Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24.
Telephone: 01-4676500 Facsimile: 01-4676501
Freephone: 1800-460-900
www.pfizer.ie

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XELJANZ▼ (tofacitinib): Increased risk of pulmonary embolism and mortality in rheumatoid arthritis patients receiving 10mg twice daily in a clinical trial

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:

Summary

- **An increased risk of pulmonary embolism (PE) and overall mortality has been reported in an ongoing clinical trial in patients with rheumatoid arthritis (RA) taking tofacitinib 10 mg twice daily. The study included RA patients >50 years of age with at least one additional cardiovascular risk factor.**

- **In this clinical trial, the overall incidence of PE was 5-fold higher in tofacitinib 10 mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib program.**

- **The 10 mg twice daily dose of tofacitinib is not approved for rheumatoid arthritis in the European Union.**

- **The prescribers should adhere to the authorised dose in the tofacitinib Summary of Product Characteristics (SmPC), which is 5 mg twice daily for RA indication.**

- **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 rheumatoid arthritis (RA) and psoriatic arthritis (PsA), with a recommended dose of 5 mg twice daily. Xeljanz is also approved as a treatment for ulcerative colitis (UC) with a recommended dose of 10 mg twice daily for the first 8 weeks and thereafter 5 mg twice daily.

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 tumor necrosis factor inhibitor (TNFi) in patients

Directors of Pfizer Healthcare Ireland:
J. Molony, Dr. D. O'Callaghan,
P. Reid (Managing), M. Riordan, M. Sheppard.
Company Secretary: M. Sheppard

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with RA. 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 additional 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. All patients entered the study on stable doses of background methotrexate.

On the basis of the preliminary review of the data in Study A3921133, an external data safety monitoring committee found a statistically and clinically important difference in the incidence of pulmonary embolism with the tofacitinib 10 mg twice daily treatment arm compared to the active TNFi control. The overall incidence per person-year in the tofacitinib 10 mg twice daily arm is more than 5-fold higher than the TNFi control arm and is approximately 3-fold higher than that observed in other studies across the tofacitinib program. Additionally, all-cause mortality in the 10 mg twice daily arm was higher compared to the tofacitinib 5mg twice daily and the TNFi groups.

The MAH is therefore modifying study A3921133, so that the patients receiving tofacitinib 10 mg BID will have their dose switched to tofacitinib 5 mg BID for the remaining duration of the study.

Further evaluation of the data from study A3921133 and their potential impact on the Product Information of all currently approved indications of Xeljanz in the EU is currently ongoing.

The prescribers are reminded that they should adhere to the licensed dose of 5 mg twice daily for the treatment of RA. 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.

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- 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.

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,

Tamas Koncz, MD, MSc, PhD
Chief Medical Officer, Inflammation and Immunology
Pfizer Inc.

Declan O'Callaghan
Country Medical Director, Ireland
Pfizer Healthcare Ireland

XELJANZ EMEA/H/C/004214
Communication

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