

These discussions should take into account any prior discussions on the need to update the RA indication and other indications held in the context of ongoing procedures.

#### Q6 Risk Management Plan (RMP) (all MAHs)

The MAHs should discuss necessary updates of their risk management plans (RMPs), including proposals on how the effectiveness of new implemented risk minimisation measures should be monitored.

The MAHs should take into account any prior discussion on updates of the RMP related to the safety concerns assessed as part this referral from other ongoing procedures.

#### Q7 Other points (All MAHs)

The MAHs are asked to inform PRAC whether a randomized clinical trial with their respective JAK inhibitor is being conducted or planned with a protocol similar to the ORAL Surveillance trial, i.e. comparing the JAK inhibitor with TNF alpha inhibitors in terms of cardiovascular and oncological risks. If so, the MAHs should comment on to what extent such clinical trial is comparable to the ORAL surveillance study and provide relevant data on the safety outcomes if available.

For baricitinib, the following is noted [A Study of Baricitinib in Participants with Rheumatoid Arthritis - Full Text View - ClinicalTrials.gov](#), and should specifically be addressed.