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EMA/309456/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

# Assessment report on provisional measures

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

Invented name: Xeljanz

INN/active substance: tofacitinib

Procedure number: EMEA/H/A-20/1485/C/4214/0017

Note:

Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

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# 1. Information on the procedure

Study A3921 133 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 tumour necrosis factor inhibitor (TNFi) 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 considering possible underlying thrombogenic effect of tofacitinib, 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.

On 15 May 2019, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Xeljanz should be maintained, varied, suspended or revoked.

In addition, the EC requested the Agency to give its opinion, as soon as possible, as to whether provisional measures were necessary to ensure the safe and effective use of this medicinal product.

The current recommendation relates only to provisional measures recommended by the PRAC for Xeljanz based on the preliminary data available at this time. These provisional measures are without prejudice to the outcome of the ongoing review under Article 20 of Regulation (EC) No 726/2004.

# 2. Scientific discussion

## 2.1. Introduction

Xeljanz contains tofacitinib which is a selective inhibitor of the Janus kinase (JAK) family of kinases. Tofacitinib is a JAK (janus kinase) 1, 2 and 3 inhibitor. It is an oral DMARD (disease modifying antirheumatic drug). Inhibition of JAK1 and JAK3 attenuates signalling of interleukins (IL2, 4, 7, 9, 15, 21) and interferons type I/II, resulting in modulation of the immune and inflammatory response.

In the EU, Xeljanz was granted a marketing authorisation on 21 March 2017, for the treatment of rheumatoid arthritis (RA). In June 2018, it was approved for treatment of psoriatic arthritis (PsA), and in July 2018, it was also approved for the treatment of ulcerative colitis (UC).

In the EU, tofacitinib is registered as a 5 and 10 mg film coated tablet. The recommended dose for RA and PsA is 5 mg twice daily, and for UC, the recommended dose is 10 mg twice a day for the first 8 weeks and thereafter 5 mg twice a day. For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. For some patients, such as those who have failed prior tumour necrosis factor antagonist therapy, consideration should be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit.

Patients who experience a decrease in response on tofacitinib 5 mg twice daily maintenance therapy may benefit from an increase to tofacitinib 10 mg administered twice daily.

## 2.2. Data on safety

From the preliminary results of study A3921133 in RA patients with cardiovascular (CV) risk factors, it is apparent that with the use of tofacitinib 10 mg BID the risk of PE is 6-fold, as compared to TNF inhibitor (TNFi) arm. This is supported by Kaplan-Meier curves, showing that there is a consistently raised risk of PE with the use of tofacitinib 10 mg BID, compared to TNFi over time. There also was a similar, dose-response, trend in risk of deep venous thrombosis (DVT) with the highest risk for tofacitinib 10 mg BID, and a higher risk for arterial thrombotic events and death (CV and all cause) for 10 mg BID as compared to TNFi. The risks for arterial thrombotic events and for death were not increased in the 5 mg BID group as compared to TNFi.

These findings are consistent with other clinical studies where there appears to be an increased risk for thrombotic events (notably PE) that is larger for tofacitinib 10 mg BID than for tofacitinib 5 mg BID. This increased risk has been observed in RA patients with an increased risk for CV events (RA P123LTE subgroup analysis) and is also suggested by PE events that occurred in patients with UC using 10 mg BID as maintenance (after 8 weeks).

It is considered reasonable that a (dose-dependent) relationship between tofacitinib and thrombotic events, including PE, becomes more prominent in patients who already have an increased risk for CV disease, beyond their auto-immune disease that forms the indication for tofacitinib. In absence of a clear mechanistic explanation for the thrombotic events, an underlying thrombogenic effect of tofacitinib cannot be excluded.

It is considered that there is also an increased risk for DVT, not only PE. This is based on the results of Study A3921133 in RA patients with CV risk factors, where dose-dependent increases in PE and DVT were seen. This is also based on the consideration that PE usually is a sequel of DVT in the pelvis or

legs, while similar to the study the occurrence of PE manifestations generally may be about thrice the occurrence of DVT (Heit 2015[1]).

Further, the data from other clinical studies suggest that the incidence rate (IR)[2] of PE among the 10 mg BID was the highest among patients with UC (0.25 [0.07 - 0.64]), followed by patients treated for RA (0.13 [0.08 - 0.21]), patients with psoriasis (PsO) (0.09 [0.04-0.19]) and patients with PsA (0 [0.0 - 0.58]).

