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**Questions and answers**

# Refusal of the marketing authorisation for Xeljanz (tofacitinib)

On 25 April 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Xeljanz, intended for the treatment of rheumatoid arthritis.

The company that applied for authorisation is Pfizer Limited. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

## What is Xeljanz?

Xeljanz is a medicine that contains the active substance tofacitinib. It was to be available as tablets (5 and 10 mg).

## What was Xeljanz expected to be used for?

Xeljanz was expected to be used in the treatment of moderate to severe active rheumatoid arthritis (an immune system disease causing damage and inflammation in the joints). It was to be used in patients in whom treatment with at least two other medicines known as disease-modifying antirheumatic drugs (DMARDs), including so-called biological DMARDs[1], had been unsuccessful either because patients were unable to tolerate treatment due to side effects, or because they did not respond adequately.

## How is Xeljanz expected to work?

The active substance in Xeljanz, tofacitinib, is an immunosuppressant (a medicine that reduces the activity of the immune system) that works by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the process of inflammation and damage of the joints that

[1] Biological DMARDs are medicines that target specific proteins in the immune system. They are produced by a method known as 'recombinant DNA technology': they are made by cells that have received a gene (DNA) that makes them able to produce the medicine.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

occurs in rheumatoid arthritis. By blocking the enzymes, tofacitinib is expected to reduce the inflammation and other symptoms of the disease.

## What did the company present to support its application?

The effects of Xeljanz were first tested in experimental models before being studied in humans.

The company presented the results of five main studies of safety and effectiveness involving over 3,300 patients with rheumatoid arthritis. These studies compared Xeljanz (in a dose of 5 or 10 mg twice daily) with placebo (a dummy treatment), either alone or as an addition to other background medicines (DMARDs). The main measures of effectiveness were changes in patient scores for signs and symptoms of disease, physical function of the patient, structural damage to joints and disease activity; these were measured after 3 or 6 months, depending on the study.

## What were the CHMP's main concerns that led to the refusal?

The Committee considered that, taken together, the data from the five main studies showed that treatment with Xeljanz resulted in an improvement in the signs and symptoms of rheumatoid arthritis and the physical function of patients. However, the studies were not sufficient to show a consistent reduction in disease activity and structural damage to joints, particularly at the lower 5-mg dose of Xeljanz and in the target population of patients in whom treatment with at least two other DMARDs has been unsuccessful.

The CHMP had major concerns about the overall safety profile of Xeljanz. There were significant and unresolved concerns about the risk and type of serious infections seen with tofacitinib, which are related to the immunosuppressant action of the medicine.

These safety concerns also included an increased risk of other severe side effects including certain cancers, gastro-intestinal perforations (holes in the wall of the gut), liver damage and problems with increased lipid (fat) levels in the blood. It was not clear that these risks could be managed successfully in medical practice. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Xeljanz did not outweigh its risks and recommended that it be refused marketing authorisation.

## What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that patients receiving tofacitinib in clinical trials will continue to receive it as planned. The company will consider future requests for compassionate use on an individual basis in accordance with local regulations.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.