Annex IV

Scientific conclusions

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Study A3921133 is an on-going open labelled clinical study that evaluates the safety of tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID compared to a tumour necrosis factor inhibitor (etanercept or adalimumab) in patients with rheumatoid arthritis (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 European Medicines Agency (EMA) that an increased risk of pulmonary embolism (PE) and overall mortality had 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 development programme. The data safety monitoring board (DSMB) recommended to modify Study A3921133 to discontinue treatment with tofacitinib 10 mg BID. Of note, the FDA subjected the continuation of the trial to the condition that subjects assigned to the 10 mg BID dose were switched to the lower 5 mg BID dose.

Following to the information received from the MAH, a direct healthcare professional communication (DHPC) was circulated in Member States at the end of March 2019 to inform prescribers about the data emerging from study A3921133. Further, the EMA started to assess the increased risk of PE and overall mortality in patients treated with tofacitinib 10 mg twice daily and its potential impact on the marketing authorisation for Xeljanz in a signal procedure. Based on the information available and assessed during the signal procedure, PRAC concluded that tofacitinib is associated with a dose dependent risk of PE.

In view of the seriousness of PE and uncertainties about the underlying mechanism, the PRAC decided that the impact of these findings on the benefit-risk balance of tofacitinib in all authorised indications and doses should be fully assessed resulting in a referral notification. In view of the seriousness of the risk, PRAC recommended the introduction of provisional measures while the review was ongoing. A second DHPC has been circulated at the end of May 2019 to inform prescribers about these provisional measures.

Xeljanz contains tofacitinib which is a selective inhibitor of the Janus kinase (JAK) family of kinases. Tofacitinib is a JAK 1, 2 and 3 inhibitor and is classified as an oral disease modifying anti-rheumatic drug (DMARD). Inhibition of JAK1 and JAK3 attenuates signalling of interleukins (IL2, 4, 7, 9, 15 and 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 authorised 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 (TNF) 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.

Overall summary of the scientific evaluation by the PRAC

The efficacy of Xeljanz in its approved different indications has been previously established and is not questioned in the present procedure.

The available data shows that tofacitinib increases the risk of venous thromboembolism (DVT and PE) in patients with RA and PsA, especially in patients treated with tofacitinib 10 mg BID, and especially in patients with risk factors for venous thromboembolism, as well as risk factors for cardiovascular events. Data from patients suffering from UC although somehow limited do not indicate an increased risk of VTE in a population already with a baseline increased risk of thrombotic events. However, the risk of VTE appears to be higher in patients with UC in remission. As it is assumed that thrombotic events share a common mode of action the results drawn from the RA study (A3921133) can be - with some caution - extrapolated to other indications.

With regards to mortality (taking into account on-drug and the 28-days off-drug data), the interim analyses of Study 1133 indicate a borderline-significant increment of two times for the low tofacitinib dose, and significantly 3 times increment for the high dose, versus active control TNFi. This was partly driven by a higher mortality rate due to infections for tofacitinib. Mortality rates due to cardiac events were about twice as high for the 10 mg BID dose as compared to the active controls (TNFi), which cannot be explained by a raise in PE events. A higher mortality rate for 10 mg as compared to 5 mg is not apparent from other studies.

Rheumatoid arthritis and psoriatic arthritis

The PRAC concluded that the dose dependent risk of thrombotic events, although serious and potentially life-threatening, can be managed with the implementation of appropriate risk minimisation measures.

In Study 1133, the size of the risk of pulmonary embolism was on average modest for the low 5 mg BID dose (in contrast to the 10 mg dose arm), which is the standard dose for the arthritis indications (incidence rate 0.27 per 100 patient years (95% CI 0.12-0.52) additive risk 1.8 /1000 PY). Of note RA patients are already a population at risk for thrombotic events as compared to the general population. However, in presence of one or more risk factors for PE/DVT, there is evidence that the risk for PE/DVT is also raised for tofacitinib 5 mg BID as compared to anti-TNF.

Therefore, treatment with tofacitinib, in patients with additional risk factors for PE/DVT, should be carefully evaluated. As such PRAC considered that it should be emphasized in the SmPC that the recommended dose of 5 mg BID should not be exceeded for RA and PsA. After consultation with experts at an ad-hoc meeting, PRAC also concluded that the provisional contra-indication was not deemed necessary. Instead, the experts were of the opinion that patients with known VTE risk factors could still be treated with tofacitinib provided that appropriate risk mitigation measures are put in place and taking an individual cautious approach by the treating physician (including avoidance of oral contraception and other risk factors for VTE where possible).

The observed increased mortality in the preliminary analyses of Study 1133 is also of concern. However, the increased mortality is not reflected in the other non-1133 RA long term extension studies for the 5 mg and 10 mg dose. Patients were allowed to switch in those studies and as such the observed contrast/difference is smaller. Mortality is included as an outcome in the existing on-going

PASS studies, which over time may provide further information about mortality of 5 mg tofacitinib as compared to other treatments.

The most frequently occurring death causes for the 5 mg, as compared to anti-TNF, were serious infections, whilst it was cardiovascular deaths for the 10mg dosage. A statement has been introduced in the SmPC in order to further highlight that the 10 mg dosage should not be used for RA and PsA.

