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Translarna: EMA re-confirms non-renewal of authorisation of Duchenne muscular dystrophy medicine

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Re-examination concludes effectiveness has not been confirmed

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Following a re-examination of available data, EMA's human medicines committee (CHMP) has confirmed its previous recommendation to not renew the conditional marketing authorisation for Translarna (ataluren). This last round of assessment concluded that the effectiveness of Translarna has not been confirmed.

Translarna is used for treating patients with Duchenne muscular dystrophy aged 2 years and older who are able to walk and whose disease is caused by a type of genetic defect called a 'nonsense mutation' in the dystrophin gene.

The CHMP issued an initial negative opinion on Translarna in September 2023, which was confirmed in January 2024 following a first re-examination requested by the company marketing the medicine. In June 2024, the Committee revisited its opinion athttps://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-duchenne-muscular-dystrophy-medicine-translarna the request of the

European Commission to take into account additional real-world data brought to the attention of the Commission during the decision-making process and consider whether the available data are comprehensive; the views of a new scientific advisory group were also considered. After this assessment the CHMP recommendation remained negative.

The company then requested another re-examination, and the CHMP re-assessed the results from a study carried out after authorisation as a specific obligation (study 041) as well as patient registries data, taking into account new analyses provided by the company.

Results from latest post-authorisation study

Study 041 was the second study carried out after authorisation that aimed to confirm the benefits of Translarna. The first post-authorisation study (study 020), carried out earlier, had failed to confirm the effectiveness of Translarna but suggested that a subgroup of patients, those with a progressive decline in their ability to walk, might be more sensitive to the treatment. The main objective of study 041 was therefore to look at the effect of Translarna in this subgroup of patients.

The results showed that the distance patients could walk in six minutes after 18 months of treatment decreased by about 82 metres in the Translarna group compared with 90 metres in the placebo (dummy treatment) group; however, this difference was not statistically significant, meaning that it may be due to chance.

Similarly, when looking at the decline in motor functions after about 18 months as measured using a standard scale called North Star Ambulatory Assessment (NSAA), the difference between patients treated with Translarna and those who received placebo was also not statistically significant. The CHMP therefore concluded that study 041 had failed to confirm the effectiveness of the medicine.

Patient registries data

As part of this latest re-examination, the CHMP also

reassessed data from a study comparing the health outcomes of patients from two registries. In the study, patients from the STRIDE registry were treated with Translarna for an average of 5.5 years between 2015 and 2022, while patients from the CINRG DNHS registry were not treated with Translarna and were followed up between 2006 and 2016.

The CHMP considered new analyses and data from the literature provided by the company. Although the results suggested a delay in the loss of ability to walk in some patients treated with Translarna compared with those in the CINRG DNHS registry, the Committee could not draw conclusions on the benefits of Translarna from these data because of several differences between the registries and biases making the comparison inconclusive. Furthermore, the Committee considered that these data do not outweigh the negative results of the two post-authorisation studies (study 041 and study 020).

In addition to these conclusions, the CHMP also noted that the mechanism of action of Translarna was not confirmed in additional studies, which showed only a very small effect of Translarna on the production of the dystrophin protein.

Throughout its review of Translarna, the CHMP consulted parents of boys and men with Duchenne muscular dystrophy of different ages. They were invited to meetings as patient experts along with other experts, including neurologists, to describe what it is like to live with this disease, and they spoke directly to the CHMP on several occasions. The patients' and parents' perspectives have been sought and captured at every stage of the evaluation of this medicine. The Committee also considered all third-party information received from parents and caregivers of boys affected by Duchenne muscular dystrophy, patient organisations, healthcare professional organisations and treating doctors.

The CHMP acknowledges the high unmet medical need for an effective treatment for patients with Duchenne muscular dystrophy. However, based on all the evidence accumulated, it concluded that the effectiveness of Translarna has not been confirmed in patients with Duchenne muscular dystrophy caused by a nonsense mutation, including those

who were expected to have a better response to treatment.

The CHMP considered that the data now available are comprehensive and recommended not renewing the medicine's marketing authorisation in the EU.

EMA will now send the CHMP's opinion to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Information for patients

- EMA has finalised its review of Translarna's benefits and concluded that the effectiveness of the medicine has not been confirmed in patients with nonsense mutation Duchenne muscular dystrophy.
- This review follows a re-examination requested by the company marketing the medicine after EMA concluded earlier this year that the marketing authorisation for Translarna should not be renewed.
- When Translarna was authorised in 2014, there was uncertainty about its effectiveness; so, in view of the lack of treatments for patients with Duchenne muscular dystrophy, the medicine was granted a conditional marketing authorisation and the company was requested to carry out new studies to fully confirm the medicine's benefits.
- Since then, two studies to confirm the benefits of Translarna were carried out. The first one failed to confirm the effectiveness of Translarna but suggested that a subgroup of patients, those with a progressive decline in their ability to walk, might be more sensitive to the treatment. A second study was therefore carried out to assess the effect of the medicine in this subgroup patients.
- This second study compared the effect of Translarna with that of placebo (a dummy treatment) after 18 months of treatment. However, the study failed to show that Translarna had a beneficial effect in these patients, although they were expected to benefit most from treatment.
- In addition, EMA reassessed data from a study comparing the health outcomes of patients from two

patient registries; one registry included patients treated with Translarna and the other included patients not treated with Translarna. However, the Committee could not draw firm conclusions on the benefits of Translarna from these data because of several differences between the registries and biases making the comparison inconclusive. In addition, EMA considered that these data do not outweigh the results of the two post-authorisation studies that did not confirm the benefits of Translarna.

