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Withdrawal of the marketing authorisation application for Radicava (edaravone)

On 24 May 2019, Mitsubishi Tanabe Pharma GmbH officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Radicava intended for the treatment of amyotrophic lateral sclerosis (ALS).

What is Radicava?

Radicava is a medicine that contains the active substance edaravone. It was to be available as a solution for infusion (drip) into a vein.

What was Radicava expected to be used for?

Radicava was expected to be used to treat patients with amyotrophic lateral sclerosis (ALS). ALS is a disease of the nervous system, where nerve cells in the brain and spinal cord that control voluntary movement gradually deteriorate, causing loss of muscle function and paralysis.

Radicava was expected to be used to slow down the worsening of the disease in patients who can still perform normal daily activities.

Radicava was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 19 June 2015 for ALS. Further information on the orphan designation can be found here.

How does Radicava work?

The exact way Radicava works in patients with ALS is not known but it is thought to neutralise oxygen-containing molecules known as 'free radicals', which have been linked to nerve damage in patients with ALS.

What did the company present to support its application?

The company presented results from a main study of 137 patients with ALS who received either Radicava or placebo (a dummy treatment). The study looked at how much patients' symptoms changed over 24 weeks, using a standard rating scale known as 'ALS functional rating scale revised'

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(ALSFRS-R). Doctors use this scale to rate how well patients can talk, breath, eat and perform other normal activities.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the CHMP had evaluated the documentation provided by the company and formulated lists of questions. After the CHMP had assessed the company's responses to the last round of questions, there were still some unresolved issues.

What was the recommendation of the CHMP at that time?

At the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Radicava could not have been approved.

The Committee noted that the main study did show significant improvements in ALSFRS-R scores in patients receiving Radicava compared with those receiving placebo. However, the study involved only a small number of patients and there was not enough evidence of improvements in other important measures, such as those related to survival, breathing and muscle strength.

Furthermore, the CHMP noted important differences between the two groups which could have influenced the final results – such as the fact that a higher number of patients in the Radicava group had less severe disease. When patients in the placebo group were later switched to Radicava there was no noticeable effect.

The CHMP was also concerned about the duration of any benefits from Radicava, noting that 24 weeks (a cut-off point in the main study) was too short and that data from the extension phase of the study were difficult to interpret.

Given the clear need for further evidence of Radicava's effectiveness, the Committee considered the possibility of a conditional approval, which would allow the company to provide more data at a later stage. The company proposed a registry study whereby patients treated with Radicava could be compared with patients who received other treatments for ALS in the past. The Committee considered the merits of such a study but had some objections, including the fact that the treatment for ALS had changed significantly over the past few years, rendering comparisons difficult.

During the evaluation, the CHMP consulted a group of experts in the field to obtain their views on the study results, the proposed registry and the patient population that could potentially benefit from treatment with Radicava. At the time of the withdrawal, the Committee was of the opinion that, because of lack of proven effectiveness, the benefits of Radicava 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 the withdrawal was based on the Committee's provisional opinion on the study data. The withdrawal letter is available here.

What consequences does this withdrawal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that the withdrawal does not have any impact on ongoing clinical trials. The company will continue with its ongoing compassionate use programmes pending discussions with national authorities that have already granted approval for compassionate use.