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EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots

EMA has concluded 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.

As a result, the Agency is recommending that Xeljanz should be used with caution in all patients at high risk of blood clots. In addition, the maintenance doses 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. Further, EMA is recommending that, due to an increased risk of infections, patients older than 65 years of age should be treated with Xeljanz only when there is no alternative treatment.

These recommendations follow the Agency's review of an ongoing study (study A3921133) in patients with rheumatoid arthritis and an increased risk of cardiovascular disease, plus data from earlier studies and consultation with experts in the field. All data combined showed that the risk of blood clots in deep veins and lungs was higher in patients taking Xeljanz, especially the 10 mg twice daily dose, and in those being treated for an extended period. Results also showed a further increased risk of serious and fatal infections in patients older than 65 years of age.

The recommendations were issued by the [EMA's safety committee \(PRAC\)](#) and have now been endorsed by the Agency's human medicines committee (CHMP). They will replace the measures put in place at the start of the review in May 2019. The changes come into force when the European Commission issues its decision.

Information for patients

- Xeljanz could increase the risk of blood clots in patients who are already at high risk.
- If you are being treated with Xeljanz your doctor will review your risk of blood clots and modify your treatment if necessary.
- 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 may also be at risk if you are taking combined hormonal contraceptives or hormone replacement therapy, will have or have recently had major surgery or are immobilised.
- To evaluate the risk your doctor will also consider your age, whether you are obese (your body mass index is above 30), have diabetes, have elevated blood pressure, or smoke.

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- If you are at high risk or older than 65 years of age, your doctor may switch your treatment if there is an alternative treatment for you.
- If you are being treated with Xeljanz, you should not change the dose or stop taking the medicine without discussing it with your doctor.
- Ask for medical attention immediately 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. These may be symptoms of a blood clot in your lungs or veins.
- If you have any concerns about your medicine, you should discuss them with a healthcare professional.

Information for healthcare professionals

- An EMA review 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 in patients taking tofacitinib.
- The review considered data from study A3921133, an ongoing open-label clinical trial evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily compared with a tumour necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. Patients in the study are 50 years of age or older with at least one additional cardiovascular risk factor. After the interim results became available, treatment with tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a signal of PE and all-cause mortality. The review also considered additional data from earlier studies.
- The review of study A3921133 showed that compared to treatment with a TNF inhibitor, tofacitinib 5 mg twice daily increased the risk of PE about 3-fold while tofacitinib 10 mg twice daily increased the risk roughly 6-fold.
- In total there were 17 cases of PE out of 3,123 patient-years with the tofacitinib 10 mg twice daily dose and 9 cases of PE out of 3,317 patient-years with the tofacitinib 5 mg twice daily dose compared with 3 cases out of 3,319 patient-years with a TNF inhibitor. Additionally, there were 28 deaths from all causes out of 3140 patient-years in the tofacitinib 10 mg twice daily arm and 19 deaths from all causes out of 3,324 patient-years in the tofacitinib 5 mg twice daily arm compared with 9 cases out of 3323 patient-years in the TNF inhibitor arm.
- As a result, tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. This includes 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.
- Other risk factors to be considered when prescribing tofacitinib include age, diabetes, obesity (BMI>30), smoking status and hypertension.
- The use of tofacitinib 10 mg twice daily for maintenance treatment in patients with ulcerative colitis 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.

- Patients should be informed about the signs and symptoms of VTE before receiving tofacitinib and be advised to seek prompt medical help if they develop these symptoms during treatment.
- Available data also showed that the risk of serious infections and fatal infections was further increased in elderly patients above 65 years of age, as compared to younger patients. Therefore, tofacitinib should only be considered in these patients if no suitable alternative treatment is available.
- A letter will be sent to all healthcare professionals expected to prescribe the medicine to inform them of the updated treatment recommendations. The physician's guide and the patient alert card will be updated with advice to minimise the risk of blood clots.

More about the medicines

Xeljanz (tofacitinib) was first authorised in the EU on 22 March 2017 to treat adults with moderate to severe rheumatoid arthritis (a disease that causes inflammation of the joints). In 2018, its use was extended to treat adults with 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). The active substance in Xeljanz, tofacitinib, works by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the process of inflammation that occurs in rheumatoid, psoriatic arthritis and ulcerative colitis. By blocking the enzymes' action, tofacitinib helps reduce the inflammation and other symptoms of these diseases.

Further information about the medicine can be found on the [EMA website](#)

More about the procedure

The review of Xeljanz was initiated on 15 May 2019 at the request of the European Commission, under [Article 20 of Regulation \(EC\) No 726/2004](#).

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which has adopted the Agency's opinion. 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.