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**QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE
MARKETING AUTHORISATION
for
MYCOGRAB**

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

On 16 November 2006, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Mycograb 2 mg/ml powder for solution for injection intended for the treatment of invasive candidiasis in adult patients, in combination with amphotericin B or a lipid formulation of amphotericin B.

The company that applied for authorisation is *NeuTec Pharma plc*. The applicant requested a re-examination of the opinion. After having considered the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 20 March 2007.

What is Mycograb?

Mycograb is a white powder that contains the active substance efungumab. The powder needs to be dissolved in sterile water before being injected into a vein.

What was Mycograb expected to be used for?

Mycograb was to be used together with amphotericin B (another antifungal medicine) to treat adult patients with invasive candidiasis. This disease is caused by infection with a common fungus (yeast) called *Candida*. In invasive candidiasis, the fungal infection spreads to the internal organs such as the liver, spleen and kidneys via the bloodstream. Invasive candidiasis is a life-threatening disease. . Because the number of patients with invasive fungal infections is low, Mycograb was designated an 'orphan medicine' (a medicine used in rare diseases) on 5 December 2001.

How is Mycograb expected to work?

The active substance in Mycograb, efungumab, is an antifungal agent. It has been designed to attach to a specific protein on the surface of the fungal cells, called Heat Shock Protein 90 (hsp90). This protein is involved in the formation and the repair of the cell wall and is essential for the survival of the fungal cells. By attaching to hsp90, efungumab blocks the protein's normal activities. This weakens the cell wall, making the fungal cells fragile and unable to grow.

Efungumab is produced by a method known as 'recombinant DNA technology'. This means that it is made by a bacterium that has received a gene (DNA), which makes it able to produce the substance.

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

The effects of Mycograb were first tested in experimental models before being studied in humans. The main study of the medicine's effects involved 139 adults with invasive candidiasis. The study compared the effects of Mycograb to those of a placebo (a dummy treatment), when they were given with amphotericin B for 5 days. The effectiveness was measured by looking at the percentage of patients responding to treatment, based on improvement of their symptoms (including fever) and elimination of the fungus from samples, as measured on day 10 (5 days after the end of Mycograb or placebo treatment).

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

In November 2006, the CHMP was concerned about some aspects of the quality of the medicine (such as the way the molecules of efungumab may fold or aggregate in the solution for injection and the level of some substances that could stimulate an immune response in patients). It also had concerns about the safety of Mycograb. The medicine is associated with 'cytokine release syndrome', a condition that can cause nausea, vomiting, pain and also hypertension (high blood pressure), but the reason for this is not clear. Too few patients have received Mycograb for its safety to be sufficiently assessed.

In March 2007, following the re-examination, the CHMP removed their concern regarding the cytokine release syndrome and hypertension, as these would be manageable in clinical practice. However, all other concerns remain.

At this point in time, the committee was of the opinion that the benefits of Mycograb in the treatment of invasive candidiasis did not outweigh its risks. Hence, the CHMP recommended that Mycograb be refused marketing authorisation.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Mycograb?

The company informed the CHMP that there are no consequences on patients currently included in clinical trials or compassionate use programmes with Mycograb. 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.