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Refusal of the marketing authorisation for Nezglyal (*leriglitazone*)

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 Nezglyal. The medicine was intended for the treatment of cerebral adrenoleukodystrophy.

Cerebral adrenoleukodystrophy is a form of an inherited disease called adrenoleukodystrophy in which fatty substances known as 'very long chain fatty acids' build up in tissues around the body, mainly in the brain, spinal cord and adrenal glands (two glands situated above the kidneys). In cerebral adrenoleukodystrophy, a build-up of these substances in the brain causes inflammation and destruction of the protective sheath (myelin) that insulates and helps signalling by nerve cells.

The Agency issued its final opinion after re-examination on 28 May 2024. The Agency had issued its initial opinion on 25 January 2024. The company that applied for authorisation of Nezglyal is Minoryx Therapeutics S.L.

What is Nezglyal and what was it intended for?

Nezglyal was developed as a medicine to be used in male adults and children aged 2 years and older with brain lesions (areas of abnormal or damaged tissue), to delay progression of cerebral adrenoleukodystrophy. The medicine contains the active substance leriglitazone and was to be available as a suspension to be taken by mouth.

Nezglyal was designated an 'orphan medicine' (a medicine used in rare diseases) on 18 November 2016 for the treatment of adrenoleukodystrophy. Further information on the orphan designation can be found on the Agency's website: ema.europa.eu/medicines/human/orphan-designations/eu3161770.

How does Nezglyal work?

The active substance in Nezglyal, leriglitazone, works by attaching to and activating receptors (targets) called 'PPAR gamma receptors', which are found inside cells, including nerve cells. PPAR gamma receptors play a role in regulating the function of mitochondria (energy-producing structures in cells), how cells respond to oxidative stress (damage caused by toxic oxygen-containing molecules known as free radicals) and inflammation. Leriglitazone was therefore expected to protect nerve cells from

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damage by reducing inflammation, improving the function of mitochondria and protecting against damage from free radicals.

What did the company present to support its application?

The company presented results from a completed main study involving 116 male adults with adrenoleukodystrophy who either took leriglitazone or placebo (a dummy treatment).

In this main study, 27% of patients had cerebral adrenoleukodystrophy at the start of the study. The main measure of effectiveness for adrenoleukodystrophy in this study was the change in the distance patients with the disease could walk in six minutes after 96 weeks of treatment. The study also looked at how often brain lesions occurred and/or worsened over time and the Loes severity score, which measures the severity of the lesions, on an MRI scan.

The company also provided data from an ongoing study in children with cerebral adrenoleukodystrophy aged from 2 to 12 years and data from patients who received Nezglyal as part of a compassionate use programme.

What were the main reasons for refusing the marketing authorisation?

During the re-examination, EMA's human medicines committee (CHMP), re-evaluated the available data and assessed the company's responses to its concerns that resulted in the initial refusal, and also consulted a group of experts in neurology.

The Agency concluded that the main study did not show that Nezglyal was effective in patients with adrenoleukodystrophy, which includes patients with cerebral adrenoleukodystrophy, based on the study's measures of effectiveness. Because of the limited data on patients with cerebral adrenoleukodystrophy, it was not possible to conclude on the benefits of Nezglyal in this group of patients. Moreover, a connection between how the medicine works and clinical progression of adrenoleukodystrophy could not be concluded, and no connection could be established between the dose of Nezglyal and the patients' response to treatment.

The Agency also concluded that a conditional authorisation, as requested by the company, should not be granted, as the applicable requirements are not met. For example, the benefit-risk balance is not positive.

Therefore, after the re-examination the Agency's concerns were not resolved and the initial refusal was confirmed.

Does this refusal affect patients in clinical trials or compassionate use programmes?

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

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