<date>

Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) – Updated recommendations to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi).

Dear Healthcare Professional,

AbbVie, Galapagos, Lilly and Pfizer in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **An increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality has been observed in patients with rheumatoid arthritis (RA) with certain risk factors using JAKi treatment compared to TNFα inhibitors.**
- **These risks are considered class effects and relevant across all approved indications of JAKi in inflammatory and dermatologic diseases.**
- **These JAKi should only be used if no suitable treatment alternatives are available in patients:**
    - **65 years of age and older;**
    - **who are current or past long-time smokers;**
    - **with other cardiovascular or malignancy risk factors.**
- **JAKi should be used with caution in patients with VTE risk factors other than those listed above.**
- **Dosing recommendations are revised for some patient groups with risk factors.**
- **Periodic skin examination is recommended for all patients.**
- **Prescribers should discuss with patients the risks associated with the use of JAKi.**

Background on the safety concern

The JAKi Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) are approved for the treatment of several chronic inflammatory disorders (rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, atopic dermatitis, and alopecia areata). The approved use differs for the different products, as outlined in the respective product information.

In March 2021, a Direct Healthcare Professional Communication (DHPC) for Xeljanz (tofacitinib)[1] was sent to healthcare professionals, informing them that data from a completed clinical trial (A3921133)[2] in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, suggest a higher risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor.

An additional DHPC[3] was sent in July 2021 to inform about an increased incidence of myocardial infarction, lung cancer, and lymphoma with tofacitinib compared to TNF-alpha inhibitors observed in the same clinical trial, as well as adopted recommendations for the product information of tofacitinib.

Preliminary findings from an observational study (B023) involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular events and VTE in patients with RA treated with Olumiant compared with those treated with TNF-alpha inhibitors.

Following the finalization of the review procedure of the available data across these five JAKi by EMA, recommendations have been adopted as specified in the "summary" above. The product information and the educational materials for healthcare professional and patients is being updated accordingly.

This letter is not intended as a complete description of the benefits and risks related to the use of these products. For further details, please refer to the updated SmPC for the respective products.

Call for reporting

< to be filled nationally>

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system. <to be filled nationally> Please find the relevant contact for each product in the table below.

Product	**Cibinqo (abrocitinib)**	**Jyseleca (filgotinib)**	**Olumiant (baricitinib)**	**Rinvoq (upadacitinib)**	**Xeljanz (tofacitinib)**
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Telephone number					
Email address					

Company contact point

< to be filled nationally>

[1] https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-initial-clinical-trial-results-increased-risk-major-adverse-cardiovascular

[2] Ytterberg, Steven R., et al. "Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis." *New England Journal of Medicine* 386.4 (2022): 316-326.

[3] https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-increased-risk-major-adverse-cardiovascular-events-malignancies-use-tofacitinib

Product	**Cibinqo (abrocitinib)**	**Jyseleca (filgotinib)**	**Olumiant (baricitinib)**	**Rinvoq (upadacitinib)**	**Xeljanz (tofacitinib)**
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Website address					
Postal address					

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib)
Marketing authorisation holder(s)	AbbVie, Galapagos, Lilly and Pfizer All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. It is also encouraged that one of the marketing authorisation holder in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State.
Safety concern and purpose of the communication	Inform about important updates in the SmPC for JAKi which concern warnings and actionable advice regarding malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality.
DHPC recipients	Allergologists, dermatologists, gastroenterologists, rheumatologists, paediatricians, The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU/EEA Member states

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	27/10/2022
DHPC and communication plan (in English) agreed by CHMP	10/11/2022
Submission of translated DHPCs to the national competent authorities for review	24/11/2022
Agreement of translations by national competent authorities	1/12/2022
Dissemination of DHPC	EC decision + 5 calendar days