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XELJANZ▼ (tofacitinib): Restriction of 10 mg twice daily use in patients who are at high risk for pulmonary embolism

Dear Healthcare Professional,

Pfizer Europe in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

EMA is reviewing the benefits and risks of Xeljanz (tofacitinib) in all authorised indications following results from an ongoing clinical study, A3921133, which showed an increased risk of pulmonary embolism (PE) with the tofacitinib 10 mg twice daily dose. The following measures have been agreed until this review is finalised.

Summary

- **Tofacitinib 10 mg twice daily is contraindicated in patients who have one or more of the following conditions:**
  - **Use of combined hormonal contraceptives or hormone replacement therapy**
  - **Heart failure**
  - **Previous venous thromboembolism, either deep venous thrombosis or pulmonary embolism**
  - **Inherited coagulation disorder**
  - **Malignancy**
  - **Patients undergoing major surgery.**
- **Additional risk factors that should be considered in determining the patient's risk for pulmonary embolism are age, obesity, smoking status and immobilisation.**
- **Patients who are currently being treated with the 10 mg twice daily dose and who are at high risk for pulmonary embolism should be switched to alternative treatments.**

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- **Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of pulmonary embolism, and be advised to seek medical attention immediately if they experience them.**

Background on the safety concern

Tofacitinib is indicated for the treatment of adult patients with moderate to severe rheumatoid arthritis or active psoriatic arthritis at a recommended dose of 5 mg twice daily. Tofacitinib is also approved as a treatment for adult patients with moderately to severely active ulcerative colitis at a recommended dose of 10 mg given orally twice daily for induction for 8 weeks and thereafter at a dose of 5 mg twice daily for maintenance. For some patients, 10 mg twice daily dose for maintenance may be used. Please refer to section 4.2 of the SmPC for full posology information.

Study A3921133 is an open-label clinical trial to evaluate the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, compared with a TNF inhibitor therapy in patients with rheumatoid arthritis. The study was requested by regulatory agencies and designed to assess the risk of cardiovascular events with tofacitinib in patients 50 years of age or older who have at least one cardiovascular risk factor, e.g. current smoker, high blood pressure, high cholesterol levels, diabetes mellitus, history of heart attack, family history of coronary heart disease, extra-articular RA disease. Malignancy is also a co-primary endpoint. All patients entered the study on stable doses of background methotrexate.

On the basis of the preliminary review of the data in study A3921133 the overall incidence of pulmonary embolism per person-year in the tofacitinib 10 mg twice daily arm was more than 6-fold higher than in the TNF inhibitor therapy control arm and approximately 3-fold higher than observed in other studies across the tofacitinib program. Additionally, all-cause mortality in the 10 mg twice daily arm was higher than that in the tofacitinib 5mg twice daily and the TNF inhibitor therapy groups.

The preliminary results of the study showed that there were 19 cases of pulmonary embolism out of 3,884 patient-years in the tofacitinib 10 mg twice-daily arm of the study compared with 3 cases out of 3,982 in the TNF inhibitor arm. Additionally, there were 45 deaths from all causes out of 3,884 patient-years in the 10 mg twice daily arm compared with 25 cases out of 3,982 patient-years in the TNF inhibitor groups.

As indicated by the Data Safety Monitoring Board and approved by the regulatory agencies, the MAH has modified study A3921133 so that patients receiving tofacitinib 10 mg twice daily had their dose switched to tofacitinib 5 mg twice daily for the remaining duration of the study.

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Further evaluation of the data from study A3921133 and their potential impact on the product information of all currently approved indications of tofacitinib is currently ongoing in a formal EMA procedure.

The prescribers are reminded that they should adhere to the licensed dose of 5 mg twice daily for the treatment of rheumatoid arthritis and active psoriatic arthritis. Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of pulmonary embolism, and be advised to seek medical attention immediately if they experience them.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with Xeljanz▼ in accordance with the national spontaneous reporting system.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

You can assist us with monitoring the safety of Xeljanz by reporting suspected adverse reactions. Suspected adverse drug reactions (ADRs) should be reported to the Health Products Regulatory Authority (HPRA):

- Online Reporting via the HPRA Website www.hpra.ie
- Using downloadable form from the HPRA website. An adverse reaction report form can be downloaded from the HPRA Website. This can be sent by Freepost to the HPRA or by email to medsafety@hpra.ie.
- By telephoning the Pharmacovigilance Section of the HPRA, (01) 676 4971

Company contact point

For more information about Xeljanz, please contact Pfizer Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Tel: 1800 633 363 and ask for Medical Information.

XELJANZ EMEA/H/C/004214
Communication

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Annexes

For more information, please see the Xeljanz Summary of Product Characteristics at https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf

Sincerely,

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