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18 Mar 2023

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 Medicines 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.

[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.

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.

▼The medicinal products Cibinqo, Jyseleca and Rinvoq are subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Call for reporting

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system Adverse Drug Reactions (ADRs). Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Malta Medicines Authority Post-licensing, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, or sent by email to: postlicensing.medicinesauthority@gov.mt. Please report the product name and batch details.

Adverse events should also be reported:

- for Cibinqo and Xeljanz, to Pfizer's local representative - Vivian Corporation Ltd, via email: pv@viviancorp.com
- for Jyseleca, to Galapagos's local representative - Sobi, via e-mail: pv.medical.info.gr@sobi.com
- for Olumiant, to Eli Lilly's local representative - Charles de Giorgio Ltd, via pv@charlesdegiorgio.com
- for Rinvoq: *n/a* (not marketed in Malta)

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 Europe MA EEIG / Vivian Corporation Ltd (local representative)	Galapagos / Sobi (local representative)	Eli Lilly Nederland B.V/Charles de Giorgio Ltd. (local representative)	AbbVie (not marketed)	Pfizer Europe MA EEIG / Vivian Corporation Ltd (local representative)
Telephone number	+30 2106785800 Local number: +356 22588600	+30 210 700 8245	+385-1-2350 999	N/A	+30 2106785800 Local number: +356 22588600

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

			Local number: +356 25600 801		
Email address	medical.information@pfizer.com Local contact: pv@viviancorp.com	pv.medical.info.gr@sobi.com	PHV_CENTRE_SEE@lilly.com	regvjsp@vjsalomone.com	medical.information@pfizer.com Local contact: pv@viviancorp.com

Company contact point

Product	**Cibinqo (abrocitinib)**	**Jyseleca (filgotinib)**	**Olumiant (baricitinib)**	**Rinvoq (upadacitinib)**	**Xeljanz (tofacitinib)**
MAH	Pfizer Europe MA EEIG / Vivian Corporation Ltd (local representative)	Galapagos / Sobi (local representative)	Eli Lilly Nederland B.V/Charles de Giorgio Ltd. (local representative)	AbbVie's local representative V.J. Salomone Pharma Ltd.	Pfizer Europe MA EEIG / Vivian Corporation Ltd (local representative)
Website address	https://www.pfizer.com/products/product-contact-information	https://sobigreece.gr/contact	https://www.lilly.com/	https://www.abbvie.com/contactus.html	https://www.pfizer.com/products/product-contact-information
Postal address	29 Tower Road, Msida, Malta	12 Sorou street, 151 25, Marousi, Greece	Triq il-Kan. K. Pirotta, B'Kara BKR1114, Malta	V.J. Salomone Pharma Limited - Upper Cross Road, Marsa, MRS 1542, Malta	29 Tower Road, Msida, Malta

Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of AbbVie, Galapagos, Lilly and Pfizer.

The MMA receives the relevant contact details from both the Medical Council and the Pharmacy Council. Should you wish to amend your details including address, you are asked to contact the Medical Council or Pharmacy Council directly, as may apply.