NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) No 726/2004

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This notification is a referral under Article 20 of Regulation (EC) No 726/2004 to the Pharmacovigilance Risk Assessment Committee made by the European Commission (EC):

Product Name	Xeljanz
Active substance	tofacitinib
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Pfizer Europe MA EEIG

Tofacitinib has been developed as an oral, immunomodulatory disease-modifying anti-rheumatic drug (DMARD). It is a synthetic molecule that selectively inhibits the Janus kinase (JAK) family, preferentially JAK3/JAK1. Inhibition of JAK1 and JAK3 attenuates signalling of interleukins and interferons type I/II, resulting in modulation of the immune and inflammatory response.

In the European Union, the medicinal product Xeljanz containing the active substance tofacitinib is indicated for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA), with a recommended dose of 5 mg twice daily.

Xeljanz is also approved as a treatment for ulcerative colitis (UC) with a recommended dose of 10 mg twice daily for the first 8 weeks and thereafter 5 mg twice daily. For patients who do not achieve adequate therapeutic benefit by the 8th week of treatment, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total on 10 mg twice daily induction dose), followed by 5 mg twice daily for maintenance. Some patients may continue the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit.

The 10 mg twice daily dose of tofacitinib is not approved for rheumatoid arthritis or psoriatic arthritis in the European Union.

Study A3921133 is an on-going open labelled study that evaluates the safety of tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID compared to a tumour necrosis factor inhibitor (TNFi) in patients with RA. The study is a post-authorisation commitment intended to assess the risk of cardiovascular events with tofacitinib in patients 50 years of age or older who have at least one additional cardiovascular risk factor, e.g. current smoker, high blood pressure, high cholesterol levels, diabetes mellitus, history of heart attack, family history of coronary heart disease, extra-articular RA disease. All patients entered the study on stable doses of background methotrexate.

On 12 February 2019 the marketing authorisation holder (MAH) informed the Agency that an increased risk of pulmonary embolism (PE) and overall mortality has been reported in Study A3921133. In this clinical trial, the overall incidence of PE was 5.96-fold higher in tofacitinib 10 mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib programme.

Further to the information received from the MAH, the Agency started to assess the increased risk of PE and overall mortality in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily and its potential impact on the marketing authorisation for Xeljanz. A direct healthcare professional communication was circulated the end of March 2019 to inform prescribers about the data emerging from study A3921133 related to these risks.

In view of the seriousness of the emerging data and as an underlying thrombogenic effect of tofacitinib cannot be excluded, the above mentioned findings should be further investigated. Their impact, as well as the impact of the risk of thrombotic events, in particular PE and deep venous thrombosis, on the benefit-risk balance of the medicinal product in the authorised indications and doses should be assessed.

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 tofacitinib containing medicinal product Xeljanz.

The EC requests the Agency to give its opinion as soon as possible on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked. The Agency is invited to consider whether their opinion can be given by 30 November 2019.

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 Pharmacovigilance Risk Assessment Committee.

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 this medicinal product.

Signed [redacted] Date 15.05.2019
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
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