Annex

Scientific conclusions

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On 28 January 2022, 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 Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

This referral procedure concerns JAKis approved for inflammatory disorders:

- Xeljanz (tofacitinib): rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA).
- Olumiant (barcitinib): RA, alopecia areata (AA) and atopic dermatitis (AD)
- Cibinqo (abrocitinib): AD
- Jyseleca (filgotinib): RA and UC
- Rinvoq (upadacitinib): RA, PsA, AS, non-radiographic axial spondyloarthritis (nr-axSpA), UC and AD

These medicinal products inhibit different JAK isoforms which attenuates signalling of interleukins and interferons, resulting in modulation of the immune and inflammatory response.

The background to this referral procedure is based on data from the ORAL Surveillance study A3921133. This is a Phase 3b/4 randomised study that evaluates the safety of tofacitinib at two doses (5 mg and 10 mg BID) versus TNFi. The 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 RA.

Interim results from the ORAL Surveillance study were assessed in 2019 in an Article 20 referral procedure (EMEA/H/A-20/1485) and a preliminary analysis of the final results were included in signal procedure (EPITT 19382) which concluded in June 2021. The PRAC concluded that tofacitinib is associated with an increased risk of venous thromboembolism (VTE) and 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. Further, there was an increased incidence of major adverse cardiovascular events (MACE) and higher risk of malignancy with tofacitinib compared to TNFi. The PI of tofacitinib, but not the other JAKis, was updated accordingly.

The final results of the completed ORAL Surveillance study confirmed the findings observed in the preliminary analysis. No randomised controlled studies have been concluded with the other JAKis to specifically evaluate the safety concerns of interest. However, preliminary results on baricitinib were made available from the observational Study I4V-MC-B023 (B023) showed an increased rate of MACE and VTE with baricitinib compared to TNFi in RA patients. A safety referral was therefore triggered to assess whether the safety concerns on MACE, VTEs, serious infections, malignancies and mortality observed in rheumatoid arthritis patients with tofacitinib are a class effect and to assess its impact on the benefit risk balance of the JAKis used in the treatment of chronic inflammatory disorders.

Following assessment of the currently available mechanistic data, together with current knowledge of the safety profiles of these substances, the PRAC considered the main safety events observed during tofacitinib treatment in the ORAL Surveillance study as general JAKi class effects. This view was also supported by the Ad Hoc Expert Group.

It is acknowledged that the extent to which the tofacitinib ORAL Surveillance data on MACE, VTE, serious infections, malignancies and mortality are applicable to all JAKis approved for inflammatory conditions, across the target populations, depends also on the similarities of the respective populations including presence of risk factors for occurrence of the observed adverse events. Overall, the ORAL Surveillance study population is considered sufficiently similar to the populations covered by the adult arthritis indications RA and PsA to allow extrapolation of data. The target populations of the other rheumatic disorders and UC are considered to be sufficiently similar, with regards to important disease characteristics and baseline risk factors, for the ORAL Surveillance data to be relevant.

For the AD population, the prevalence of risk factors (including age and co-morbidities) is different compared to a RA population, mainly explained by lower age and disease specific differences. Patients with AD are already due to their underlying disease at increased risk for cardiovascular comorbidities compared to the general population (e.g. Ivert et al., 2019), which supports extrapolation of the findings in RA in the ORAL surveillance study to AD. Regarding treatment of severe AA, the PRAC acknowledged that this patient group generally has less risk factors for the main serious safety outcomes compared with e.g. RA patients, as they are at least not associated to the underlying disease.

Nevertheless, as also pointed out by the Ad Hoc Expert Group, if a patient has risk factors in any of the authorised indications, the patient would be equally at risk for the safety findings being the focus of this review. JAKis are used for indications requiring chronic treatment, potentially exposing patients without risk factors for prolonged periods of time. Thus, even a small increase in absolute risk of serious adverse events may be clinically relevant. These risks are monitored and will be further characterised in ongoing PASSes.

Therefore, since the safety events are considered class effects and because the risk factors for these events can emerge in populations treated with any of the JAKis, the PRAC concluded that these important safety concerns are relevant to all approved indications including the AD and AA populations.

