13 November 2020
EMA/601698/2020
EMEA/H/C/005031

Approval of the marketing authorisation for Elzonris (tagraxofusp)

Re-examination leads to recommendation to approve

After re-examining its initial opinion, the European Medicines Agency has recommended approving the marketing authorisation for the medicine Elzonris for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN).

The Agency had initially refused the application on 23 July 2020 for Elzonris to be used for the treatment of BPDCN regardless of whether patients had been previously treated with other medicines or not. After re-examination, on 12 November 2020 the Agency recommended that marketing authorisation under exceptional circumstances could be granted but for a restricted indication in patients who had not yet received any treatment for BPDCN (so called first-line treatment).

The company that applied for authorisation is Stemline Therapeutics B.V.

What is Elzonris and what is it to be used for?

Elzonris is a medicine that is to be used for treating adults with BPDCN, a rare and aggressive type of acute myeloid leukaemia (blood cancer). In BPDCN, the bone marrow (the spongy tissue inside the large bones, where blood cells are produced) produces large numbers of immature white blood cells called plasmacytoid dendritic cells. These build up in the bone marrow, taking the place of normal blood cells, and spread to the skin: most patients develop non-itchy damaged areas, which often look like bruises or nodules. The disease may also cause enlargement of the spleen or liver and a reduction of the number of circulating blood cells. There is no approved treatment for BPDCN in the EU.

Elzonris contains the active substance tagraxofusp and will be available as an infusion (drip) given into a vein.

Elzonris was designated an 'orphan medicine' (a medicine used in rare diseases) on 11 November 2015 for the treatment of BPDCN. Further information on the orphan designation can be found on the Agency's website: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151567.

How does Elzonris work?

The active substance in Elzonris, tagraxofusp, is made up of a toxin (a substance which is poisonous to cells) called diphtheria toxin, which has been linked to a protein called interleukin-3. The interleukin-3

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attaches to receptors (specific targets) which are found at high levels on the surface of BPDCN cancer cells. Once attached to cancer cells, it is taken up by them, allowing the toxin to be released inside, which kills them. This is expected to prevent cancer spread and reduce symptoms of the disease.

What did the company present to support its application?

The company presented results from a single small study involving 84 adults with BPDCN that could not be treated in other ways. The main measure of effectiveness, which was recorded in a group of 13 patients receiving first-line treatment, was the number of patients without any signs of disease (complete response) after treatment or with just minimal skin damage remaining.

What were the main reasons for initially refusing the marketing authorisation?

The Agency was concerned that due to the design of the study and the small number of patients involved, it was not possible to be sure how effective the medicine was in treating BPCDN. In addition, the medicine could cause capillary leak syndrome (an unpredictable, potentially life-threatening side effect due to increased permeability of small blood vessels), which had led to some fatal outcomes.

Therefore, at the time of the initial refusal, the Agency's opinion was that the benefits of Elzonris did not outweigh its risks and it recommended refusing marketing authorisation.

What happened during the re-examination?

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 specialising in blood cancers.

What were the conclusions of the re-examination?

EMA noted that although the study was small, the benefits shown are relevant for patients with this rare disease for which no treatment is available. Patients who achieved a complete response with Elzonris were able to undergo allogeneic stem cell transplantation (ASCT, 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), which was successful and contributed to long survival for some patients. The safety of Elzonris was considered acceptable with specific measures in place to minimise the risk of the most serious side effects.

After considering experts' advice on the study results and the challenges of conducting larger studies for this rare disease, the Agency concluded that the benefits of Elzonris outweigh its risks in patients with BPCDN who had not yet received other treatments. However, the data from the group of patients in whom previous treatments did not work was not sufficient to draw the same conclusion.

The Agency recommended granting a marketing authorisation for Elzonris under 'exceptional circumstances'. This is because it was not possible to obtain complete information about Elzonris due to the rarity of the disease. To further characterise the effectiveness and safety of Elzonris, the company is required to submit the results of a study based on a registry of patients with BPCDN.