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Refusal of the marketing authorisation for Gamifant (emapalumab)

Re-examination confirms refusal

After re-examining its initial opinion, the European Medicines Agency has confirmed its recommendation to refuse marketing authorisation for the medicine Gamifant. The medicine was intended for the treatment of primary haemophagocytic lymphohistiocytosis (HLH) in children under 18 years of age.

The Agency issued its opinion after re-examination on 12 November 2020, following its initial opinion on 23 July 2020. The company that applied for authorisation of Gamifant is Swedish Orphan Biovitrum AB (publ).

What is Gamifant and what was it intended for?

Gamifant was developed as a medicine for the treatment of children under 18 years of age with refractory or recurrent HLH (when the disease does not respond to treatment or has come back), or intolerance to conventional HLH therapy (usually a combination of the medicines dexamethasone and etoposide).

Primary HLH (pHLH) is a genetic disease characterised by an overactive immune system (the body's natural defences) in which the body produces too many macrophages and lymphocytes (cells of the immune system) which accumulate in the body's tissues and organs, including the liver, spleen, bone marrow, brain and skin. HLH can also occur following an infection or in association with cancer (so-called secondary HLH). Usually, the macrophages and the lymphocytes should destroy infected and damaged cells of the body, but in HLH the immune system damages the patient's healthy cells.

Symptoms of the disease may include fever, enlarged liver and spleen, skin rash, jaundice (yellowing of the skin and eyes) and pancytopenia (low blood cell counts), and often appear between 1 and 6 months of age.

HLH can be cured by haematopoietic stem cell transplantation (HSCT), a procedure where the patient's bone marrow is replaced by stem cells from a donor to form new bone marrow that produces healthy cells, but patients require an intense treatment first in order for this to be successful.

Gamifant contains the active substance emapalumab and was to be given by infusion (drip) into a vein.

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Gamifant was designated an 'orphan medicine' (a medicine used in rare diseases) on 9 June 2010 for the treatment of HLH. Further information on the orphan designation can be found on the Agency's website: www.ema.europa.eu/medicines/human/orphan-designations/eu310749.

Gamifant was granted eligibility to PRIME[1] on 26 May 2016 for the treatment of pHLH.

How does Gamifant work?

The active substance in Gamifant, emapalumab, is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a substance called interferon gamma. Patients with HLH have high levels of interferon gamma, which is thought to be responsible for the excessive inflammatory response causing the disease. By attaching to interferon gamma, emapalumab is expected to block its activity and is therefore thought to improve the symptoms of HLH.

What did the company present to support its application?

The company presented the results of one main study involving 34 patients with pHLH, 27 of whom had received previous treatment. The main measure of effectiveness was the number of patients who had a partial or complete response or HLH improvement, based on improvement in their symptoms and results of laboratory tests after 4 to 8 weeks of treatment.

What were the main reasons for refusing the marketing authorisation?

In July 2020, the Agency was concerned that, although several patients responded to treatment with Gamifant and went on to receive HSCT, the results of the study were not considered sufficient to conclude that Gamifant was effective in the treatment of pHLH.

The study involved only a small number of patients who also received other medicines to treat HLH. Additionally, symptoms vary over time; therefore, it was not possible to conclude that the response seen in some patients was due to the effect of Gamifant. Furthermore, the effect of emapalumab could not be sufficiently supported by available data on how the medicine works, and the role of interferon gamma in how pHLH develops is not fully understood.

The design of the study also made it difficult to collect data on Gamifant's side effects, which are needed to characterise the safety profile of the medicine. In addition, upon an inspection of the way the study data were collected and managed, the reliability of the data could not be confirmed.

Therefore, at the time of the initial refusal, the Agency's opinion was that it could not conclude that the benefits of Gamifant outweigh its risks in the treatment of pHLH. Hence, the Agency recommended refusing marketing authorisation.

At the company's request, the Agency re-examined its initial opinion. During the re-examination, the Agency looked at the available data and took additional advice from a group of experts in the field.

In November 2020, after the re-examination, the concern over the safety profile of Gamifant had been satisfactorily addressed, but the other concerns remained. Therefore, the Agency's opinion was still that the benefits of Gamifant did not outweigh its risks and it recommended that the medicine be refused marketing authorisation.

[1] PRIME is an EMA scheme to enhance support during the development of medicines that target an unmet medical need. More information is available here: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

Does this refusal affect patients in clinical trials?

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

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