HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
19 JANUARY 2022

The legally binding text is the original French opinion version

Pitolisant (hydrochloride)
OZAWADE 4.5 mg film-coated tablets
OZAWADE 18 mg film-coated tablets

First assessment

Key points

Favourable opinion for reimbursement only to improve wakefulness and reduce excessive daytime sleepiness (EDS) in patients with moderate to severe obstructive sleep apnoea (OSA) and who are:

- compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated,
- or who have not tolerated primary OSA therapy.

Unfavourable opinion for reimbursement in the other clinical situations of the MA.

What therapeutic improvement?

Therapeutic improvement in the management of the condition in patients compliant with primary OSA therapy, in the same way as SUNOSI (solriamfetol).

Therapeutic improvement in the management of the condition in patients who have not tolerated primary OSA therapy.

Role in the care pathway?

Lifestyle and dietary measures must be put in place in all OSA patients.

Treatment depends on the severity of the OSA, taking into account two components: the apnoea–hypopnoea index (AHI) and the severity of the daytime sleepiness after excluding any other cause for sleepiness.

The reference treatment is nasal ventilation by continuous positive airway pressure (CPAP), the efficacy of which has been demonstrated only in the event of adequate compliance. CPAP is currently included in the list of products and services qualifying for reimbursements and funded in accordance with the indications established in view of the clinical symptoms reported (with exclusion of any other sleep disorder) and an AHI score that must be ≥ 15.

The initial prescription and the quality of treatment initiation (particularly the first three months) are key factors in patients' subsequent compliance with their treatment. The prescriber and the service provider and equipment distributor (PSDM) must implement the measures required to encourage compliance, particularly in the event of intolerance to treatment (mask-patient interface problems, upper airway dryness, etc.)

Mandibular advancement devices (MADs) may be proposed as second-line options following refusal of or intolerance to CPAP. As regards surgical procedures, there are no recommendations with a high level of evidence in favour of surgery (in particular surgery of the jaw or base of the tongue); it may be envisaged in paediatric cases when the cause of the OSA is anatomical.

The proprietary medicinal product SUNOSI containing solriamfetol, evaluated by the Committee in 2020, is a first-line medicinal treatment in treatment-compliant patients whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.

Role of the medicinal product in the care pathway

Based on:

- the demonstrated efficacy of pitolisant versus placebo, a relevant comparator on the date of implementation of these studies, on the ESS score in two randomised, double-blind studies conducted in patients with moderate to severe OSA,
- with the respective inclusion criteria of these two studies having been restricted to patients presenting residual sleepiness:
  - o despite regular nasal CPAP treatment with good compliance, this compliance being an essential prerequisite in this disease,
  - o or refusing CPAP treatment (without specifying the reason for refusal),

the Committee considers that OZAWADE (pitolisant) is a first-line medicinal treatment in **patients with moderate to severe OSA, who are compliant with primary OSA therapy,** such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated, **or who have not tolerated primary OSA therapy**.

In the absence of data, OZAWADE (pitolisant) has no role in the care pathway in the other clinical situations of the MA, corresponding to:

- either patients with mild OSA,
- or patients with moderate to severe OSA and who are non-compliant with primary OSA therapy, such as CPAP, with persistent sleepiness.

According to article L. 165-1 of the French Social Security Code "Patient compliance is assessed over a period of 28 consecutive days. During this period, the patients must actually use their CPAP device for at least 112 hours", i.e., an average of 4 hours per night.

In addition the Committee highlights the absolute need to assess intolerance to primary OSA therapy, based on a strict algorithm, before considering the initiation of treatment with OZAWADE (pitolisant). In particular, this can be defined by persistent intolerance after all the corrective measures aimed at eliminating its causes have been taken, either concerning the interface (mask adjustment/modification; type, size, straps, leak management, etc.), the pressure setting/level (manual or automatic), any humidification, etc. It is highlighted that the efficacy of CPAP depends on adequate compliance and that the initial prescription of primary OSA therapy and the appropriate initiation of this treatment (particularly the first three months) are key factors in patients' subsequent compliance with their treatment.

Primary OSA therapy should be maintained in parallel with medicinal treatment for sleepiness, or periodically rechallenged in patients not tolerating primary OSA therapy.

The Committee highlights that OZAWADE (pitolisant) is not a therapy for the underlying airway obstruction in patients with OSA.

In the absence of comparative data between OZAWADE (pitolisant) and SUNOSI (solriamfetol), in clinical situations of residual sleepiness under primary OSA therapy, the choice between these two proprietary medicinal products should be made, in particular, on the basis of the patient's characteristics, the respective efficacies and safety profiles of the medicinal products and the resulting contraindications.

