NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission:

Products Names	Olumiant Xeljanz Rinvoq Jyseleca Cibinqo
Active substances	Baricitinib tofacitinib upadicitinib filgotinib abrocitinib
Pharmaceutical form(s)	All
Strengths	All
Routes of Administration	All
Marketing Authorisation Holders	Eli Lilly Nederland B.V. Pfizer Europe MA EEIG AbbVie Deutschland GmbH & Co. KG Galapagos NV

Janus Kinase inhibitors (JAKi) are a group of oral immunomodulatory disease-modifying anti-rheumatic drugs (DMARDs). These medicinal products inhibit different JAK isoforms. Inhibition of JAK attenuates signalling of interleukins and interferons, resulting in modulation of the immune and inflammatory response. Dysregulation of the JAK pathway is involved in the process of inflammation for several inflammatory disorders (including rheumatoid, psoriatic or juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis) and myeloproliferative disorders.

The following JAKi are centrally authorised products indicated for the treatment of inflammatory disorders in the European Union:

- Olumiant (baricitinib) is indicated for the treatment of rheumatoid arthritis and atopic dermatitis.

- Xeljanz (tofacitinib) is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and juvenile idiopathic arthritis.

- Rinvoq (upadicitinib) 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.

Two other JAKi are authorised in the treatment of myeloproliferative disorders (Jakavi (ruxolitinib) and Inrebic (fedratinib)).

ORAL Surveillance study (Study A3921133) is a Phase 3b/4 randomised, parallel arm, open-label study that evaluates the safety of tofacitinib at two doses (5 mg and 10 mg BID) versus TNF-alpha inhibitors (TNFi). This study is 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).

Interim results from the ORAL Surveillance study were assessed in 2019 in an Article 20 referral procedure (EMEA/H/A-20/1485). The Pharmacovigilance Risk Assessment Committee (PRAC) concluded that tofacitinib is associated with an increased risk of venous thromboembolic events (VTE), especially in patients with risk factors for venous thromboembolism. PRAC also concluded that there is a potential risk regarding increased mortality. This was partly driven by a higher mortality rate due to serious infections for tofacitinib and was particularly apparent for patients aged 65 years and above. The product information of tofacitinib was updated accordingly.

Preliminary analysis of the final results from the ORAL Surveillance study showed an increased incidence of major adverse cardiovascular events (MACE) (including myocardial infarction, stroke, and cardiovascular death) and higher risk of malignancy with tofacitinib compared to TNFi in patients with RA. These preliminary results were assessed as part of a signal procedure (EPITT 19382) following Emerging Safety Issue (ESI) notification to the European Medicines Agency (Agency) in January 2021. The signal procedure was concluded in June 2021 and the product information of tofacitnib was varied to include the available information on the increased risk of MACE and malignancies. The safety concerns of MACE and malignancies are monitored for the other JAKi in inflammatory disorders as part of the respective periodic safety update reports.

Final results of the completed ORAL surveillance study are now available. In addition to the higher incidence on MACE and malignancies reported in the preliminary analysis, full study results also indicate a higher incidence on VTEs, all-cause mortality and serious infections, in patients treated with tofacitinib as compared to TNFi.

No randomised controlled studies have been conducted with the other JAKi to evaluate these safety concerns. However, preliminary results on baricitinib are available for Study I4V-MC-B023 (B023), which is an observational study including data from several healthcare databases of RA patients, and they show an increased rate of MACE and VTE with baricitinib compared to TNFi in RA patients.

Considering:

- the safety findings on higher incidence of serious cardiovascular related events, VTEs, serious infections, malignancies and all-cause mortality of the large prospective safety study for tofacitinib;
- the available data from the observational study B023 with baricitinib suggesting increased risk for VTE and MACE;
- the comparable mechanism of action of these products,

it seems possible that the safety concerns observed in rheumatoid arthritis patients with tofacitinib may be a class effect of relevance to other JAKi used in similar patient populations. Concerns are also raised that this emerging safety information can influence the benefit risk balance of JAKi used in patient populations with inflammatory disorders.

In view of the seriousness of the emerging data, a safety review on MACE (particularly myocardial infarction), VTE, serious infections, malignancies and mortality should be performed for all JAKi authorised in inflammatory diseases. The impact of these serious events on the benefit risk balance of all JAKi authorised in inflammatory diseases in the authorised indications should be assessed.

Following the advice from EMA, it is noted that with respect to the JAKi used in the treatment of myeloproliferative disorders, namely Jakavi (ruxolitinib) and Inrebic (fedratinib), the patient populations with myeloproliferative disorders are different in terms of background risks, co-morbidities, life expectancy etc. from the patient populations with inflammatory disorders for which the other JAKi are indicated. Therefore, notwithstanding the possibility that the findings for tofacitinib are indeed a class effect, the impact of these findings for ruxolitinib and fedratinib would require different considerations. Consequently, at this stage, JAKi used in the treatment of myeloproliferative disorders are not included in the scope of the referral.
However, if an assessment of the emerging evidence points to a different conclusion with respect to these products, the Agency should inform the Commission promptly to consider the need for additional regulatory actions within or complementary to this assessment.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal products Olumiant, Xeljanz, Rinvoq, Jyseleca and Cibinqo.

The EC requests the Agency to give its opinion by 30 September 2022 on whether the marketing authorisation for these products should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the PRAC.

In addition, the EC requests the Agency to give its opinion as soon as possible, as to whether provisional measures are necessary to ensure the safe and effective use of these medicinal products.

E-Signed Date 28/01/2022

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