EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

01.02.2023 | Circular Number P02/2023

Information on Janus kinase inhibitors

- The Janus kinase (JAK) inhibitors subject to this review[1] are used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, atopic dermatitis, and alopecia areata).

- The active substances in these medicines work by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the process of inflammation that occurs in these disorders. By blocking the enzymes' action, the medicines help reduce the inflammation and other symptoms of these disorders.

Some JAK inhibitors (Jakavi and Inrebic) are used to treat myeloproliferative disorders; the review did not include these medicines. The review also did not cover the use of Olumiant in the short-term treatment of COVID-19, which was under assessment by EMA at the time.

The following products are authorised via centralised procedure.

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
Baricitinib	Olumiant	Film-coated tablet	POM	EMEA/H/C/004085	Eli Lilly Nederland B.V.
Tofacitinib	Xeljanz	Film-coated tablet	POM	EMEA/H/C/004214	Pfizer Europe MA EEIG

Information from the EMA about the safety concern

- The review of JAK inhibitors in the treatment of inflammatory disorders was initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004.
- The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations on 27 October 2022. The PRAC recommendations were forwarded to the EMA's human medicines committee

[1]Olumiant (baricitinib), and Xeljanz (tofacitinib).

(Committee for Medicinal Products for Human Use (CHMP)), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. On 23 January 2023, CHMP endorsed the measures recommended by the PRAC to minimise the risk of serious side effects with JAK inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

- Following further review of its recommendation of October 2022, the PRAC issued an update on 12 January 2023 to further align dosing recommendations for the medicines concerned by the procedure. The PRAC's revised recommendations were sent to the CHMP, which has adopted the Agency's opinion. The CHMP's opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.
- The recommendations follow a review of available data, including the final results from a clinical trial of the JAK inhibitor Xeljanz (tofacitinib) and preliminary findings from an observational study involving Olumiant. The review also included advice from an expert group of rheumatologists, dermatologists, gastroenterologists and patient representatives.
- These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.
- JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

Information to Healthcare Professionals

- An EMA review has found that, compared with TNF-alpha inhibitors, JAK inhibitors used to treat chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata) are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality.
- The review confirmed Xeljanz increases the risk of major cardiovascular problems, cancer, VTE, serious infections and death due to any cause when compared with medicines belonging to the class of TNF-alpha inhibitors. EMA has now concluded that these safety findings apply to all approved uses of JAK inhibitors in chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata). The review included the final results from an open-label clinical trial (ORAL Surveillance study)[2] of the JAK inhibitor Xeljanz (tofacitinib) in patients with rheumatoid arthritis and

[2] Ytterberg SR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *New Engl J Med* 2022;*3*86(4):316-326. doi: 10.1056/NEJMoa2109927

cardiovascular risk factors which found a higher risk of these events with Xeljanz than with TNF-alpha inhibitors.

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

- EMA concluded that the identified risks apply to all JAK inhibitors[3] approved for the treatment of chronic inflammatory disorders. These medicines should only be used in the following patients if no suitable treatment alternatives are available: those aged 65 years or above, those who are current or past long-time smokers, those with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or those with other malignancy risk factors. Cautious use is also recommended in patients with known risk factors for VTE other than those listed above.

- If JAK inhibitors[4] are needed in patients with these risk factors, a lower dose may be recommended, depending on the medicine, the indication and the specific risk factor. Healthcare professionals should discuss the risks associated with JAK inhibitors with their patients. It is recommended that healthcare professionals carry out periodic examinations of their patients' skin to check for skin cancer, particularly for patients at risk for skin cancer.

- A letter will be sent to all healthcare professionals expected to prescribe these medicines to inform them of the outcome of the review. Full treatment recommendations will be included in the updated summary of product characteristics and the educational material for the respective products.

Information to patients

- JAK inhibitors used to treat chronic inflammatory disorders have been found to increase the risk of major cardiovascular problems (such as heart attack or stroke), cancer, blood clots in the lungs and in deep veins, serious infections and death when compared with TNF alpha inhibitors.

- These JAK inhibitors are used to treat one or more of the following chronic inflammatory disorders: rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata.

- If you are aged 65 years or above, have an increased risk of major cardiovascular problems or cancer or if you smoke or have done so for a long time in the past, you should only be prescribed these medicines if there are no suitable treatment alternatives for you. If you have certain risk factors, your doctor may reduce the dose of your JAK inhibitor or switch

[3]Olumiant (baricitinib), and Xeljanz (tofacitinib)

treatment depending on your inflammatory disorder and the JAK inhibitor you are taking to treat it.

- If, at any stage during your treatment, you experience chest pain or tightness (which may spread to arms, jaw, neck and back), shortness of breath, cold sweat, light headedness, sudden dizziness, weakness in arms and legs or slurred speech, contact your doctor immediately. Examine your skin periodically and let your doctor know if you notice any new growths on the skin. If you have any questions about your treatment, speak to your doctor.

For more information, please see the European Medicines Agency's press release.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance with Janus kinase inhibitors[5]. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to: Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 **or** online to http://www.medicinesauthority.gov.mt/adrportal or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate

Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

[5]Olumiant (baricitinib), and Xeljanz (tofacitinib).

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health.

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

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Pharmacovigilance Section

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