17 March 2026
EMEA/H/C/003870/X/0039
EMA/380366/2025

# Refusal of a change to the marketing authorisation for Hetlioz (tasimelteon)

Re-examination confirms refusal

After re-examining its initial opinion, the European Medicines Agency has confirmed its recommendation to refuse a change to the marketing authorisation for Hetlioz. The change concerned an extension of indication to include the treatment of nighttime sleep disturbance in children aged 3 to 15 years with Smith-Magenis syndrome.

The Agency issued its opinion after re-examination on 16 March 2026. It had issued its initial opinion on 11 December 2025. The company that had applied for the change to the medicine's authorisation is Vanda Pharmaceuticals Netherlands B.V.

## What is Hetlioz and what is it used for?

Hetlioz is a medicine used to treat totally blind adults with non-24-hour sleep-wake disorder. Non-24-hour sleep-wake disorder is a condition that occurs almost exclusively in people who are completely blind, where patients have sleep patterns that are not synchronised with day and night and often follow a cycle that is longer than the standard 24-hour clock. As a result, patients fall asleep and wake up at unusual times.

Hetlioz contains the active substance tasimelteon.

Further information on Hetlioz's uses can be found on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/hetlioz.

## What change had the company applied for?

The company applied to extend the use of Hetlioz to add the treatment of nighttime sleep disturbance in children aged 3 to 15 years old with Smith-Magenis syndrome. Smith-Magenis syndrome is a rare hereditary disorder characterised by developmental delay, behavioural problems, and sleep disturbance. Sleep problems in people with Smith-Magenis syndrome are caused by an abnormal

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

production pattern of melatonin (a hormone that plays a key role in co-ordinating the body's sleep-wake cycle).

Hetlioz was designated an 'orphan medicine' (a medicine used in rare diseases) on 22 May 2023 for the treatment of Smith-Magenis syndrome. Further information on the orphan designation can be found on the Agency's website: ema.europa.eu/en/medicines/human/orphan-designations/eu-3-23-2832.

## How does Hetlioz work?

Melatonin is involved in coordinating the body's sleep cycle by acting on cells in specific areas of the brain and helping to bring about sleep. Its levels in the blood normally increase after the onset of darkness and peak in the middle of the night. The active substance in Hetlioz, tasimelteon, acts on the same receptors as melatonin to promote sleep and regulate sleep patterns. By taking it at a suitable time each day it can help to reset the sleep-wake cycle to more standard timing.

In Smith-Magenis syndrome, Hetlioz was expected to work in the same way as it does in its existing use.

## What did the company present to support its application?

The company presented the results of a study involving 26 people with Smith-Magenis syndrome who were experiencing nighttime sleep disturbance (11 children aged 3 to 15 years and 15 adults and adolescents aged 16 and older). The study compared the effect of Hetlioz on sleep disturbance with that of placebo (a dummy treatment) over 4 weeks. The main measure of effectiveness was an improvement in nighttime sleep based on average sleep quality and average total sleep time, evaluated by caregivers using a post-sleep questionnaire.

## What were the main reasons for refusing the change to the marketing authorisation?

At the time of the initial evaluation, the Agency considered that there were concerns about the design of the study, the statistical analysis of the results and the way the study had been conducted, which resulted in uncertainties in the observed treatment effects. There was also uncertainty as to how well the safety of Hetlioz in children with Smith-Magenis syndrome had been investigated due to issues relating to the design of the study and how it had been carried out.

Therefore, the Agency's opinion was that the benefits and risks of Hetlioz in the treatment of children aged to 3 to 15 years with Smith-Magenis syndrome could not be established. Hence, the Agency recommended refusing the change to the marketing authorisation.

Following re-examination of the available data, the Agency's concerns were not resolved and the initial refusal was confirmed.

## What is happening with Hetlioz for the treatment of non-24-hour sleep-wake disorder?

There are no consequences for Hetlioz in its authorised use for non-24-hour sleep-wake disorder.