HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
20 OCTOBER 2021

The legally binding text is the original French opinion version

midazolam
MIDAZOLAM MYLAN 1 mg/ml, 5 mg/ml solution for injection or rectal solution

Indication extension
Availability in the community setting

Key points

Favourable opinion for reimbursement in **community and hospital settings** in the indication **sedation in palliative care**.

MIDAZOLAM MYLAN is reimbursable in the community medicine setting in this indication only.

What therapeutic improvement?

Therapeutic improvement in management of sedation in palliative care.

Role in the care pathway?

In the sedation in palliative care indication

Sedation practices in palliative care situations were the subject of HAS guidelines in 2020.
The medicinal products cited do not have an indication validated by an MA, except for midazolam-based medicinal products.

There are two categories of sedation practices:
- proportionate sedation, i.e., with a depth and duration proportionate to relief of the symptom, with certain situations of vital distress requiring urgent relief (asphyxia syndrome, severe haemorrhage, for example);
- continuous deep sedation inducing altered consciousness maintained until death (CDSUD).

The objective of CDSUD inducing altered consciousness maintained until death is to achieve a depth of sedation (Richmond Agitation - Sedation Scale [RASS] - 4, - 5), irrespective of the requirements related to the patient's suffering. In this context, artificial life-sustaining treatments, including nutrition and hydration, should be stopped.
The indications, decision-making processes, organisation, assessment and monitoring of CDSUD were developed in the HAS care pathway guide, in particular the obligation to implement the legally-required collegial procedure. This collegial obligation is maintained in the outpatient setting.

Outside the specific context of CDSUD, the use of proportionate palliative sedation is only recommended following the application of all good practices for symptom control. Sedation is not intended to treat a symptom or suffering that has not yet been adequately assessed or treated.
Clinical assessment is recommended throughout sedation to assess the effects and detect insufficient efficacy, using standardised assessment tools (see HAS care pathway guide).
In addition to the clinical assessment of the care team, the three criteria that will lead to a dose adjustment or addition or change of product are:
- depth of the sedation, assessed using the Richmond Agitation-Sedation Scale (RASS);
- degree of relief of the patient: relief from refractory symptoms using hetero-assessment scales;
- adverse effects: awakening with confusional syndrome, tachyphylaxis with need to increase doses, respiratory depression, vomiting, etc.

In CDSUD, analgesics must be systematically used, whether these are introduced, continued or stepped up.
In all cases, analgesics alone - in particular opioid analgesics - cannot be used as sedatives.

The organisational aspects and different patient profiles should be taken into consideration depending on the care context, in particular at home, in a residential care home (EHPAD) or in another healthcare facility.
The team caring for the patient is supported by available structures with a team with palliative care expertise, in particular networks, the community palliative care team (EMSP) and/or HAH (hospital at home) team when the patient is at home. In their absence, it should contact a team specialised in palliative care to have a contact physician, with expertise in palliative care, alerted and reachable for pharmacological advice (see HAS care pathway guide).

The drawing up of a protocol of advance directives is recommended in order to anticipate sedation practices appropriate to these emergency situations and the place of care concerned.
Sedation practices, including CDSUD, can be performed at any place of care, including at home. However, in the event of sedation outside the hospital sector and given the organisational constraints, the possibility of the need to transfer the patient to hospital must be considered.

Medicinal products used in proportionate sedation

Midazolam is recommended as a first-line treatment in the context of proportionate sedation. Wherever possible, it is administered intravenously. If no venous approach is accessible, the subcutaneous route should be used.
In the event of insufficient efficacy, it is recommended that the use of second-line sedative medicines be promptly envisaged. Depending on the second-line sedative used, midazolam will be continued or

progressively withdrawn. A switch from midazolam to another benzodiazepine and the combination of several benzodiazepines are not recommended.
Neuroleptics are second-line medicinal products, in particular chlorpromazine in the event of IV sedation and levomepromazine, which is more sedative, in the event of SC sedation.
In this situation, the opinion of a physician experienced in sedation practices is recommended for the prescription. The availability and competence of caregivers monitoring sedation are also necessary.
Other drugs may be used as second-line treatment provided that they are prescribed by an experienced physician and administered in an appropriate monitoring context. These include:

- ketamine, particularly in the event of associated pain (potentiation, co-analgesia);
- propofol;
- dexmedetomidine.

Phenobarbital and gamma hydroxybutyrate (oxybate) are no longer used in these situations.

