HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
15 DECEMBER 2021

The legally binding text is the original French opinion version

eszopiclone
NOXIBEN 1 mg, 2 mg and 3 mg film-coated tablets

First assessment

Key points

Favourable opinion for reimbursement in the treatment of insomnia in adults, generally for a short period of time and only if insomnia is severe, disabling or causing the patient extreme distress.

Role in the care pathway?

In all cases of insomnia, it is important to ensure compliance with the rules for good sleep hygiene and a balanced sleep/wake cycle. These rules can sometimes be sufficient to restore sleep in the event of mild insomnia without comorbidities. In the event of comorbidities, it will be left to the clinician's decision whether to treat the insomnia or the comorbidity(ies) first or both at the same time.

Cognitive behavioural therapies (CBT) may be proposed as first-line treatment in the event of anything other than occasional insomnia. When sleep hygiene rules are not enough, the prescription of a hypnotic is envisaged as second-line treatment. A hypnotic benzodiazepine or related substance should only be prescribed as part of a short-term strategy. The lowest effective dose for each individual should be sought and prescribed for a limited period of time, of a few days to a maximum of 4 weeks, including the dose tapering period. The accumulation of several medicinal products with a sedative effect is to be avoided, since it does not bring any additional effect but potentiates the sometimes serious adverse effects.

The choice of hypnotic depends on:
- the patient's insomnia profile (difficulty falling asleep, difficulty maintaining sleep or early morning awakening),
- the time to onset (Tmax) and duration of the product's action, related to the dose used and the half-life,
- the risk of interactions with other medicinal products, particularly other psychotropic drugs (avoid the accumulation of several psychotropic drugs where possible),
- the patient's physiological condition (age, renal and hepatic function),
- the type of activities liable to be carried out by the patient following administration of the medicinal product.

In all cases of prescription of a hypnotic benzodiazepine or related substance, patients should be informed of the treatment conditions, the adverse effects and the precautions to be followed. In particular, they should be informed about the low effect of these medicines, the risks of memory disturbances, drowsiness, behavioural disturbances and falls, as well as the phenomenon of tolerance and dependence. Prescription should be avoided in patients at risk of developing dependence (patients already on benzodiazepines, using high doses or with a history of other types of dependence, on a medicinal product or otherwise). Switching from one medicinal product to another is only justified if the patient has adverse effects directly related to the product used, or potentially in the context of withdrawal.

Discontinuation should always be gradual to minimise withdrawal effects.

Irrespective of the treatment chosen, a second consultation at least is recommended at the end of the prescription period for reassessment of the situation, if only because of the risk of the disorder becoming chronic. It is important to remember that these treatments can be a factor in terms of maintaining insomnia, in particular due to the rebound insomnia they can cause on discontinuation.

In the elderly, the general objective of insomnia management should be to promote daytime wakefulness, physical or intellectual activities, a late bedtime and a regular wake/sleep rhythm. Non-pharmacological treatments should be favoured. The use of benzodiazepine hypnotics or related substances exposes elderly patients, in particular, to a risk of falls and their consequences (notably loss of autonomy), as well as to cognitive impairment and road traffic accidents. It is recommended that the benefits and risks of benzodiazepine use and discontinuation be discussed with each patient.

Role of NOXIBEN (eszopiclone) in the care pathway:

The Committee considers that NOXIBEN (eszopiclone), like all benzodiazepine hypnotics and related substances, is part of a short-term strategy for the second-line treatment of insomnia in adults, only if insomnia is severe, disabling or causing the patient extreme distress, in view of the medicinal alternatives available.

From the time of initiation of treatment, physicians must explain the treatment duration and discontinuation methods to patients due to the treatment-related risks.

