22 April 2022
EMA/219136/2022
EMEA/H/C/005433

Withdrawal of application for the marketing authorisation of Miplyffa (arimoclomol)

Orphazyme A/S withdrew its application for a marketing authorisation of Miplyffa for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older in combination with miglustat (another medicine to treat NPC).

The company withdrew the application on 22 March 2022.

What is Miplyffa and what was it intended to be used for?

Miplyffa was intended for use in patients aged 2 years and older to treat NPC, a disease which belongs to a group of inherited disorders belonging to the larger family of metabolic disorders called 'lysosomal storage diseases', in which fats accumulate within lysosomes (parts of the body's cells that break down nutrients and other materials) caused by changes in two genes called *NPC1* and *NPC2*.

Miplyffa contains the active substance arimoclomol and was to be available as capsules to be taken by mouth.

Miplyffa was designated an 'orphan medicine' (a medicine used in rare diseases) on 19 November 2014 for the treatment of NPC. Further information on the orphan designation can be found on the Agency's website: ema.europa.eu/medicines/human/orphan-designations/eu3141376

How does Miplyffa work?

In NPC the build-up of fatty substances in the lysosomes reduces their ability to function normally and makes the membrane around the lysosome unstable. The active substance in Miplyffa, arimoclomol, is intended to stimulate the cell's natural mechanisms for coping with damage, by increasing the production of proteins called heat shock proteins in cells that are under stress. These proteins are thought to help to stabilise the protein produced by the *NPC1* gene and the membrane around the lysosomes, and thereby improve the ability of the lysosome to function and break down certain fats. This is expected to avoid the build-up of fats in the lysosomes and help reduce the symptoms of the disease, which include behavioural problems, learning disabilities, and difficulty moving and speaking.

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What did the company present to support its application?

The company provided results of one main study which looked at the effectiveness of Miplyffa on slowing disease progression over time. The results were based on 50 patients aged between 2 and 18 years who received either Miplyffa or placebo (a dummy treatment) for one year, in addition to the patient's routine clinical care (including miglustat where applicable). Effectiveness was measured by using a standard scale (5-domain NPCCSS) recording severity of symptoms over time.

The company also presented data from an early access programme (EAP) where Miplyffa was given with or without miglustat.

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

The application was withdrawn after the European Medicines Agency had evaluated the information from the company and prepared questions for the company. After the Agency had assessed the company's responses to the last round of questions, there were still some unresolved issues.

What did the Agency recommend at that time?

Based on the review of the available information, at the time of the withdrawal, the Agency had concerns and its provisional opinion was that Miplyffa could not have been authorised for the treatment of NPC.

The Agency considered that the results of the study did not sufficiently show that Miplyffa was effective at improving symptoms related to NPC or in slowing disease progression, neither in the short nor long term (after one year and longer). In particular, the Agency had concerns about the way results from the study were proposed to be interpreted. Also, the benefits of adding Miplyffa to miglustat were not confirmed.

Therefore, at the time of the withdrawal, the Agency was not able to draw a positive conclusion on the effectiveness of Miplyffa in treating NPC and its opinion was that the benefits of Miplyffa in this use did not outweigh its risks.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of the application, the company stated that they withdrew their application following EMA's concerns and their estimate that these could not be addressed in the time available.

Does this refusal affect patients in clinical trials?

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

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