The MAH was requested to evaluate whether patients at increased risk for death during treatment with tofacitinib could be identified. Although clear risk factors could not be identified, for patients around 65 years of age and above, the risk for mortality is increased. This increase was higher for tofacitinib as compared to anti-TNF, and was mainly attributable to serious infections. A warning has been included in the SmPC highlighting that tofacitinib should only be considered in patients over 65 years of age if no suitable alternative treatment is available and the educational materials was amended accordingly.

As mentioned above, although the risk of PE and mortality are considered very serious PRAC concluded that the risk can be appropriately managed with the inclusion of warnings for patients at increased risk for thrombotic events.

Ulcerative colitis

Inflammatory bowel disease itself is associated with an approximately two-fold increase [relative risk 2.20 (95% CI 1.83 – 2.65)] risk of VTE compared to a general population without inflammatory bowel disease[3]. Furthermore, VTE in UC patients is associated with considerable morbidity and mortality with higher rates of death from pulmonary embolism in IBD patients than in the general population[1],[2].

Neither PE nor DVT were observed upon tofacitinib 10 mg BID induction treatment in studies A3921094 and A3921095 in patients with moderately to severely active UC. However, venous thrombo-embolic events PE (n= 4 out of 1157) and DVT (n= 1 out of 1157) were observed upon prolonged treatment (i.e. 217 to 1149 days) with tofacitinib 10 mg BID in UC patients in remission. All respective patients had one or more risk factors for cardiovascular disease. Despite the limited number of observed VTE cases among UC patients treated with tofacitinib, it is noted that all cases of VTE occurred during tofacitinib maintenance treatment at tofacitinib dosages of 10 mg BID, while no VTE cases were observed at tofacitinib induction treatment at the same dosage. These results show that disease activity may be of relevance with respect to the evaluation of the risk of VTE in UC patients. Tofacitinib may reduce the absolute risk of VTE in patients with active UC by virtue of its anti-inflammatory properties. Due to the (almost) absence of inflammation in patients with UC in remission, the anti-inflammatory properties of tofacitinib will not compensate for the thrombogenic potential of tofacitinib. This would explain why all VTE cases were observed during tofacitinib maintenance treatment for UC in remission.

Despite the limited data on the risk of VTE during tofacitinib maintenance treatment for UC as compared to RA, it is plausible that tofacitinib may increase the risk of VTE in UC patients as was shown in RA patients, as it is unlikely that the safety profile of the active substance tofacitinib itself is substantially different for different indications. Therefore the above mentioned warnings are also relevant in this indication.

In patients who are at increased risk of venous thromboembolic events (e.g. obesity, advanced age, history of VTE) maintenance treatment with tofacitinib 10 mg is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available. A warning

[1] Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008;103:2272–80.''
[2] Jess T, Gamborg M, Munkholm P, Sorensen TI. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol. 2007;102:609–17.

has been included in the product information accordingly. Further treatment with the 10 mg dose should be as short as possible in these patients.

In summary, the available data does not allow definitive conclusions with respect to the risk of VTE in UC patients treated with tofacitinib as compared to tofacitinib-treated RA patients. However, in RA patients a dose-dependent increase in VTEs and serious infections was shown upon tofacitinib treatment. It is plausible that similar effects may occur in UC patients. The tofacitinib related risk of VTE appears to be higher in patients with no active disease, i.e. disease in remission. It is unknown to what extent observations with respect to the VTE risk in RA patients seen in 1113 study may be extrapolated to UC patients. Nevertheless, the benefit/risk balance of tofacitinib in the treatment of UC remains positive. In patients with known risk factors for VTE, treatment with tofacitinib should be used with caution regardless of indication and dosage. In addition, tofacitinib 10 mg BID maintenance treatment should be prescribed for the shortest duration possible based on a careful weighing of benefits and risks in individual patients.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Xeljanz (tofacitinib).
- PRAC considered the totality of the data submitted during the referral in relation to the risk of venous thromboembolism and overall mortality, including the responses submitted by the marketing authorisation holder in writing as well as the outcome of a consultation with an Ad-hoc expert group meeting.
- PRAC concluded that tofacitinib is associated with an increased risk of venous thromboembolic events (VTE), both for deep venous thrombosis as well as pulmonary embolism, especially in patients with risk factors for venous thromboembolism. The PRAC further concluded that the risk of venous thromboembolism events is dose-dependent.
- PRAC concluded that although the data for patients with ulcerative colitis and psoriatic arthritis are limited, the results from study A3921133 in rheumatoid arthritis patients are relevant for the other indications.
- Based on the interim analyses of Study A3921133 the 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. This was particularly apparent for patients aged 65 years and above and as such tofacitinib should be considered in these patients only if no suitable alternative treatment is available.
- To minimise these risks, PRAC recommended warnings to be introduced in the product information regarding the increased risk of VTE observed in patients taking tofacitinib especially for patients with known risk factors for VTE. The PRAC also recommended that treatment with tofacitinib is discontinued in patients with suspected VTE.
- Furthermore, PRAC introduced a warning that tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available. Clarifications on the posology have also been added particularly for UC patients in maintenance.
- PRAC recommended an update of the educational materials accordingly.

- PRAC also agreed on a direct healthcare professional communication, together with the timelines for its distribution.

In view of the above, the Committee considers that the benefit-risk balance of Xeljanz (tofacitinib) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Xeljanz (tofacitinib).

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.