Impact of class effects on the benefit-risk balance of all JAKis under review

With regards to the benefits of the JAKis, no new data has emerged within this review. Importantly, in general, their benefits seem clinically relevant also for subjects not responding to anti-TNF (in the non-dermatological indications) or previous systemic AD-treatment, respectively.

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes increase with dose, current dosing advice (SmPC section 4.2) is recommended to be revised for all products to lower the dose in patients with risk factors for MACE, VTEs, or malignancy and in patients 65 years of age and older, as applicable.

The special warnings and precautions (SmPC section 4.4) were updated for all products to align with the current recommendations for use for tofacitinib based on the ORAL Surveillance study. Currently, it is recommended that tofacitinib should be used only if no suitable treatment alternatives are available in patients over 65 years of age, in patients who are current or past smokers, and patients with other cardiovascular risk factors. Cautious use is recommended in patients with known risk factors for VTE.

The Ad Hoc Expert Group (AHEG) also recommended strengthening the existing warning of Xeljanz to state that the product should be used with caution in patients with risk factors and being above 50 years of age, in accordance with the inclusion criteria of the ORAL Surveillance study. However, patients with similar risk factors as those included in the ORAL Surveillance study are already targeted by the existing warning of tofacitinib, as outlined above.

The warnings recommended during this review still included some updates to the existing warning for tofacitinib:

- The warning on MACE is updated to include *history of atherosclerotic cardiovascular disease* as risk factor, as supported by a post hoc analysis of the Oral Surveillance Study.
- The warnings on MACE and malignancies were updated to indicate that the risk factors apply to *long-time* smokers in accordance with the long duration of smoking for patients of the ORAL Surveillance study.
- All-cause mortality is added as a risk for patients 65 years of age and older.
- The risk factors for VTE were updated to exclude those overlapping with malignancy and MACE, to avoid discrepant information across the warnings since different recommendations are given.

In order to specifically highlight the most important considerations for prescribers before and during use of these JAKis, the PRAC recommended the addition of a boxed warning in SmPC Section 4.4 to indicate the groups of patients for whom JAKis should be only used if no other treatment alternatives are available.

The impact of the safety concerns identified in the ORAL Surveillance study across all approved indications for all JAKis under review, were considered. The PRAC acknowledged the fact that, as also outlined by the AHEG, the ORAL Surveillance population constitutes a high CV risk population which did not include individuals with low CV risk, based on inclusion criteria. This enriched population with respect to CV risk had a mean RA disease duration of more than 10 years (Ytterberg et al. 2022), which could in many aspects differ from the EU populations targeted by the approved JAKis indications. The PRAC also noted that the magnitude of the absolute risks observed in the ORAL Surveillance study likely is lower in populations with lower baseline risk. The main challenge is to estimate the magnitude of the absolute risks in different patient groups with lower baseline risk, and disease characteristics to weigh these risks against the observed/expected benefits and conclude on proportionate risk mitigation measures. For this evaluation, some guidance can be derived from the post hoc analysis of subgroups in the ORAL Surveillance study but there are also uncertainties deriving from e.g. the degree of generalisability of the ORAL Surveillance data to all populations targeted by the approved JAKi indications.

Taking all data available and the AHEG's view into account, the PRAC considered that an approach aiming at more precision and focus on readily identifiable individual risk factors, instead of limiting use across the respective target populations, is the preferred option to retain a positive benefit-risk balance without depriving patients with low risk of adverse events of an effective treatment option. Therefore, the PRAC recommended implementing warnings applicable to patients with certain risk factors in SmPC Section 4.4 of *all* approved JAKis to aid the prescribers in their assessment of benefits and risks for the individual patient.

For all products, the PRAC also recommended updates of the key elements of the existing educational materials according to the risk minimisation measures recommended during this procedure, updates to the existing PASSes in place to monitor the new risks identified and updates to the existing drug utilisation studies (DUSs), or the implementation of new DUS, if none are in place, to evaluate the effectiveness of the newly recommended risk minimisation measures. The PRAC acknowledged the recommendation from the AHEG to consider additional pharmacovigilance activities. However, the PRAC did not consider such additional activities necessary as there are a number of ongoing PASS for the 5 JAKis. The PRAC agreed that a DHPC should be distributed to the HCP in order to inform about the recommended risk minimisation measures.