Medicinal products used in continuous deep sedation until death (CDSUD)

Close monitoring of the efficacy and safety of sedation by a nurse and collaboration with a specialised palliative care team are recommended for any CDSUD given the expected sedative effect.
Although there is a risk of tachyphylaxis in the event of prolonged use of benzodiazepines, midazolam by injection is also recommended as a first-line medicine in the context of CDSUD. It is recommended that midazolam be administered intravenously. If intravenous administration is impossible, the subcutaneous route may be envisaged.
Combination with an analgesic is recommended to prevent any risk of pain.
The second-line medicinal products are similar to those described for proportionate sedation.
In the event of insufficient efficacy of sedation, transfer to a hospital department is recommended.

Specific contexts of the practice related to the place of care

The place of care also determines the products used, based on the training and experience of the palliative care contact physicians and the care team, as well as monitoring capacities.

- Sedation in medical, surgical and obstetric departments

In a hospital unit including designated palliative care beds, as in routine care units, the choice of products depends on their availability, the experience of the medical and care teams and the degree of involvement and availability of specialised palliative care contact physicians.

- Sedation in palliative care units

In a dedicated palliative care unit, the organisational conditions for putting in place sedation are theoretically met with, in particular, experienced teams.

- Sedation in intensive care units

The organisational conditions for putting in place sedation are also met, with, in particular, teams experienced in sedation practices. Liaison with specialised palliative care contact physicians should be encouraged, particularly in decision-making processes and for medicinal arrangements in the event of proportionate sedation. The formalisation of department protocols is recommended. If the patient is already sedated and the fixed objectives are met, there is no need to change the medicinal product. Irrespective of the type of sedation, if the objective is not met or in the event of care that could cause discomfort, it is recommended to administer additional boluses with or without adjustment of the continuous dose.

- Sedation at home, in residential care homes or other medico-social facilities

In the context of proportionate sedation, midazolam remains the first-line treatment. When second-line medicinal treatment is insufficient (such as the midazolam – neuroleptic combination), transfer to a specialised department should be discussed.
For continuous deep sedation until death (CDSUD), its implementation at home systematically requires the support of a specialised palliative care team, in accordance with the conditions of the HAS quick reference guide on “How to implement continuous deep sedation until death”, particularly with respect to the methods for administration, adjustment and monitoring of medicinal products, as well as support for family and friends, and professionals.
In addition to the legally-required eligibility criteria, particularly close attention should be paid to the operational feasibility of sedation, the expected result (depth of sedation), particularly in terms of comfort and security for the patient, and to the role and experience of the patient’s family and friends.
Midazolam is recommended as first-line treatment, administered by the IV route.

The conditions for implementation of CDSUD are as follows (see HAS care pathway guide) and must be strictly followed:

- prior collegial procedure defined by the regulations;
- presence of a physician during titration;

- physician who can be contacted 24 hours a day with the possibility of home medical visits;
- personnel trained in the techniques, administration and monitoring of the treatments used;
- palliative care teams or network involved, even in HAH;
- availability of a fallback bed, preferably in a palliative care unit, or, failing that, in a department with a good command of sedation practices.

Summary of the role of MIDAZOLAM MYLAN in the care pathway:

In the sedation in palliative care indication, which includes proportionate sedation and continuous deep sedation, MIDAZOLAM MYLAN (midazolam) is a first-line treatment according to the HAS guidelines, for use in both hospitals and the community setting, provided that the prerequisites of the recommended care pathway are met.

The indications relative to anaesthesia and sedation in intensive care units by their nature only concern hospital structures, where midazolam retains its important role in the management of patients.

In the indication relative to conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia, given the severity of patients concerned by this indication and/or their essential monitoring with the help of human and technical resources related to the disease but also to the administration of midazolam, the latter must only be carried out in appropriate care structures and not in the patient's home.
In sum, in the indications concerning conscious sedation, anaesthesia and sedation in intensive care units, MIDAZOLAM MYLAN (midazolam) is not intended for use in a community setting.

Special recommendations

Concerning the prescribing conditions for midazolam, it is highlighted, in particular, that when midazolam is indicated for sedation in palliative care, it may be administered in all places of care, including at home. However, it systematically requires the support of a specialised palliative care team. The team caring for the patient must be supported by available structures with a team with palliative care expertise (in particular networks, the community palliative care team (EMSP) and/or HAH (hospital at home) team) when the patient is at home. In their absence, it should contact a team specialised in palliative care to have a contact physician, with expertise in palliative care, alerted and reachable for pharmacological advice. A physician and a nurse must be reachable 24 hours a day, with the nurse able to travel to attend the patient.