The higher IR of PE among UC patients on 10 mg BID cannot be explained entirely by the higher background risk for PE in this patient population, as the IR among patients treated with 5 mg BID is lower. Also, among the patients with RA, a lower IR for PE was observed among those treated with 5 mg compared to the 10 mg BID, although the difference between these is very small. Dose response relationship for PE is also suggested for CV enriched pooled trial database analysis. Even within the patients with higher CV risk, the IR of PE is higher for patients on 10mg BID when compared to those on 5 mg BID. These findings suggest a possible dose response relationship which requires further in depth assessment.

Further information is necessary to evaluate the risk in different indications and dosing regimens. However, the high risk of PE seen in the RA study associated to 10 mg tofacitinib twice daily cannot be excluded for UC patients also treated with 10 mg twice daily, who are at high risk of developing PE.

# 3. Benefit-risk balance

Based on the information currently available, tofacitinib is associated with a dose dependent risk of pulmonary embolism. Based on the interim results of study A3921133, this risk is significant for patients receiving 10 mg twice daily

Pulmonary embolism (PE) is a serious, life-threatening occurrence and a positive benefit-risk balance of Xeljanz is dependent on the ability to effectively prevent this risk.

There are currently no measures in place to adequately minimise the risk of PE for patients receiving tofacitinib 10 mg twice daily who are at higher risk for developing PE.

Therefore, in view of the risk and of the seriousness of the event, PRAC recommended provisional measures to restrict the use of tofacitinib in patients eligible to tofacitinib 10mg twice daily, while a full review of the data is ongoing. Patients can receive tofacitinib 10 mg twice daily only if they do not risk factors for PE.

The above provisional measures should be reflected in the product information of tofacitinib and communicated to HCPs via a dedicated letter. The adequacy of these provisional measures will be reviewed as part of the ongoing Article 20.

[1] John A. Heit Epidemiology of venous thromboembolism Nat Rev Cardiol. 2015 Aug; 12(8): 464–474. doi: 10.1038/nrcardio.2015.83

[2] The IR estimates were calculated by inclusion of events occurring up to 28 days beyond the last dose (or to the data cut-off date for ongoing studies). Exposure was defined as the total follow up time calculated up to the day of the first event within the event counting period for patients with the event or the last dose day plus a risk period of 28 days beyond the last dose (or to the data cut-off date for ongoing studies) for patients without events.

# 4. Risk management

## *4.1. Risk minimisation activities*

### 4.1.1. Amendments to the product information

The PRAC considered that amendments to sections 4.3 and 4.4 of the SmPC were necessary, as provisional measures, to minimise risk for patients while the review is ongoing.

The PRAC considered that Xeljanz 10 mg twice daily should be contraindicated in patients who have one or more of the following conditions:

- Use of combined hormonal contraceptives or hormone replacement therapy
- Heart failure
- Previous venous thromboembolism, either deep venous thromboembolism or pulmonary embolism
- Inherited coagulation disorder
- Malignancy
- Patients undergoing major surgery

A warning relating to the risk of pulmonary embolism associated with the use of Xeljanz was also included.

The Package Leaflet was amended accordingly.

### 4.1.2. Direct Healthcare Professional Communication/Communication plan

A DHPC was adopted by PRAC to communicate the warnings and restrictions described above to healthcare professionals. In addition to provide information to the HCPs on the new contraindications and warnings abovementioned, instructions on the management of patients currently under treatment are provided. The PRAC also agreed on a communication plan.

# 5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Xeljanz, in particular the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004, taking into account the grounds set out in Article 116 of Directive 2001/83/EC.
- The PRAC reviewed the available data from Study A3921133 on the increased risk of pulmonary embolism and overall mortality in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (BID).
- The PRAC concluded that a statistically and clinically important difference in the occurrence of pulmonary embolism with the tofacitinib 10 mg BID treatment arm compared to the active TNF inhibitor control was observed. The overall incidence of pulmonary embolism was 6-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. An increase in all-cause mortality in the 10 mg BID arm was also noted.

- Therefore, considering this serious risk PRAC is of the view that until a thorough review is finalised, it is appropriate to limit the number of patients with known risk factors for pulmonary embolism exposed to tofacitinib 10 mg BID. Therefore, the PRAC recommended as provisional measures to amend the product information to contraindicate the use of tofacitinib 10 mg BID in patients who have known risk factors for pulmonary embolism. The PRAC also introduced warnings regarding the risk of pulmonary embolism in the product information.

In view of the above, the Committee considers that the benefit-risk balance of Xeljanz (tofacitinib) remains favourable subject to the agreed provisional amendments to the product information. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Xeljanz (tofacitinib).