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Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs

EMA's safety committee (PRAC) is recommending that doctors must not prescribe the 10 mg twice daily dose of Xeljanz (tofacitinib) in patients who are at high risk of blood clots in the lungs. These include patients who have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients who take combined hormonal contraceptives, are receiving hormone replacement therapy or are undergoing major surgery.

In addition, doctors should consider other factors that may increase the risk of blood clots in the lungs including age, obesity, smoking or immobilisation.

Xeljanz is currently authorised for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis.

The PRAC's recommendation follows results from an ongoing study (study A3921133) in patients with rheumatoid arthritis. This study showed an increased risk of blood clots in the lungs and death when the 10 mg twice daily dose was used, which is double the recommended dose for rheumatoid arthritis.

The new advice means that, since 10 mg is the only recommended starting dose for ulcerative colitis, patients with this condition who are at high risk of blood clots must not be started on Xeljanz. Patients at high risk currently taking this dose for any condition must be switched to alternative treatments.

Patients should not stop or change their dose of Xeljanz without talking to their doctor. They should seek medical attention immediately if they experience symptoms such as difficulty breathing, pain in the chest or upper back and coughing up blood, which could indicate the presence of a blood clot in the lungs.

The new recommendations are temporary and follow previous PRAC advice not to exceed the recommended 5 mg twice daily dose when treating rheumatoid arthritis. The PRAC will now carry out a review of all available evidence, and updated guidance will be provided to patients and healthcare professionals once the review is concluded.

Information for patients

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

[1] Update to correct the number of patient-years for the 10 mg twice daily arm of the Xeljanz study.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

- This dose is higher than the approved dose of 5 mg twice daily for rheumatoid arthritis. However, this dose is used for the initial treatment of patients with ulcerative colitis (for up to 16 weeks) and may also be used in some patients when continuing treatment.
- While an in-depth review of Xeljanz is ongoing, if you are being treated with Xeljanz 10 mg twice daily and you are at high risk of blood clots in the lungs, your doctor may switch you to an alternative treatment.
- You may be at high risk of blood clots in the lungs if you:
  - have heart failure (when the heart does not work as well as it should)
  - have inherited blood clotting disorders
  - have had blood clots in the veins
  - are taking combined hormonal contraceptives or hormone replacement therapy
  - have cancer
  - will have or have recently had major surgery.
- Your doctor will also take into account your age, whether you are obese (your body mass index is above 30), smoke or are immobilised when evaluating your risk of blood clots.
- 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 observed 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 that there were 19 cases of pulmonary embolism out of 3,884 patient-years in the tofacitinib 10 mg twice daily arm of the study compared with 3 cases out of 3,982 in the TNF inhibitor arm. Additionally, there were 45 deaths from all causes out of 3,884 patient-years in the 10 mg twice daily arm compared with 25 cases out of 3,982 patient-years in the TNF inhibitor group.
- While an in-depth review of these risks is ongoing, doctors must not prescribe the 10 mg twice daily dose in patients:
  - with heart failure
  - with inherited coagulation disorders

  - who have had venous thromboembolism, either deep venous thrombosis or pulmonary embolism
  - who use combined hormonal contraceptives or hormone replacement therapy
  - with malignancy
  - who are undergoing major surgery.
- Additionally, other risk factors to be considered when prescribing tofacitinib 10 mg twice daily include age, obesity (BMI>30), smoking and immobilisation.
- Patients who are already treated with the 10 mg twice daily dose and are at high risk of pulmonary embolism should be switched to alternative treatments.
- 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 and psoriatic 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 temporary treatment recommendations.

More about the medicine

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: ema.europa.eu/medicines/human/EPAR/xeljanz.

More about the procedure

This review of Xeljanz has been initiated at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004. It follows a previous review of Xeljanz, which had been carried out in the context of a safety signal.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. The PRAC recommendations will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human

use, which will adopt an opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.