Benefit-risk balance of individual JAKis under review

Cibinqo (abrocitinib)

Cibinqo has recently been approved, for the treatment of AD. With regards to the benefit, abrocitinib has proven to be efficacious for the treatment of **AD**; both in monotherapy and combination studies. Effects in patients having received prior systemic immunosuppressant treatment were consistent with the results in the overall study population. Long-term prevention of AD flare was achieved in a majority of patients with the induction-maintenance regimen. The product is currently approved with a posology to use 200 mg QD as induction treatment, with an aim to rapidly achieve disease control followed by dose reduction to the lowest effective dose for maintenance treatment for most patients. A starting dose of 100 mg once daily is recommended for patients 65 years of age and older, and there is a reference to SmPC sections 4.4 and 4.8 for other patient groups who may benefit from a starting dose of 100 mg.

Regarding the established risks, the available long term safety data are limited. Nevertheless, thromboembolic events including pulmonary embolism are already listed as uncommon ADRs. Furthermore, herpes zoster including ophthalmic zoster (common), and pneumonia (uncommon) are already listed as ADRs. For MACE, although currently available data are still not mature for final conclusion, there is a trend for a dose dependency, and a higher occurrence than in the comparative arm in studies.

Considering the results from the ORAL Surveillance study, showing that increased risks for some of the key safety concerns only became apparent until after more than 2 years treatment, there are uncertainties regarding the long-term safety with abrocitinib. Nevertheless, as results from this study are considered relevant for all substances covered by this referral, the main outcomes are considered safety concerns also for abrocitinib. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis. Further revisions of the warnings on malignancies and VTEs (SmPC section 4.4) were also made following review of abrocitinib-specific data during this procedure.

In addition, since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, the PRAC recommended updating the posology (SmPC Section 4.2) to recommend a starting dose of 100 mg in patients at higher risks of VTE, MACE and malignancy and that the use of the 200 mg dose may be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for MACE, VTE and malignancy or patients with an inadequate response to 100 mg. The dose should be decreased to 100 mg once daily upon disease control. In addition, the PRAC recommended the use of 100 mg once daily in patients 65 years of age and older.

Jyseleca (filgotinib)

With respect to the established benefit of filgotinib, the available data support that filgotinib is an effective treatment for **RA** and **UC.** Additionally, overall data presented by the MAH support that for patients with RA or UC, who failed to achieve therapeutic response to a TNF inhibitor, could still benefit from using filgotinib. The currently recommended dose for Jyseleca is 200 mg once daily, a starting dose of 100 mg is recommended in patients 75 years of age and older.

Overall, the main safety outcomes of the ORAL Surveillance study with increased risk for VTE, MACE, serious infections and malignancy with tofacitinib versus TNFi) are considered class effects relevant to all JAKis in their approved indications, and the SmPC Section 4.4 is updated to implement class warnings. Further, SmPC section 4.8 is updated following review of filgotinib specific data during this procedure, to add sepsis as an ADR (frequency: uncommon).

Since data from the ORAL Surveillance study suggest that the risks of MCAE, VTE and malignancy increase with dose, the PRAC recommended the use of 100 mg once daily for the treatment RA and for maintenance treatment of UC, in patients at increased risk of VTE, MACE, malignancy and in patients 65 years and older. The dose may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.

Olumiant (baricitinib)

With respect to the established benefits of baricitinib, the available data support that baricitinib is an effective treatment in its approved indications.

For **AD**, the benefit/risk balance of baricitinib was considered positive in patients treated with systemic therapy (ciclosporin) prior to baricitinib, based on clinical studies. Dupilumab was the second available approved systemic therapy at the time of the application of baricitinib. No head-to-head comparison studies with ciclosporin or dupilumab have been performed. Regarding efficacy in AD patients treated with systemic therapy prior to baricitinib, the developmental programme comprised patients who are candidates for systemic therapy only. In the All BARI AD data set, 51% of the patients received prior treatment, and one study was performed in patients previously treated with ciclosporin. In this study, the proportion of patients reaching EASI75 at week 16 was significantly larger than in placebo and secondary outcomes supported these findings. The effects lasted at least until 52 weeks.