Special recommendations

The Committee highlights the fact that the prescription duration for eszopiclone, as with all hypnotic benzodiazepines and related substances, must not exceed 4 weeks.
As regards the care pathway of patients, the Committee points out that:
- in the event of failure of sleep hygiene measures, the use of non-medicinal treatments, such as cognitive behavioural therapy, should be favoured before initiating any treatment with a hypnotic medicinal product,
- an accurate and complete assessment of patients' medical, psychological and social situation, and of their sleep habits, is necessary before prescribing any hypnotic treatment,
- no hypnotic benzodiazepines or related substances are indicated in the treatment of chronic insomnia; furthermore, the safety profile of these medicinal product exposes patients to a risk of harmful consequences that are exacerbated as the exposure duration increases (particularly in at-risk individuals, such as the elderly),
- dependence on these products is possible, even in the absence of any risk factors for dependence.

In addition, the Committee maintains its recommendations:

- better public information on the risks of chronic use of these medicinal products and on their proper use through the implementation of a strong and repeated media campaign aimed at the general public,
- reinforcement of the initial and ongoing training of healthcare professionals on the proper use of benzodiazepines and how to discontinue them,
- development of the use of and access to non-medicinal treatments (cognitive behavioural therapies),
- support for measures that may be recommended by the ANSM, within the framework of its missions to improve the use of these products.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Sleep disturbances and the associated daytime repercussions can have harmful consequences on daily functioning and the occurrence or exacerbation of physical or psychological conditions. Occasional or temporary insomnia can become chronic and can thus lead to personal and social complications with socio-professional repercussions.
◗ The proprietary medicinal product NOXIBEN (eszopiclone) is a symptomatic medicinal product.
◗ The efficacy/adverse effects ratio of NOXIBEN (eszopiclone) is, like all benzodiazepine hypnotics and related substances, low in the short term and insufficient beyond a period of 4 weeks.
◗ There are numerous therapeutic alternatives, including non-medicinal therapies and benzodiazepines and related substances.
◗ NOXIBEN (eszopiclone), like all benzodiazepine hypnotics and related substances, is part of a short-term strategy for the second-line treatment of insomnia in adults, generally for a short period of time and only if insomnia is severe, disabling or causing the patient extreme distress, in view of the medicinal alternatives available.

Public health impact
Considering:
- the disabling nature of sleep disorders with an impact on daily life and long-term consequences,
- the high prevalence of these conditions,
- the partially met medical need,
- the lack of additional response to the identified need:
    - the absence of an additional impact on morbidity given the limited efficacy and safety data available, which is primarily short-term and versus placebo,
    - the lack of a demonstrated additional impact on quality of life in the absence of data,
- the lack of a demonstrated additional impact on the organisation of care in the absence of data,
- and the risk of the onset of harmful consequences of this medicinal product in view of those observed for the class of benzodiazepines and related substances, with an impact on the community (accidents, falls, dependence, drug addiction, etc.),

NOXIBEN (eszopiclone) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of NOXIBEN (eszopiclone) is low in the treatment of insomnia in adults, generally for a short period of time and only if insomnia is severe, disabling or causing the patient extreme distress.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 15%**

Clinical Added Value

Considering:

- **demonstration of a superiority of eszopiclone versus placebo in 7 randomised double-blind studies (3 with a duration ≤ 4 weeks and 4 with a duration of 6 weeks to 6 months), with a small size effect of around 5 to 50 minutes versus placebo for sleep parameters: sleep latency (+10.8 to +36.9 minutes), wake time after sleep onset (+5.5 to +12.0 minutes) and total sleep time (+21.6 to +44.1 minutes),**
- **demonstration of non-inferiority of eszopiclone versus zopiclone in terms of insomnia severity index (ISI) assessed during a 4-week single-centre study,**
- **the absence of data enabling assessment of the superiority of eszopiclone compared to the non-medicinal therapies recommended as first-line treatment in the event of failure of sleep hygiene measures, and compared to other hypnotics,**
- **the safety profile similar to that of other benzodiazepines and related substances associated with harmful consequences that are exacerbated as the exposure duration increases,**

the Committee deems that NOXIBEN (eszopiclone) provides no clinical added value (CAV V) in the treatment of insomnia in adults, generally for a short period of time and only if insomnia is severe, disabling or causing the patient extreme distress.