Xeljanz: the EMA confirms to use the medicine cautiously in patients at high risk of blood clots

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Information on Xeljanz

- Xeljanz (tofacitinib) is authorised to treat adults with moderate to severe rheumatoid arthritis (a disease that causes inflammation of the joints), psoriatic arthritis (red, scaly patches on the skin with inflammation of the joints) and severe ulcerative colitis (a disease-causing inflammation and ulcers in the lining of the gut)
- Tofacitinib is the active substance in Xeljanz which acts by blocking the action of enzymes known as Janus kinases. In the process of inflammation that occurs in rheumatoid, psoriatic arthritis and ulcerative colitis, these enzymes play an important role. Blocking the enzymes' action, tofacitinib helps to reduce the inflammation and other symptoms of these diseases.

In Malta Xeljanz is authorised through a centralised procedure.

Information from the EMA about use of Xeljanz in patients at risk of blood clots

Results from the review carried out by the Pharmacovigilance Risk Assessment Committee (PRAC) show that Xeljanz (tofacitinib) could increase the risk of blood clots in the lungs and in deep veins in patients who are already at high risk.

The review concerned the ongoing study A3921133 carried out on patients with rheumatoid arthritis and an increased risk of cardiovascular disease, in addition to data from earlier studies and consultation with experts in the field. Results showed that patients treated with Xeljanz had a higher risk to develop blood clots in deep veins and lungs, especially when taking the recommended dose of 10 mg twice daily, and in those being treated for an extended period. All the data in patients older than 65 years of age also showed a further increased risk of serious and fatal infections.

Following the review, EMA's recommendations are:

- Xeljanz is to be used cautiously in patients with existing risk of blood clots
- The dose of 10 mg twice daily should not be used in patients with ulcerative colitis who are at high risk of blood clots unless there is no suitable alternative treatment
- For patients older than 65 years of age Xeljanz should be only used if no other treatment option is available due to increased risk of infections.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

In Malta

For Healthcare Professionals

- An EMA review in patients taking Xeljanz (tofacitinib), has found a dose-dependent increased risk of serious venous thromboembolism (VTE), including pulmonary embolism (PE) (some cases of which were fatal) and deep vein thrombosis
- Reviewed data comes from study A3921133, an ongoing open-label clinical trial evaluating the safety of Xeljanz (tofacitinib) 5 mg twice daily and Xeljanz (tofacitinib) 10 mg twice daily compared with a tumour necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. The age of the patient in the study was 50 years old or older, with at least one additional cardiovascular risk factor. After the interim results became available and due to a signal of PE and all-cause mortality, treatment with Xeljanz (tofacitinib) 10 mg twice daily was stopped and patients were switched to 5 mg twice daily. Additional data from earlier studies was also considered
- The review carried out on the study A3921133 showed that compared to treatment with a TNF inhibitor, Xeljanz (tofacitinib) 5 mg twice daily increased the risk of PE about 3-fold while Xeljanz (tofacitinib) 10 mg twice daily increased the risk roughly 6-fold
- Out of 3,123 patient-years in the Xeljanz (tofacitinib) 10 mg twice daily arm, 17 cases of PE were found and out of 3,317 patient-years in the Xeljanz (tofacitinib) 5 mg twice daily arm, 9 cases of PE were found. This result was compared with the TNF inhibitor arm, where out of 3,319 patient-years, 3 cases of PE were found. In addition, there were 28 deaths from all causes out of 3140 patient-years in the Xeljanz (tofacitinib) 10 mg twice daily arm and 19 deaths from all causes out of 3,324 patient-years in the Xeljanz (tofacitinib) 5 mg twice daily arm compared with 9 cases out of 3323 patient-years in the TNF inhibitor arm
- As a result, caution in the use of Xeljanz (tofacitinib) is recommended in patients at a high risk of blood clots, regardless of indication and dosage, including patients who have had a heart attack or have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, are undergoing major surgery or are immobile
- Age, diabetes, obesity (BMI>30), smoking status and hypertension, are other risk factors to be considered when prescribing Xeljanz (tofacitinib)
- In patient with ulcerative colitis who have known VTE risk, the treatment of Xeljanz (tofacitinib) 10 mg twice daily for maintenance is not recommended
- The recommended dose of 5 mg of Xeljanz (tofacitinib) twice daily for the treatment of rheumatoid arthritis and psoriatic arthritis should not be exceeded
- Patients should be informed about signs and symptoms of VTE before receiving Xeljanz (tofacitinib) and be advised to seek medical help immediately if they develop these symptoms during treatment
- Available data in patients older than 65 years of age also showed a further increased risk of serious and fatal infections. Therefore, Xeljanz (tofacitinib) should only be considered in these patients if no suitable alternative treatment is available

A DHPC letter with the updated information of the treatment recommendation will be disseminated to HCPs in Malta. Archived DHPC letters are available online at http://www.medicinesauthority.gov.mt/dhpc.

A physician's guide and a patient alert card will be updated with advice to minimise the risk of blood clots.

Information for Patients

- In patients who are already at high risk, Xeljanz (tofacitinib) could increase the risk of blood clots
- Your treatment will be reviewed by your doctor to check if it remains appropriate or it is necessary to modify it
- You may be at high risk of blood clots in the lungs and in deep veins if:
  - You have had a heart attack or have heart failure, cancer, inherited blood clotting disorder or a history of blood clots
  - You are taking combined hormonal contraceptives or hormone replacement therapy, will have or have recently had major surgery or are immobilised
- Your doctor will also consider your age, obesity (your body mass index is above 30), presence of diabetes, blood pressure, or smoking habit, to evaluate your risk
- If you are at high risk or older than 65 years of age, and there is an alternative treatment for you, your doctor may switch your treatment
- You should not change the dose or stop taking Xeljanz (tofacitinib) without discussing it with your doctor
- If you develop sudden shortness of breath or difficulty in breathing, chest pain or pain in your upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm, you should ask for medical attention immediately. These may be symptoms of a blood clot in your lungs or veins
- If you have any questions or concerns about your treatment, you should discuss with a healthcare professional.

For more information, visit the European Medicines Agency's Xeljanz referral page

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Xeljanz (tofacitinib). 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.

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 formt (address side up), stapling the ends and then posting (no stamp required)

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Pharmacovigilance Section

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