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Withdrawal of application to change the marketing authorisation for Orencia (*abatacept*)

Bristol-Myers Squibb Pharma EEIG withdrew its application for the use of Orencia in the prevention of acute (sudden) graft-versus-host disease (when transplanted cells attack the body).

The company withdrew the application on 19 February 2024.

What is Orencia and what is it used for?

Orencia is a medicine that is often used in combination with methotrexate (a medicine that acts on the immune system) to treat inflammatory conditions including:

- rheumatoid arthritis (an immune system disease causing damage and inflammation in the joints) and psoriatic arthritis (arthritis combined with psoriasis, a condition causing red, scaly patches on the skin) in adults;
- polyarticular juvenile idiopathic arthritis (a rare childhood disease causing inflammation of many joints) in children.

Orencia has been authorised in the EU since May 2007. It contains the active substance abatacept and is available as a powder that is made up into a solution for infusion (drip) given into a vein and as a solution for injection, in both pre-filled syringes and pre-filled pens, given under the skin.

Further information on Orencia's current uses can be found on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/orencia

What change had the company applied for?

The company applied to extend the use of Orencia for the prevention of acute graft-versus-host disease in adults and children from 2 years of age with cancers that affect blood cells. Orencia was intended to be used with methotrexate and a calcineurin inhibitor (a medicine that suppresses the activity of the immune system) in patients undergoing haematopoietic stem cell transplantation (HSCT; a procedure where the patient's bone marrow is replaced by cells from a donor to form new bone marrow that produces healthy blood cells), with an unrelated donor who is fully or almost fully matched with respect to their Human Leukocyte Antigen (HLA) gene alleles (8/8 or 7/8 matched for the 8 alleles at the HLA -A, -B, and -DRB1 loci). HLA gene alleles are different variations of genes that provide instructions for making proteins on the surface of cells that play a role in the immune system's

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

ability to distinguish between self and non-self cells. Acute graft-versus-host disease is a complication that may occur soon after HSCT when certain cells, known as T cells (cells of the immune system involved in inflammation), from the donor's transplant recognise the patient's body as foreign and attack the patient's organs.

How does Orencia work?

The active substance in Orencia, abatacept, is a protein that suppresses the activation of T cells. T cells are immune system cells that are involved in causing the inflammation in rheumatoid, psoriatic and polyarticular juvenile idiopathic arthritis. T cells are activated when signal molecules attach to receptors on the cells. By attaching to signal molecules called CD80 and CD86, abatacept stops them activating the T cells, helping to reduce the inflammation and other symptoms of the rheumatoid, psoriatic and polyarticular juvenile idiopathic arthritis. In the prevention of acute graft-versus-host disease, Orencia is expected to work in the same way as it does in its existing uses.

What did the company present to support its application?

The company submitted data from a main study involving 186 patients, aged from 6 years and weighing at least 20 kilograms, with blood cancers who were undergoing HSCT from an unrelated donor. Patients within the study were divided into two groups; those who were fully matched with their donor (142 patients) and those who were almost fully matched (44 patients). Within the group who were fully matched with their donor, Orencia was compared with placebo (a dummy treatment), both given with methotrexate and a calcineurin inhibitor. In the group who were almost fully matched with their donor, Orencia, given with methotrexate and a calcineurin inhibitor, was not compared with placebo or another medicine. The study looked at the proportion of patients who did not experience severe, acute graft-versus-host disease and were still alive up to 180 days after the HSCT.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the European Medicines Agency had evaluated the information from the company and had prepared questions for the company. After the Agency had assessed the company's responses to the questions, there were still some unresolved issues.

What did the Agency recommend at that time?

Based on the review of the information and the company's response to the Agency's questions, at the time of the withdrawal, the Agency had some concerns, and its provisional opinion was that Orencia could not have been authorised for the prevention of acute graft-versus-host-disease.

The main study did not show that Orencia prevented severe, acute graft-versus host disease. Although there appeared to be an initial benefit, this decreased over time. Furthermore, there were uncertainties about whether Orencia may have a negative effect on the risk of chronic (long-term) graft-versus-host disease compared with placebo. In addition, there were uncertainties regarding the long-term effectiveness of Orencia in preventing graft-versus-host disease due to the limited follow-up of patients in the main study (i.e. after 180 days).

Therefore, at the time of the withdrawal, the Agency's opinion was that the benefits of Orencia in the prevention of acute graft-versus-host-disease did not outweigh its risks.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of application, the company stated that it withdrew its application based on the Agency's considerations that uncertainties concerning the effectiveness of Orencia for the prevention of acute graft-versus-host disease did not allow it to conclude that the benefits of the medicine outweigh its risks for this use.

Does this withdrawal affect patients in clinical trials?

The company informed the Agency that there are no consequences for patients in clinical trials using Orencia.

If you are in a clinical trial and need more information about your treatment, speak with your clinical trial doctor.

What is happening with Orencia for the treatment of other diseases?

There are no consequences on the use of Orencia in its authorised uses.