For **AA**, two main studies in 1200 adults with severe alopecia areata showed that baricitinib was effective at reducing hair loss compared to placebo. In these studies, after 36 weeks of treatment, the extent of hair loss improved from over 50% to under 20% of scalp hair in 34% of the participants taking 4 mg of baricitinib and in 20% of the participants taking 2 mg of baricitinib, compared with 4% of the participants taking placebo.

The main source for comparison of safety between baricitinib and TNFi currently stems from the observational B023 study in **RA**, which suggests an increased risk for MACE (IRR 0.92; 1.27 – 2.91) and VTE (IRR 1.34; 0.84 – 2.14) for baricitinib versus TNFi. This higher risk for VTE was also found in a clinical trial directly comparing baricitinib and TNFi. VTE is already listed/known ADR for baricitinib and is included in the PI. Furthermore, the observed increased risks of MACE and VTE seem consistent across tofacitinib and baricitinib and taking the assumed JAKi class effect into account; the main safety outcomes of the ORAL Surveillance study are considered relevant also for baricitinib. Finally, there are data showing that baricitinib has a clinically relevant effect also in patients with previous inadequate response to adalimumab (TNFi).

Overall, the main safety outcomes of the ORAL surveillance study (increased risk for VTE, MACE, serious infections and malignancy (excluding NMSC) with tofacitinib versus TNFi) are considered class effects of all JAKis. Additionally, the available clinical study data on baricitinib show trends of increased incidence of some of the adverse events of interests also with baricitinib. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis, and to apply to all indications of baricitinib, including the AA indication.

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, the current recommendation to use the 2mg dose in patients ≥75 years is updated to recommend the use of lower dose of 2mg once daily for patients 65 years and older and in patients at higher risk of VTE, MACE and malignancy. A dose of 4 mg once daily may be considered in case of inadequate response.

Rinvoq (updadacitinib)

The overall benefit of upadacitinib treatment is considered unchanged by the current procedure and thus consistent with the presentation of efficacy data in section 5.1 of the approved SmPC. The data presented by MAH support benefits of upadacitinib also in patients with RA, PsA and AS who previously failed to achieve therapeutic response to TNF inhibitors.

Regarding **AD**, upadacitinib has a clinically relevant efficacy, with short onset, and it is given via oral administration. Furthermore, long-term safety of upadacitinib is presently not established, which is an additional uncertainty.

For the recently approved indications i.e. UC and nr-axSpA, the safety profile and concerns regarding the benefit/risk are consistent with those of the other approved indications.

As concluded in the current review, the main safety outcomes of the ORAL Surveillance study data are considered class effects of all JAKis. Additionally, the available clinical study data on upadacitinib further support these being main safety concerns. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis. Further revisions of the wording of warnings on serious infections and malignancy in SmPC Sections 4.4 and SmPC Section 4.8 were made following review of upadacitinib specific data to add sepsis (frequency: uncommon) and NMSC (frequency: common) as ADRs.

In light of the dose dependency of the safety events of MACE, VTE and malignancy observed in the ORAL Surveillance study that are considered relevant to the class of JAKis, the PRAC recommended to update the posology (SmPC Section 4.2) of Rinvoq for the treatment of AD and maintenance treatment of UC, to recommend the use of 15 mg once daily in patients with risk factors for VTE, MACE and malignancy. A dose of 30 mg once daily can be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for VTE, MACE and malignancy, or for patients with an inadequate response to 15 mg. Lowest effective dose during maintenance treatment of both settings is also recommended.

Xeljanz (tofacitinib)

With respect to the established benefits of tofacitinib, the available data support that tofacitinib is an effective treatment in its approved indications. The MAH has now provided support also for the efficacy of tofacitinib in patients previously treated with TNFi.