- In its assessment, EMA consulted parents of boys with Duchenne muscular dystrophy of different ages, neurologists and healthcare professionals. It also took into account information received from parents or caregivers of boys affected by Duchenne muscular dystrophy, patient organisations, healthcare professional organisations and treating doctors.
- EMA acknowledges the need for an effective treatment for patients with Duchenne muscular dystrophy; however, it considers that the benefits of Translarna have not been confirmed. The Agency therefore recommended that the marketing authorisation for Translarna should not be renewed. If this recommendation is confirmed by the European Commission, the medicine will no longer be authorised in the EU.
- If you or your child is receiving Translarna, you should speak to your doctor about this decision and what it means for you or your child’s treatment.

Information for healthcare professionals

- EMA has reviewed the benefits of Translarna and concluded that the effectiveness of the medicine has not been confirmed in patients with nonsense mutation Duchenne muscular dystrophy.
- This review follows a re-examination requested by the company marketing the medicine after EMA concluded earlier this year that the marketing authorisation for Translarna should not be renewed.
- At the time of the approval of Translarna in 2014, there was uncertainty about its effectiveness; however, in view of the lack of treatments for patients with

Duchenne muscular dystrophy, the medicine was granted a conditional marketing authorisation and the company was requested to carry out new studies to confirm the medicine's benefits.

- A first post-authorisation study (study 020) failed to confirm the effectiveness of Translarna but indicated that a subgroup of patients, those with a progressive decline in their ability to walk, might be more sensitive to the treatment.
- In 2016, the CHMP therefore requested the MAH for Translarna to conduct a new study on the medicine's efficacy, looking in particular at patients in the ambulatory decline phase (ADP) of their disease, as they were expected to have a better response to treatment.
- Study 041 was a phase 3, randomised (1:1), double-blind, placebo-controlled trial carried out in 360 patients aged 5 years or older with nonsense mutation Duchenne muscular dystrophy. A 72-week double-blind phase was followed by an open-label extension of another 72 weeks where patients who received placebo switched to Translarna.
- The primary endpoint was the change from baseline in the 6-minute walking distance (6MWD) at 72 weeks. In ADP patients (n=185), the mean change from baseline in 6MWD was -81.83 meters in the Translarna group versus -90.09 meters in the placebo group, a non-significant difference of 8.26 meters (95% confidence interval [CI]: -26.05; -9.53, p=0.36).
- Change in North Star Ambulatory Assessment (NSAA) total score was a key secondary efficacy in this study. In ADP patients, the difference in the NSAA score between the Translarna and placebo groups was also not statistically significant, both for the NSAA total score (p=0.126) and the NSAA linear score (p=0.066).
- The CHMP concluded that study 041 failed to confirm Translarna's efficacy. These results were considered particularly relevant since the study included a population of patients expected to be most sensitive to the medicine.
- The CHMP also re-assessed data from a study comparing the health outcomes of patients from two patient registries. In the study, patients from the

STRIDE registry were treated with Translarna for an average of 5.5 years between 2015 and 2022, while patients from the CINRG DNHS registry were not treated with Translarna and were followed between 2006 and 2016.

- The Committee could not draw conclusions on the benefits of Translarna from these data because of several differences between the registries and biases making the comparison inconclusive.
- In addition, the Committee considered that these data do not outweigh the results of the two post-authorisation studies that did not confirm the benefits of Translarna.
- Consequently, EMA has recommended not renewing the marketing authorisation for Translarna. If this recommendation is confirmed by the European Commission, the medicine will no longer be authorised in the EU.

More about the medicine

Translarna was authorised in the EU on 31 July 2014 for the treatment of patients with Duchenne muscular dystrophy whose disease is caused by a 'nonsense mutation' in the dystrophin gene.

Duchenne muscular dystrophy is a serious and rare condition for which very few treatment options are available. It is a genetic disease that causes a gradually increasing weakness and loss of muscle function, leading to death due to respiratory muscle weakness or cardiomyopathy. Patients with this disease lack normal dystrophin, a protein found in muscles that helps protect muscles from injury as they contract and relax.

In patients with Duchenne muscular dystrophy caused by a nonsense mutation, production of a normal dystrophin protein is stopped prematurely, leading to a shortened dystrophin protein that does not function properly. The active substance in Translarna, ataluren, is expected to work by enabling the protein-making apparatus in cells to move past the genetic mutation, allowing the cells to produce a functional dystrophin protein.

More about the procedure

The application for the renewal of the marketing authorisation for Translarna was assessed by EMA's Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted EMA's initial opinion on 14 September 2023.

The company that markets Translarna asked for re-examination of the CHMP's opinion on 4 October 2023. After conducting the re-examination, the CHMP issued an opinion on 25 January 2024 which was forwarded to the European Commission for a final legally binding decision.

On 24 May 2024, the European Commission asked the CHMP to further consider whether the data available on Translarna were sufficiently comprehensive to conclude on the medicine's benefit-risk balance, and whether additional real-world data brought to the attention of the Commission during its decision-making process might have impacted the CHMP conclusion on the benefit-risk profile of Translarna.

In addition, following the appellate judgment of the Court of Justice of the European Union of 14 March 2024 in Case C-291/22 P, EMA decided to convene a new scientific advisory group on neurology (SAG-N) for Translarna. The assessment was therefore reset to this stage of the initial renewal procedure.

The CHMP adopted a new opinion on 27 June 2024. The company asked for re-examination of this latest CHMP's opinion on 11 July 2024.

The CHMP has now re-examined its opinion, and its recommendation will be sent to the European Commission for a legally binding decision applicable in all EU Member States.

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