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Questions and answers

Withdrawal of the application for a change to the marketing authorisation for Tysabri (natalizumab)

On 14 May 2013, Elan Pharma International Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw an application to extend the use (indication) of Tysabri in treating multiple sclerosis. The application was for the treatment of relapsing-remitting multiple sclerosis that is not highly active in patients who do not have antibodies against the JC virus.

The withdrawn application was part of a grouped application which included another extension of indication (to include patients with high disease activity after glatiramer acetate has failed). This other extension applied for is not affected by the withdrawal.

What is Tysabri?

Tysabri is a medicine that contains the active substance natalizumab. It is already used to treat highly active relapsing-remitting multiple sclerosis (MS). MS is a disease in which inflammation destroys the protective sheath around the nerves. 'Relapsing-remitting' means that the patient has flare-ups of symptoms (relapses) followed by periods of recovery (remissions). Tysabri is used when the disease has failed to respond to a beta-interferon (another type of medicine used in MS), or is severe and getting worse rapidly.

Tysabri is available as a concentrate that is made up into a solution for infusion (drip) into a vein. It has been authorised since June 2006.

What was Tysabri expected to be used for?

Tysabri was also expected to be used to treat patients with MS that is not highly active and who do not have antibodies against the JC virus in their blood.

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The JC virus is commonly present in the general population but it can lead to a severe brain infection known as progressive multifocal leukoencephalopathy (PML) in patients whose immune system is weakened. As Tysabri is known to reduce the activity of the immune system, its use in non-highly active MS was only for patients who do not have the JC virus in the blood and this was to be determined by testing for antibodies against the virus (antibodies will be present in patients who have or have recently had the virus).

How is Tysabri expected to work?

In the new indication, Tysabri is expected to work in the same way as it does in its existing indications.

The active substance in Tysabri, natalizumab, is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a specific part of a protein called 'integrin'. Integrins are found on the surface of most leucocytes (the white cells in the blood that are involved in the inflammation process). By blocking the integrin, natalizumab stops the leucocytes from going from the blood into the brain. This reduces the inflammation and nerve damage caused by MS.

What did the company present to support its application?

The company presented data from one of the main studies that were submitted for the initial authorisation of the medicine in 2006. The study involved over 900 patients with mild to moderate disease activity and compared Tysabri with placebo (a dummy treatment). The main measures of effectiveness were based on the reduction in the number of relapses and changes in the patients' levels of disability.

The company also presented additional data from patients who did not have antibodies against the JC virus, which were used to evaluate the risk of PML in this population.

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

The application was withdrawn after the CHMP had evaluated the initial documentation provided by the company and formulated a list of questions. The CHMP was assessing the company's responses to the questions at the time of the withdrawal.

What was the recommendation of the CHMP at that time?

Based on the review of the data and the company's response to the CHMP list of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Tysabri could not be approved for treating patients with relapsing-remitting multiple sclerosis that is not highly active and who do not have antibodies against the JC virus.

Although the medicine has been shown to significantly reduce relapse rates and to slow down the worsening of disability, there were concerns about its use in patients whose disease is not highly active. There is a risk of over-treating patients with benign forms of MS who rarely develop a more severe disease and in these patients the risks with Tysabri may outweigh the benefits. With regard to the risk of PML, the Committee noted that a patient's JC virus antibody status could change over time or be incorrectly shown to be negative. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the balance of the medicine's benefits and risks in the new indication needed to be further clarified.

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 the application because the additional data it had to address the CHMP's questions were still provisional. The company expressed a wish to discuss the additional data for a future application.

The withdrawal letter is available here.

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

The company informed the CHMP that this withdrawal has no impact on patients participating in clinical trial or compassionate use programmess.

The full European Public Assessment Report for Tysabri can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.