The Committee therefore recommends that when the prescription of midazolam is envisaged in this indication, the caregiving team should be supported by a palliative care and HAH team, involving the formalisation of an appropriate care network organisation.

If these conditions are not met, hospital care must be favoured.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

Sedation in palliative care

- The end of life refers to the last moments of life of a person in the advanced or terminal phase of a serious and incurable disease/condition, inflicting physical or psychological suffering that cannot be alleviated or that the person considers to be intolerable.
  Sedation proportionate to the severity of the symptoms can allow the patient to maintain a relational life; it may be transient, intermittent and potentially reversible. It must be accessible to advanced or terminal patients to respond to refractory suffering.
  A patient can request CDSUD in the following two situations:
  • if a patient presents suffering refractory to treatments, when he/she has a serious and incurable condition which is life-threatening in the short term
  • if a patient with a serious and incurable condition decides to stop treatment, and this decision has life-threatening consequences in the short term and is likely to result in unbearable suffering
- MIDAZOLAM MYLAN (midazolam) is a symptomatic medicinal product.
- The efficacy/adverse effects ratio of midazolam in palliative care is high.
- There is another midazolam-based medicinal product with an indication for sedation in palliative care.
- In the sedation in palliative care indication, which includes proportionate sedation and continuous deep sedation, MIDAZOLAM MYLAN (midazolam) is a first-line treatment according to the HAS guidelines, for use in both hospitals and the community setting, provided that the prerequisites of the recommended care pathway are met.

Public health impact

Considering:

- the serious condition of the patients concerned by the use of midazolam at the end of life,
- the unmet medical need in palliative care sedation in the community setting,
- the response to the identified need with an impact on quality of life, albeit not demonstrated, with no deterioration in morbidity and mortality,
- the expected impact on the care pathway of patients, for which the organisation in the community setting nonetheless needs to be formalised with the availability of midazolam,

MIDAZOLAM MYLAN (midazolam) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of MIDAZOLAM MYLAN (midazolam) is substantial in sedation in palliative care.

The Committee issues a favourable opinion for inclusion of MIDAZOLAM MYLAN (midazolam) in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in sedation in palliative care.

- **Recommended reimbursement rate: 65%**

- The indications concern patients with conditions that may be life-threatening.
- MIDAZOLAM MYLAN (midazolam) is a symptomatic medicinal product.
- The efficacy/adverse effects ratio of midazolam in these indications is high. The efficacy and safety of midazolam have been well established due to its frequent use in hospitals for many years.
- There are other midazolam-based medicinal products with an indication in conscious sedation, anaesthesia and sedation in intensive care units.
- The indications relative to anaesthesia and sedation in intensive care units by their nature only concern hospital structures, where midazolam retains its important role in the management of patients.

  In the indication relative to conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia, given the severity of patients concerned by this indication and/or their essential monitoring with the help of human and technical resources related to the disease but also to the administration of midazolam, the latter must only be carried out in appropriate care structures and not in the patient's home.

  In sum, in the indications concerning conscious sedation, anaesthesia and sedation in intensive care units, MIDAZOLAM MYLAN (midazolam) is not intended for use in a community setting or has no role in the care pathway in the community setting.

Public health impact

Considering:

- the potentially serious condition of the patients concerned by the use of midazolam,
- the absence of an identified medical need in the community setting,
- the potentially negative impact on the patient's life pathway in view of the risks inherent to administration of midazolam in the community setting,
- the need for monitoring of patients in care facilities,

in the community setting, MIDAZOLAM MYLAN (midazolam) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of MIDAZOLAM MYLAN (midazolam) is insufficient in conscious sedation, anaesthesia and sedation in intensive care units justify its funding in the community setting by the French national health insurance system.

The Committee issues an unfavourable opinion for inclusion of MIDAZOLAM MYLAN (midazolam) in the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications for conscious sedation, anaesthesia and sedation in intensive care units justify its funding in the community setting.

Clinical Added Value

In the sedation in palliative care indication

Considering:

- the identified substantial medical need, partially met in the hospital setting and unmet in the community setting,
- the known efficacy and safety profile of midazolam in view of experience of its use,
- the expected substantial improvement in the end-of-life care pathway and care conditions of patients,
- the undemonstrated but expected impact on patients' quality of life,

the Transparency Committee considers that MIDAZOLAM MYLAN (midazolam) provides a minor clinical added value (CAV IV) in the care pathway for sedation in palliative care.