The final results of the ORAL Surveillance study (A3921133) show an increased incidence for major safety risks that are known ADRs of tofacitinib, including MACE, MI, VTE, malignancy and death, NMSC and serious infections in patients treated with tofacitinib compared to TNFi, and this pattern was observed for both approved tofacitinib doses (i.e. 5 mg BID and 10 mg BID). Dose-dependency was observed for several safety outcomes, with increased risks of all-cause mortality, thromboembolic events and serious infections in tofacitinib 10 mg BID compared to tofacitinib 5 mg BID and TNFi.

The SmPC of tofacitinib is updated to include the final results of the ORAL Surveillance study in SmPC Sections 4.8 and 5.1.

The existing warning on VTE, malignancies and MACE in SmPC Section 4.4 is updated as described above.

Further, the PRAC recommended updating the posology recommendation on the 10 mg BID maintenance dose in UC patients in SmPC Section 4.2 to align with the warnings on MACE and malignancies in SmPC Section 4.4.

Overall, the PRAC concluded that the benefit-risk balance of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz remains positive subject to changes to the product information and implementation of risk minimisation measures recommended by the PRAC.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for the JAKis used in the treatment of inflammatory disorders. The concerned products are Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz.
- The PRAC considered the totality of the data submitted during the referral in relation to the risks of major adverse cardiovascular events (MACEs), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality. This included the responses submitted by the marketing authorisation holders in writing and during oral explanations as well as the outcome of an Ad hoc expert group meeting.
- The PRAC concluded that, based on the currently available data, the increased risk for MACE, VTE, malignancy, serious infections and all-cause mortality observed in the ORAL Surveillance study with tofacitinib compared with TNF-inhibitors are considered JAKis class effects. The PRAC also concluded that these safety findings observed in patients with rheumatoid arthritis apply to all approved indications for the JAKis used in the treatment of chronic inflammatory disorders. However, the magnitude of the absolute risk depends on the background risk in the respective populations.
- To minimise these risks, the PRAC recommended implementing warnings for all JAKis included in this review that these products should only be used in patients 65 years of age and older, who are current or past long-time smoker, with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or with other malignancy risk factors (e.g. current, or history of malignancy) if no suitable treatment alternatives are available. Cautious use is recommended in patients with known risk factors for VTE, other than those listed above.
- The PRAC recommended revising current dosing advice to lower the dose in certain patient groups with risk factors since the occurrence of MACEs, VTEs, malignancies, serious infections and all-cause mortality have been observed in a dose dependent manner.
    - For Cibinqo, a lower starting dose is recommended in patients at higher risk for VTE, MACE, and malignancy with the possibility of a dose escalation in case of inadequate response. The lower dose is recommended for use in patients 65 years and older.
    - For Jyseleca, in the treatment of RA and for maintenance treatment of UC, a lower dose is recommended in patients at higher risk for VTE, MACE, and malignancy and in patients 65 years and older, with the possibility of a dose escalation in case of inadequate response.
    - For Olumiant, a lower dose is recommended for patients at higher risk of VTE, MACE and malignancy, for patients 65 years and older and for patients with history of chronic and recurrent infections, with the possibility of a dose escalation in case of inadequate response.
    - For Rinvoq, in the treatment of AD and maintenance treatment of UC, a lower dose is recommended in patients at higher risk for VTE, MACE, malignancy and in patients 65

years and older, with the possibility of a dose escalation in case of inadequate response.

    - For Xeljanz, the high dose is no longer recommended for the treatment of ulcerative colitis patients with CV and malignancy risk factors, unless there is no suitable alternative treatment available.

- Based on the clinical data presented, the PRAC recommended including new adverse reactions for Jyseleca with the addition of sepsis (frequency: uncommon) and for Rinvoq with the addition of sepsis (frequency uncommon) and non-malignant skin cancer (frequency: common).
- The PRAC recommended an update of the key elements of the educational materials accordingly.
- PRAC recommended updates of the risk management plans including studies of drug utilisation accordingly.
- The PRAC also agreed on a direct healthcare professional communication, together with the timelines for its distribution.

In view of the above, the PRAC concluded that the benefit-risk balance of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz

- is favourable subject to changes to the product information and other risk minimisation measures as described above.

CHMP opinion

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