HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Janus Kinase inhibitors (JAKi) – Recommendations to mitigate risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality when used in the treatment of chronic inflammatory disorders

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended measures to minimise the risk of a number of serious adverse reactions considered to be class effects of certain Janus kinase (JAK) inhibitors used in the treatment of several chronic inflammatory disorders. The recommendations apply to Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib).*

The recommendations have been made following a review of available data by PRAC, including the final results from a clinical trial (study A3921133)[1] of Xeljanz (tofacitinib) and preliminary findings from an observational study (B023)[2] involving Olumiant (baricitinib). Findings from study A3921133 have shown an increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality in patients with rheumatoid arthritis (RA) 50 years of age or older with at least one additional cardiovascular risk factor using tofacitinib compared to TNF-alpha inhibitors. Preliminary findings from observational study B023 have also suggested an increased risk of MACE and VTE in patients with RA treated with baricitinib, compared with those treated with TNF-alpha inhibitors.

Previous recommendations for Xeljanz (tofacitinib)

Following a previous review of interim results from study A3921133 in 2020, PRAC recommended tofacitinib should be used with caution in patients with known risk factors for VTE due to a dose dependent increased risk of VTE including pulmonary embolism (PE) and deep vein thrombosis (DVT). Additionally, the use of tofacitinib twice daily for maintenance treatment in patients with ulcerative colitis with known VTE risk factors was no longer recommended, unless there was no suitable alternative treatment. Recommendations also included that due to an increased risk of infections, patients older than 65 years of age should be treated with tofacitinib only when there is no suitable alternative treatment. Educational materials were updated accordingly to include a warning about VTE in the prescriber's brochure and treatment checklists as well as the patient alert card.

Following the further evaluation of the completed study A3921133, a Direct Healthcare Professional Communication (DHPC)[3] was distributed in March 2021 informing that data suggested a higher risk of MACE and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor. In July 2021 an updated DHPC informed healthcare professionals of an increased incidence of myocardial infarction, lung cancer, and lymphoma observed in completed study A3921133 with tofacitinib compared to TNF-alpha inhibitors, along with the recommended product information updates.

Updated PRAC recommendations for class of JAKiused to treat chronic inflammatory disorders

The findings from study A3921133 have been considered in the most recent PRAC review, encompassing all JAKi used to treat chronic inflammatory disorders, together with the preliminary findings from study B023, and the PRAC has now concluded that these safety findings apply to all approved uses of the JAKi in chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata).

The PRAC has recommended that these medicines should only be used if no suitable treatment alternatives are available in patients:

- 65 years of age and older,
- with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors,

- who are current or past long-time smokers,
- with malignancy risk factors (e.g. current malignancy or history of malignancy).

The PRAC also recommended that these medicines should be used with caution in patients with VTE risk factors other than those listed above including previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy and inherited coagulation disorder.

If treatment with a JAKi is needed in patients with risk factors for serious adverse reactions, a lower dose may be recommended, depending on the medicine, the indication and individual patient characteristics.

In addition to the above measures, periodic skin examination is now also recommended for all patients.

Healthcare professionals should discuss these risks with their patients.

Product information** and educational materials for Cibinqo, Olumiant, Rinvoq and Jyseleca will now be updated with the new recommendations and warnings. The warnings in the product information and educational materials for Xeljanz will also be revised.

JAKi used in the treatment of myeloproliferative disorders, including Jakavi (ruxolitinib) and Inrebic (fedratinib) did not fall within the scope of this review. The review also did not cover the use of Olumiant in the short-term treatment of COVID-19, which is under assessment by EMA.

References

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

2. European Medicines Agency's (EMA's) Public Health Communication confirming measures to minimise risk of serious side effects with Janus Kinase inhibitors for chronic inflammatory disorders. Available on the EMA website.

3. Direct Healthcare Professional Communications (DHPC) are available on the HPRA website.

Key Message

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has finalised a review of the Janus Kinase inhibitors (JAKi) Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib).

An increased incidence of major cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and mortality has been observed in patients with rheumatoid arthritis (RA) and certain risk factors using JAKi treatment compared to TNF-alpha inhibitors.These risks are considered class effects and relevant across all approved indications of JAKi in inflammatory and dermatological diseases.

These JAKi should only be used if no suitable treatment alternatives are available in patients:
- 65 years of age and older,
- with history of atherosclerotic cardiovascular disease or other cardiovascular riskfactors,
- who are current or past long-time smokers,
- with malignancy risk factors (e.g. current malignancy or history of malignancy).

JAKi should be used with caution in patients with VTE risk factors other than those listed above.
A lower dose of JAKi may be recommended for patients with risk factors for serious adverse reactions, depending on the medicine, the indication and individual patient characteristics.
Periodic skin examination is recommended for all patients.
Healthcare professionals should discuss these risks with their patients.

**Further information on JAKi is available on www.hpra.ie and www.ema.europa.eu.*
*** The approved product information is comprised of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available from www.hpra.ie and www.ema.europa.eu.*