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**QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE
MARKETING AUTHORISATION
for
NATALIZUMAB ELAN PHARMA 300 MG**

International non-proprietary name (INN): ***natalizumab***

On 19 July 2007, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Natalizumab Elan Pharma 300 mg concentrate for solution for infusion, intended for the treatment of Crohn's disease. The company that applied for authorisation is Elan Pharma International Ltd. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Natalizumab Elan Pharma 300 mg?

Natalizumab Elan Pharma 300 mg is a concentrated solution that is diluted to make a solution for infusion (drip into a vein). It contains the active substance natalizumab.

What was Natalizumab Elan Pharma 300 mg expected to be used for?

Natalizumab Elan Pharma 300 mg was expected to be used to treat moderate to severe, active Crohn's disease, a disease causing inflammation of the gut. It was to be used in patients who had an inadequate response to or could not take conventional treatments for the disease, and who have evidence of active inflammation. It was to be used alone, or in combination with other medicines for Crohn's disease.

How is Natalizumab Elan Pharma 300 mg expected to work?

The active substance in Natalizumab Elan Pharma 300 mg, natalizumab, is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and bind to a specific structure (called an antigen) that is found on certain cells in the body. Natalizumab has been designed to bind to specific types of integrin ($\alpha 4 \beta 1$ and $\alpha 4 \beta 7$ integrins), proteins found on the surface of most leucocytes (the white cells in the blood that are involved in the inflammation process). By blocking the $\alpha 4 \beta 7$ integrin, natalizumab was expected to prevent the leucocytes from attaching to the surface of cells within the gut. This was expected to prevent them from moving from the bloodstream into the gut wall, reducing the inflammation in the gut and improving the symptoms of Crohn's disease.

The active substance in Natalizumab Elan Pharma 300 mg, natalizumab, has been available in the European Union for the treatment of multiple sclerosis since 2006 as TYSABRI.

What documentation did the company present to support its application to the CHMP?

The effects of Natalizumab Elan Pharma 300 mg were first tested in experimental models before being studied in humans.

The effects of Natalizumab Elan Pharma 300 mg were tested in two main studies involving a total of 905 patients with moderate to severe Crohn's disease. The first study compared the effects of starting treatment with Natalizumab Elan Pharma 300 mg with that of placebo (a dummy treatment) in all 905 patients. The main measure of effectiveness was the proportion of patients whose symptoms improved after 10 weeks.

The 354 patients who responded to treatment with Natalizumab Elan Pharma 300 mg then went on to enter the second study, in which the effects of Natalizumab Elan Pharma 300 mg in maintaining the

response to treatment were compared with those of placebo. The main measure of effectiveness was the proportion of patients maintaining a response over an additional nine months of treatment.

What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?

The CHMP was concerned that there was insufficient evidence to show the effectiveness of Natalizumab Elan Pharma 300 mg. In the study of patients starting treatment with Natalizumab Elan Pharma 300 mg, the effects of the medicine were modest. There was also insufficient evidence of maintenance of the medicine's effects. The CHMP also had concerns over the safety of Natalizumab Elan Pharma 300 mg in patients with Crohn's disease, because of a risk of serious infections, including the brain infection progressive multifocal leukoencephalopathy (PML). Therefore, at that point in time, the CHMP was of the opinion that the benefits of Natalizumab Elan Pharma 300 mg in the treatment of Crohn's disease did not outweigh its risks. Hence, the CHMP recommended that Natalizumab Elan Pharma 300 mg be refused marketing authorisation.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Natalizumab Elan Pharma 300 mg?

The company informed the CHMP that there are no clinical trials or compassionate use programmes using Natalizumab Elan Pharma 300 mg ongoing in the European Union for the treatment of Crohn's disease.

What is happening for TYSABRI for the treatment of multiple sclerosis?

There are no consequences of this opinion on the use of TYSABRI, which also contains natalizumab, in its authorised indication. The balance of benefits and risks for TYSABRI remains unchanged.