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Withdrawal of the marketing authorisation application for Prohippur (sodium benzoate)

On 3 April 2018, Lucane Pharma officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application for a marketing authorisation for Prohippur, for the treatment of non-ketotic hyperglycinaemia and urea cycle disorders.

What is Prohippur?

Prohippur is a medicine containing the active substance sodium benzoate. It was to be available as granules.

What was Prohippur expected to be used for?

Prohippur was expected to be used to treat the following inherited disorders:

- non-ketotic hyperglycinaemia, where abnormally high levels of the amino acid glycine occur in the blood.
- urea cycle disorders, a group of conditions where abnormally high levels of nitrogen occur in the body in the form of ammonia.

Both glycine and ammonia are harmful in high amounts and can cause severe brain damage. The conditions are caused by a lack of enzymes needed to remove them.

Prohippur was designated an 'orphan medicine' (a medicine to be used in rare diseases) for non-ketotic hyperglycinaemia on 11 September 2002 and for urea cycle disorders on 14 July 2016, 29 August 2016 and 18 November 2016. Further information on the orphan designation can be found here.

How does Prohippur work?

The active substance in Prohippur, sodium benzoate, helps reduce harmful levels of glycine by attaching to glycine and forming a substance that is more easily removed by the kidneys. Prohippur also helps remove excess nitrogen from the body, thereby lowering levels of ammonia.

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What did the company present to support its application?

The company presented data from published studies on the use of sodium benzoate in patients with non-ketotic hyperglycinaemia and urea cycle disorders. Prohippur was not studied directly in patients with these conditions.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the CHMP had evaluated the documentation provided by the company and formulated lists of questions. The company had not responded to the last round of questions at the time of the withdrawal.

What was the recommendation of the CHMP at that time?

At the time of the withdrawal, the CHMP had some concerns. The CHMP noted that the published studies submitted by the company did not provide enough evidence of the effectiveness and safety of sodium benzoate in the various disorders. Furthermore, as Prohippur was not used in clinical trials, the company should have provided data to show that Prohippur granules worked in the same way as the sodium benzoate used in the published studies. Finally, the CHMP had questions about the high levels of a substance in Prohippur (butylated methacrylate copolymer), the method of administration and quality control of the medicine in general.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Prohippur 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 it needed more time to prepare adequate answers to questions raised by the CHMP.

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 there are no ongoing clinical trials with Prohippur and that a compassionate use programme approved in France will continue as planned.

If you are in a compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.