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Increased risk of blood clots in lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis

EMA is advising healthcare professionals and patients not to exceed the recommended dose of Xeljanz (tofacitinib) when treating rheumatoid arthritis. The advice follows early results from an ongoing study (study A3921133) in patients with rheumatoid arthritis which showed an increased risk of blood clots in the lungs and death when the normal dose of 5 mg twice daily was doubled.

In the EU, 5 mg twice daily is the authorised dose for rheumatoid arthritis and psoriatic arthritis. The higher dose of 10 mg twice daily is approved for the initial treatment of patients with ulcerative colitis.

EMA is assessing the early results and will consider if any regulatory action is needed. In the meantime, patients with rheumatoid arthritis who are receiving Xeljanz at 10 mg twice daily in study A3921133 will have their dose reduced to 5 mg twice daily for the remaining duration of the study.

The aim of the study was to look at the risks of heart and circulatory problems with Xeljanz in patients 50 years of age or older who were already at higher risk of these, and to compare its safety with that of another medicine called a TNF inhibitor.

While full results are awaited, EMA is recommending that healthcare professionals monitor patients for signs and symptoms of blood clots in the lungs. Patients should not stop or change their dose of Xeljanz without talking to their doctor. Patients should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back and coughing up blood.

Healthcare professionals are being informed in writing of the preliminary results of the study and the current treatment recommendations.

There are other ongoing clinical trials in the EU with Xeljanz at a dose of 10 mg twice daily. Patients taking part in clinical trials with Xeljanz should speak to the doctor giving it to them if they have any questions or concerns.

Information for patients

- A new ongoing study in patients with rheumatoid arthritis showed that when Xeljanz was given at a high dose of 10 mg twice daily there was an increased risk of dangerous blood clots in the lungs and death.

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- This dose is higher than the approved dose of 5 mg twice daily for rheumatoid arthritis.
- If you are being treated with Xeljanz, you should not change the dose or stop taking the medicine without discussing it with your doctor.
- You should seek medical attention immediately if you experience the following symptoms which may be signs of a blood clot in your lungs: difficulty breathing, chest pain or pain in your upper back, coughing up blood, excessive sweating and bluish skin.
- If you have any concerns about your medicine, you should discuss them with a healthcare professional.

Information for healthcare professionals

- An increased risk of pulmonary embolism and overall mortality has been seen in a study with tofacitinib 10 mg twice daily in rheumatoid arthritis.
- These results come 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.
- The preliminary results of the study showed the overall incidence of pulmonary embolism to be 5-fold higher in the 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. Additionally, all-cause mortality in the 10 mg twice daily arm was higher compared with the tofacitinib 5 mg twice daily and the TNF inhibitor groups.
- As a consequence, patients receiving tofacitinib 10 mg twice daily in study A3921133 will have their dose reduced to 5 mg twice daily for the remaining duration of the study.
- While further assessment of the study results continues, prescribers should continue to adhere to the authorised dose of 5 mg twice daily for the treatment of rheumatoid 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.
- A letter is being sent to all healthcare professionals expected to prescribe the medicine to inform them of the preliminary results of the study and the current treatment recommendations.

More about the medicine

Xeljanz is authorised to treat adults with moderate to severe rheumatoid arthritis (a disease that causes inflammation of the joints) and psoriatic arthritis (red, scaly patches on the skin with inflammation of the joints). In these indications, Xeljanz is used together with methotrexate after treatment with one or more medicines known as disease-modifying anti-rheumatic drugs (DMARDs) has not worked well enough or has led to troublesome side effects.

In patients with rheumatoid arthritis, Xeljanz can also be used alone in patients who cannot take or are intolerant to methotrexate.

Xeljanz is also authorised to treat adults with moderate to severe ulcerative colitis (a disease causing inflammation and ulcers in the lining of the gut), after treatment with other medicines has not worked well, has stopped working or has led to troublesome side effects.

Further information about the medicine can be found on the EMA website: ema.europa.eu/medicines/human/EPAR/xeljanz.

More about the procedure

This review of Xeljanz is being carried out in the context of a safety signal. A safety signal is information on a new or incompletely known adverse event that is potentially caused by a medicine and that warrants further investigation.

The review is carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines.

Since Xeljanz is a centrally authorised medicine, any PRAC recommendations for regulatory action (e.g. amendment of the product information) will be submitted to EMA's Committee for Medicinal Products for Human Use (CHMP) for endorsement.