HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 JULY 2021

The legally binding text is the original French opinion version

sodium oxybate
XYREM 500 mg/ml oral solution

New indication

Key points

Favourable opinion for reimbursement only in the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years.

Unfavourable opinion for reimbursement in the absence of drug resistance.

What therapeutic improvement?

Therapeutic improvement in the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years.

Role in the care pathway?

In children over the age of 6 years and adolescents, only immediate-release methylphenidate (RITALINE 10 mg scored tablets) has an MA in the second-line treatment of narcolepsy with or without cataplexy in the event of an inadequate response to modafinil (MODIODAL). According to the 2017 French consensus, the management of narcolepsy in children and adolescents is based on the same first and second-line psychostimulant and anti-cataplexy treatments as in adults. The following substances are thus cited for off-label use in children and adolescents:

- modafinil (MODIODAL) in the treatment of excessive daytime sleepiness (EDS)
- methylphenidate in prolonged-release form for the treatment of narcolepsy in children from the age of 6 years,
- antidepressants.

Role of the medicinal product in the care pathway

XYREM (sodium oxybate) is a therapeutic option in the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years.

XYREM (sodium oxybate) has no role in the care pathway in the absence of drug resistance.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Type 1 narcolepsy is a chronic disease primarily manifested by excessive daytime sleepiness and cataplexy attacks. These symptoms are incapacitating to various degrees depending on their severity, with severe forms very significantly impairing quality of life.
◗ This is a symptomatic medicinal product.
◗ Considering:

- the superiority of sodium oxybate with a clinically relevant effect size, but only versus placebo and in the short term (2 weeks) assessed in adolescents and children from the age of 7 years,
- the absence of comparison versus an active comparator in a context in which half of patients (50%) had received prior treatment with stimulants (mainly methylphenidate (21%) and modafinil (17%)) then concomitantly throughout the study,
- the paediatric safety profile similar to that already known in adults and marked, in particular, by a risk of respiratory depression and depressive disorder, a suicide risk, as well as the risks of abuse or misuse,

the efficacy/adverse effects ratio is:

- high only in the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years;
- inadequately established in the other clinical situations of the MA indication extension, corresponding to non-drug-resistant adolescents and children from the age of 7 years.

◗ There are alternatives in the treatment of narcolepsy with cataplexy.
◗ This is a therapeutic option in the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years.
In the other clinical situations of the MA indication extension, corresponding to non-drug-resistant adolescents and children from the age of 7 years, XYREM (sodium oxybate) has no role in the care pathway.

<u>Public health impact</u>

Considering:

- the seriousness of the disease, which substantially impairs patients' quality of life in these severe forms,
- its prevalence,
- the partially met medical need,
- the very partial response to the partially met medical need, with
    - an expected additional impact on morbidity despite limited efficacy and safety data in children and adolescents, and on the basis of experience of its use in adults, but the absence of a demonstrated impact on quality of life,
    - the lack of demonstrated impact on the organisation of care and the patient's life pathway,

XYREM (sodium oxybate) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of XYREM (sodium oxybate) is:

- **substantial only in the treatment of narcolepsy with cataplexy in <u>drug-resistant</u> adolescents and children from the age of 7 years;**
- **insufficient to justify public funding cover in the other situations of the MA indication extension, corresponding to non-drug-resistant adolescents and children from the age of 7 years.**

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years, and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other situations of the MA indication extension concerned, corresponding to non-drug-resistant adolescents and children from the age of 7 years.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

In the presence of drug resistance

Considering:

- **demonstration of the superiority of sodium oxybate compared to placebo assessed during a 2-week double-blind, randomised-withdrawal study in adolescents and children aged from 7 years with narcolepsy with cataplexy:**
  - **for the primary endpoint of change in median number of weekly cataplexy attacks, with a clinically relevant difference (0 attacks in the sodium oxybate group versus 12.7 in the placebo group; p=0.0002), and**
  - **for the two ranked secondary clinical endpoints of clinical global impression of change score (CGIc) for the severity of cataplexy attacks and the daytime Epworth Sleepiness Scale (ESS-CHAD),**
- **the absence of data versus an active comparator in a context in which half of patients (50%) had received prior treatment with stimulants (mainly methylphenidate and modafinil) then concomitantly throughout the study,**
- **the paediatric safety profile similar to that already known in adults and marked, in particular, by a risk of respiratory depression and depressive disorder, a suicide risk, as well as the risks of abuse or misuse,**
- **the absence of robust data on quality of life,**
- **the medical need only partially met by the recommended therapeutic alternatives, some of which are used off-label,**

the Committee deems that XYREM (sodium oxybate) provides a minor clinical added value (CAV IV) in the care pathway for the treatment of narcolepsy with cataplexy in drug-resistant adolescents and children from the age of 7 years.