HAUTE AUTORITÉ DE SANTÉ

NEUROLOGY
New medicinal product
June 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

SLENYTO (melatonin), hypnotic

High clinical benefit in the treatment of insomnia in children and adolescents aged from 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient and minor clinical improvement in the therapeutic strategy.

Main points

- SLENYTO has been granted a marketing authorisation for the treatment of insomnia in children and adolescents aged from 2 to 18 years with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.
- The superiority of melatonin LP over the placebo has been demonstrated on the improvement in total sleep time at 13 weeks with a moderate effect size: +32 minutes for patients with a total sleep time of approximately 7 hours 30 min.

Therapeutic strategy

- The initial management of sleep-wake rhythm disorders is based on identifying the factors contributing to their onset or continuation (including environmental factors), followed by the implementation of educational and non-medicinal therapeutic measures. In the event of sleep disorders having a severe impact on the learning abilities or quality of life of the patient or family members, and in the event of a lack of efficacy or insufficient efficacy of non-medicinal alternative measures, the prescription of melatonin may be envisaged subject to medical monitoring of the benefit-to-risk ratio.
- Melatonin is currently available in the form of tablets containing 2 mg within the scope of a temporary recommendation for use (RTU) for children over 6 years of age and in the form of compounding/hospital preparations for children under 6 years of age.
- Other medicinal alternatives may be proposed alongside continued sleep-facilitating hygiene measures. Hypnotics, benzodiazepines or related drugs, with known adverse effects, may be proposed for the treatment of transient or occasional insomnia for a limited period, combined with management of contributing factors, but use for chronic insomnia is not recommended. Similarly, psychotropic drugs should be prescribed only in exceptional cases for children/adolescents with pervasive developmental disorders, and their prescription should be temporary and not considered to be definitive. Antidepressants (sedatives), melatonin agonists and antihistamines may also be beneficial according to the context of the disorder.
- **Role of the medicinal product in the therapeutic strategy**

  SLENYTO, alongside continued sleep-facilitating hygiene measures, is a second-line treatment for insomnia in its indication.

  In order to initiate treatment, regular monitoring of the patient is required with a view to assessing the effect on sleep and envisaging any potential treatment adaptation.

  Given its specific indications, it is recommended that the initial prescription of SLENYTO be restricted to paediatricians, neurologists, and psychiatrists.

  Moreover, the availability of two new dosages (1 and 5 mg) in this indication enables paediatric dose adaptation. However, the tablet form may involve a risk of false passage, particularly in young children or children with swallowing difficulties and eating disorders, and no 2 mg dosage, equivalent to the initial treatment set-up dosage, is available.

  Therefore, the Committee recommends providing these patients with a more suitable pharmaceutical form and a 2 mg dosage.

Clinical data

A double-blind randomised trial assessed the efficacy of melatonin LP versus placebo on sleep disorders in children with autism spectrum disorders or neurodevelopmental disorders associated with neurogenetic disease. The primary endpoint was the variation of the total sleep time (TST) after 13 weeks of treatment, defined as “the time at which the child wakes up in the morning – bedtime – the time to onset of sleep – the total duration of nocturnal awakenings” and calculated based on the data from the nap and sleep diary completed by parents.

- The superiority of melatonin over the placebo was demonstrated at 13 weeks with a difference in TST of 32 minutes (±15.1) on average between the melatonin LP and placebo groups, estimated on the basis of an adjusted increase in the mean TST of 51 minutes (±10.5) in the melatonin group and of 18.7 minutes (±10.8) in the placebo group (p=0,035) for patients with a mean TST at inclusion of 460 minutes, i.e. approximately 7 hrs 30 min (±1 hr 40 min).
  Quality of life was assessed as an unranked exploratory secondary endpoint using 4 validated questionnaires. An impact of melatonin LP on quality of life for patients and carers was suggested, without any robust evidence, however.
- Severe adverse events were reported by 25% of the patients in the melatonin group and 20% of the patients in the placebo group, primarily of the following type: agitation (10 and 5% respectively), fatigue (7 and 3%), mood swings (7 and 8%).

Benefit of the medicinal product

- The actual clinical benefit* of SLENYTO is high.
- SLENYTO provides clinical added value** (CAV IV, minor) in the therapeutic strategy.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 26 June 2019 (CT-17549) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement"