EMA starts safety review of Janus kinase inhibitors for inflammatory disorders

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Information on Janus kinase inhibitors

- The Janus kinase 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 and atopic dermatitis).
- 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; at this stage the review will not include these medicines.

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 has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004.
- The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. The PRAC recommendations will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt an

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

opinion. The final stage of the review procedure is the adoption by the EC of a legally binding decision applicable in all EU Member States.

- The safety review pertains to Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, and atopic dermatitis).
- The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections, and blood clots in the lungs and in deep veins (venous thromboembolism, VTE).
- In addition, preliminary findings from an observational study involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.
- In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC will therefore carry out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders[2] and whether the marketing authorisations for these medicines should be amended.
- Some measures to minimise these risks are already in place for Xeljanz as result of a review finalised in 2020, which analysed the interim results of study A3921133. In addition, the product information for Xeljanz was further updated in 2021 to reflect the increased risk of major cardiovascular problems and cancer observed after the release of additional data from this study.

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

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

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance with Janus kinase inhibitors[3]. 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.

[3]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).

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