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

Janus Kinase inhibitors (JAKi)

Xeljanz (tofacitinib) EMEA/H-A20/1517/C/004214/0048

Cibinqo (abrocitinib) EMEA/H-A20/1517/C/005452/0003

Olumiant (baricitinib) EMEA/H-A20/1517/C/004085/0032

Rinvoq (upadacitinib) EMEA/H-A20/1517/C/004760/0017

Jyseleca (filgotinib) EMEA/H-A20/1517/C/005113/0014

Divergent statement

The below named CHMP Members consider that a restriction of indications of above mentioned products is necessary to maintain their positive Benefit/Risk balance, taking into account the availability of authorized alternatives, based on the following grounds:

- ORAL is a Phase 3b/4 randomized study specifically designed to evaluate safety of tofacitinib at two doses (5 mg and 10 mg BID) vs TNFi and methodologically represents the strongest possible base for conclusion. Results of this study showed higher incidence on MACE, malignancies, VTEs, serious infections, and most importantly mortality in patients aged ≥50 years with moderate to severe RA and at least one additional cardiovascular risk factor treated with tofacitinib vs TNFi.
- Preliminary results of I4V-MC-B023 (B023) observational study, including data from several healthcare databases of RA patients, showed an increased rate of MACE and VTE with baricitinib vs TNFi in RA patients.
- Safety concerns under review are identified ADRs class effect for JAKi and are therefore expected in both patients *with* and *without* risk factors.
- In patients *without* risk factors, absolute risk of serious safety outcomes is expected to be low but is not negligible. In patients without risk factors (e.g. children, adolescents), the serious safety outcomes of JAKis under review are of great concern, especially in the view of the expected long-term treatment.
- Restriction of indication in the updated AR and below is needed to ensure positive benefit/risk balance also in patients without risk factors in view of potentially fatal ADRs under review, in addition to the risk minimisation measures for patients *with* risk factors.
- Restriction of indications is considered the most effective measure in affecting factual prescription behaviour.
- There may be long-term unintended consequences of implementing a warning only for patients with risks factors without restriction of indications. The use of the JAK inhibitors may be channeled to indications where patients have less risk factors for MACE and malignancy, however higher doses may be used. These populations include children and adolescents and

that is of concern particularly due to risk of malignancy with this treatment (including lymphoma) in these populations.

Based on the presented evidence in their totality, we are of the following opinion:

To ensure a positive B/R balance for the concerned products, next to the warning for patients 65 years of age or older and patients with risk factors for MACE and malignancy, the indications should be restricted to patients who:

- responded inadequately or are intolerant to TNFi or for whom TNFi is inappropriate (RA, PsA, UC, AS, JIA indications)
- responded inadequately or are intolerant to at least one prior systemic therapy or for whom alternative systemic therapies are inappropriate (AD indication)
- responded inadequately or are intolerant to alternative treatment options or for whom alternative treatment options are inappropriate (AA indication).

CHMP Members expressing a divergent opinion:

- Margareta Bego (Croatia)
- Armando Genazzani (Italy)
- Blanka Hirschlerová (Co-opted member for Quality (non-biologicals) and Pharmacokinetics)
- Johann Lodewijk Hillege (Netherlands)
- Ondřej Slanař (Czechia)
- Alexandre Moreau (France)