Direct Healthcare Professional Communication

21 November 2019

▼XELJANZ (tofacitinib): increased risk of venous thromboembolism and increased risk of serious and fatal infections

Dear Healthcare Professional,

Pfizer Europe in agreement with the European Medicines Agency and the Medicines Authority would like to inform you of the following:

Summary

- **A dose dependent increased risk of serious venous thromboembolism (VTE), including cases of pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT) is observed in patients taking tofacitinib.**
- **Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.**
- **Use of tofacitinib 10 mg twice daily for maintenance treatment in patients with ulcerative colitis (UC) who have known VTE risk factors is not recommended, unless there is no suitable alternative treatment available.**
- **For treatment of rheumatoid arthritis and psoriatic arthritis, the recommended dose of 5 mg twice daily should not be exceeded.**
- **Inform patients of the signs and symptoms of VTE before they start tofacitinib therapy and advise them to seek prompt medical help if they develop these symptoms during treatment.**
- **Patients over 65 years of age are at further increased risk of serious infections and mortality due to infections. Therefore, tofacitinib should only be considered in these patients if no suitable alternative treatment is available.**

Background on the safety concern

Tofacitinib is a JAK-inhibitor and indicated as treatment for

- adult patients with moderate to severe rheumatoid arthritis or active psoriatic arthritis in patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs.
- adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

In May 2019, following the preliminary analyses of the results from A3921133 study (see below), temporary measures with regards the use of tofacitinib in patients with VTE risk factors were introduced and communicated to healthcare professionals in writing. Following the finalisation of a formal review procedure these temporary measures are being replaced with updated recommendations, as specified in the "summary" above.

The product information of Xeljanz and the educational materials for healthcare professional and patients will be updated accordingly.

Long-term safety study A3921133 in patients with rheumatoid arthritis

This is an ongoing open-label clinical trial (N=4,362) to evaluate the cardiovascular safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, compared with a TNF inhibitor therapy in patients with rheumatoid arthritis who were 50 years of age or older and with at least one cardiovascular risk factor.

After the interim results, study treatment with tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a signal of VTE and all-cause mortality.

Venous thromboembolism (PE and DVT)

In the interim analysis, an increased and dose-dependent incidence of VTE was observed in patients treated with tofacitinib as compared to TNF inhibitors. The incidence rates (95%CI) for PE for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.54 (0.32 – 0.87), 0.27 (0.12 – 0.52), and 0.09 (0.02 – 0.26) patients with events per 100 patient-years, respectively. The hazard ratio (HR) for PE with tofacitinib was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily respectively. The incidence rates (95%CI) for DVT for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.38 (0.20 – 0.67), 0.30 (0.14 – 0.55), and 0.18 (0.07 – 0.39) patients with events per 100 patient-years, respectively. The HR for DVT with tofacitinib 10mg twice daily was 2.13 (0.80-5.69) and for 5 mg twice daily the HR was 1.66 (0.60-4.57), compared with TNF-inhibitors.

In a subgroup analysis in patients with VTE risk factors in study A3921133, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) and 3.92 (0.83-18.48) for 10 mg twice daily and 5 mg tofacitinib twice daily respectively.

Mortality

In the interim analysis of study A3921133, increased mortality within 28 days of last treatment was observed in patients treated with tofacitinib compared to TNF-inhibitors. The incidence rates (95%CI) were 0.89 (0.59 – 1.29) for tofacitinib 10 mg twice daily, 0.57 (0.34 – 0.89) for tofacitinib 5 mg twice daily, and 0.27 (0.12 – 0.51) for TNF-inhibitors; with a HR (95%CI) of 3.28 (1.55 – 6.95) for 10 mg twice daily and of 2.11 (0.96 – 4.67) for 5 mg twice daily, versus TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

For cardiovascular mortality within 28 days of last treatment, the incidence rates (95%CI) per 100 patients-years were 0.45 (0.24-0.75) for tofacitinib 10 mg twice daily, 0.24 (0.10-0.47) for tofacitinib 5 mg twice daily, and 0.21 (0.08-0.43) for TNF inhibitors; with an incidence rate ratio (IRR) (95%CI) of 2.12 (0.80 – 6.20) for 10 mg twice daily and of 1.14 (0.36 – 3.70) for 5 mg twice daily, versus TNF inhibitors.

For fatal infections within 28 days of last treatment, mortality rates per 100 patient-years were 0.22 (0.09-0.46), 0.18 (0.07-0.39), and 0.06 (0.01-0.22) for tofacitinib 10 mg twice daily and 5

mg twice daily, and TNF-inhibitors, respectively, with an IRR of 3.70 (0.71 – 36.5) for 10 mg twice daily and 3.00 (0.54 – 30.4) for 5 mg twice daily, versus TNF-inhibitors.

Serious infections

For non-fatal serious infections, the incidence rates per 100 patients-years were 3.51 (2.93 - 4.16), 3.35 (2.78 - 4.01), and 2.79 (2.28 - 3.39), for tofacitinib 10 mg twice daily and 5 mg twice daily, and TNF inhibitors, respectively. In this study, which enrolled patients > 50 years and with CV risk factors, the risk of serious infections and fatal infections was further increased in elderly patients above 65 years of age, as compared to younger patients.

Patient with ulcerative colitis (UC) and VTE

In the UC ongoing extension trial, cases of PE and DVT have been observed in patients using tofacitinib 10 mg twice daily and with underlying VTE risk factor(s).

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. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent to ADR reporting/Post-Licensing Directorate/Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann, Malta, or sent by email to: Postlicensing.medicinesauthority@gov.mt

▼ 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.

Company contact point

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