Special recommendations

The Committee warns that it is important to adhere to the prescription restrictions indicated in the MA, in particular:

- to monitor good compliance with primary CPAP therapy, with objective measurements of compliance and the course of the OSA,
- the absolute need to assess intolerance to primary OSA therapy, based on a strict algorithm

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Excessive daytime sleepiness is one of the dominant clinical symptoms in OSA, incapacitating to various degrees depending on its severity, which significantly impairs quality of life in severe forms.

◗ The proprietary medicinal product OZAWADE (pitolisant) is a symptomatic treatment.

◗ Considering:

- demonstration of the superiority of pitolisant with a modest effect size deemed to be clinically relevant versus placebo and in the short term in two randomised double-blind studies conducted in patients with moderate to severe OSA,
- with the inclusion criteria of the two respective studies having been restricted to patients with residual sleepiness:
    - despite regular nasal continuous positive airway pressure (CPAP) treatment with good compliance,
    - or refusing CPAP treatment (without specifying the reason for refusal),
- the short and medium-term safety profile assessed in this OSA indication,
- the lack of robust quality of life data in a context in which this is particularly impacted in this disease,

the efficacy/adverse effects ratio of OZAWADE (pitolisant) is:

- high to improve wakefulness and reduce excessive daytime sleepiness (EDS) in patients with moderate to severe OSA, who are compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated, or who have not tolerated primary OSA therapy,
- inadequately established in the other clinical situations of the MA corresponding either to patients with mild OSA, or to patients with moderate to severe OSA and who are non-compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), with persistent sleepiness.

◗ OZAWADE (pitolisant) is a first-line medicinal treatment in patients with moderate to severe OSA, who are:

- either compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated,
- or who have not tolerated primary OSA therapy.

In the other clinical situations of the MA, corresponding to:

- either patients with mild OSA,
- or patients with moderate to severe OSA and who are non-compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), with persistent sleepiness,

OZAWADE (pitolisant) has no role in the care pathway in the absence of data in these patients.

Public health impact

Considering:

- the seriousness of the condition and its prevalence
- the medical need:
  - that is partially met in cases in which patients have been declared as being compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated,
  - that is not met in situations of intolerance to primary OSA therapy.
- the partial response to the identified need, with:
  - an additional impact on morbidity but without a demonstrated impact on mortality,
  - the absence of data demonstrating an additional impact on quality of life,
  - the absence of a demonstrated impact on the organisation of care and the absence of demonstrative data on the care or life pathway,

OZAWADE (pitolisant) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of OZAWADE (pitolisant) is:

- **substantial to improve wakefulness and reduce excessive daytime sleepiness (EDS) in patients with moderate to severe OSA and who are:**
  - **either compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated,**
  - **or who have not tolerated primary OSA therapy**
- **insufficient to justify its public funding cover in all other clinical situationsof the MA, corresponding to:**
  - **either patients with mild OSA,**
  - **or patients with moderate to severe OSA and who are non-compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), with persistent sleepiness.**

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 indication to improve wakefulness and reduce excessive daytime sleepiness (EDS) in patients with moderate to severe OSA who are:**
  - **either compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated,**
  - **or who have not tolerated primary OSA therapy**
- **an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other clinical situations of the MA, corresponding to:**
  - **either patients with mild OSA,**
  - **or patients with moderate to severe OSA and who are non-compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), with persistent sleepiness.**

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

In patients with moderate to severe OSA, considering:

- demonstration of the superiority of pitolisant compared to placebo in two randomised, double-blind phase 3 studies in patients with moderate to severe OSA in terms of change in the daytime Epworth Sleepiness Scale (ESS) score after 12 weeks, assessed subjectively by the patient (primary endpoint) with a mean difference estimated to be -2.6 points (CI95% [-3.9;-1.4]) to -2.8 points CI95% [-4.0; -1.5],
- the relevance of this score in the assessment of EDS in OSA, with an effect size deemed to be clinically relevant versus placebo, although modest,
- the medical need that is not met in situations of intolerance to primary OSA therapy, and partially met by the proprietary medicinal product SUNOSI (solriamfetol) in the case of patients declared as compliant with primary OSA therapy

but in view of:

- the absence of robust data relative to the objective assessment of sleep disorders and quality of life, with these having been assessed as exploratory secondary endpoints,
- the absence of direct comparative data versus solriamfetol authorised in patients compliant with primary OSA therapy, considered to have been developed concomitantly, however,

the Committee considers that OZAWADE (pitolisant) provides:

- **a minor clinical added value (CAV IV), in the same way as SUNOSI (solriamfetol), in the current therapeutic strategy to improve wakefulness and reduce excessive daytime sleepiness (EDS) in patients compliant with primary OSA therapy, such as continuous positive airway pressure (CPAP), and whose EDS has not been satisfactorily treated,**
- **a minor clinical added value (CAV IV) in the current therapeutic strategy to improve wakefulness and reduce excessive daytime sleepiness (EDS) in patients who have not tolerated primary OSA therapy.**