20 May 2019
EMA/PRAC/269837/2019

PRAC List of questions

To be addressed by the marketing authorisation holder for Xeljanz

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

Xeljanz - EMEA/H/A-20/1485/C/4214/0017

Marketing authorisation holder(s): Pfizer Europe MA EEIG

INN/active substance: tofacitinib

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1. Background

An increased risk of pulmonary embolism (PE) and overall mortality was observed in study A3921133. In view of the seriousness of the emerging data and as an underlying thrombogenic effect of tofacitinib cannot be excluded, the 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 will be assessed.

2. Questions

The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1

Provide an overview of the marketing status and exposure to tofacitinib in European Union (EU) Member States, Iceland and Norway and worldwide 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 sources for tofacitinib in EU, Iceland and Norway should be stratified per dosing regimen used.

Question 2

Provide a cumulative review of the available evidence regarding pulmonary embolism (PE), deep vein thrombosis (DVT), arterial thromboembolic events (ATE), major adverse cardiovascular events (MACE) and mortality with tofacitinib observed so far from all clinical trials as well as during the post-marketing period for tofacitinib for all indications (rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC)) and dosing used . An integrated causality assessment should be proposed separately for the different risk (PE, DVT, ATE, MACE), and mortality.

a. The MAH should provide a clear overview of all available clinical trials used for this analysis. The MAH should provide comparative analyses of PE, DVT, ATE, MACE events, and mortality in tofacitinib treated patients compared with the comparator arm or placebo based in pooled clinical trial data per indication. Please provide absolute number of cases, incidence rates (IRs), hazard ratios (HRs) and Kaplan-Meier curves, and time to event information. All analyses should be provided for each of the indications stratified for the 5 mg twice daily (BID) and 10 mg BID. This analysis should be also conducted in a cardiovascular (CV) enriched population from pooled clinical trial data (enriched with risk factors similar to those in study A3921133) for each of the indications.

b. The MAH should provide analyses to identify possible risk factors for DVT and PE in patients using tofacitinib based on the clinical trial data for each of the indications. These analyses should include univariate and multivariate analyses of potential risk factors and covariates in A3921133. This should include but not limited to analyses of the used dosage, relevant comorbidities, age, sex, other known risk factors for DVT/PE as well as the relevant laboratory test results (eg lipid levels, coagulation test results where available) over time in the different treatment groups, as well as co-medications that could play a role in developing thrombotic events, including but not limited to oral contraceptives and hormone replacement therapy. In addition, co-medications that may prevent development of DVT/PE (anticoagulants/antiplatelets) should also be included in the analyses.

c. The MAH should provide further analysis and discussion on the substantial differences in PE and mortality findings from A3921133 and non-3921133 studies.

d. The potential impact of tumour necrosis factor (TNF) inhibitors on the risk of pulmonary embolism/venous thromboembolism in the comparative groups should also be assessed in study A3921133.

e. The MAH should provide comparative analyses of PE, DVT, ATE, MACE events, and mortality in tofacitinib treated patients compared with the comparator arm or placebo based on pooled data for each of the indications in *a subpopulation of patients who have risk factors for PE* as identified in question 2b above.

f. The MAH should provide detailed information on all cases (narratives and tabulated format) of PE and DVT cases, including cases from clinical studies, and spontaneous reports. This should include a description of the cases, time to onset (and time since last dose), number of doses received, management and outcome, laboratory findings, and include information regarding PE risk factors (e.g. prior history of DVT/PE, oral contraceptive use, obesity, etc) as well as CV risk factors, where available. These analysis should also provide an overview in tabulated format where the number of cases is presented per data sources, per indication and per used dosage, as well as an overview of cases stratified by country and sex should also be provided.

g. The MAH should provide a literature review of PE and DVT risk in tofacitinib indications (RA, PsA, UC), including a discussion on background rate of PE expected in each of the tofacitinib approved indications. The MAH should discuss the rates of PE and DVT seen in clinical trials for each of the indications in view of the background risk expected.

Question 3

The MAH should provide a discussion regarding the observed dose-response effect for DVT, PE and all-cause mortality in clinical studies.

Question 4

The MAH is requested to discuss the potential mechanism for developing PE in humans. Non-clinical data indicates a potential dysregulation of thrombopoetin turnover. The MAH should elaborate on this mechanism observed in non-clinical data and how it can be translated to humans. Any other relevant mechanisms should also be discussed. Considering the potentially increased incidence of PE in patients treated with tofacitinib, patient-related factors need to be considered to explain the potential association between tofacitinib treatment and PE. The MAH should discuss whether thrombopoetin or other biomarkers could be used to identify patients at risk.

Question 5

The MAH should provide data regarding the use of anticoagulants and antiplatelets (including acetylsalicylic acid) in clinical studies, and provide a discussion regarding the possible role of these agents in the prevention of DVT including PE in patients with CV risk factors.

Question 6

Based on the review of all available data, please identify the populations at high risk for developing DVT/PE and discuss appropriate risk minimisation measures addressing the risk of DVT/PE for all approved indications and dosing regimens, including changes to the product information. Proposals for monitoring of effectiveness of proposed risk minimisation measures should be also provided. Communication activities (e.g. direct healthcare professional communication), as appropriate, should also be discussed.

Question 7

The MAH should provide a detailed benefit/risk balance evaluation for tofacitinib for each of the currently approved indications (RA, PsA, and UC) in view of the PE risk of tofacitinib.

In addition, for UC indication, a separate benefit-risk evaluation should be provided for 10mg twice daily for maintenance therapy in patients who have failed prior TNF antagonist therapy and in patients who have experienced a decrease in response on tofacitinib 5 mg twice daily. This request does not preclude benefit-risk evaluation of tofacitinib 10 mg twice daily for initiation of therapy and 5 mg twice daily for maintenance.