HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 JULY 2021

The legally binding text is the original French opinion version

esketamine
ESKETAMINE IDD 5 mg/ml and 25 mg/ml, solution for injection/infusion

First assessment

Key points

Favourable opinion for reimbursement in:

- induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics;
- anaesthesia and pain relief (analgesia) in emergency medicine;
- pain control in artificial respiration (intubation).

Unfavourable opinion for reimbursement for supplementation of regional or local anaesthesia, in view of the available alternatives.

What therapeutic improvement?

No clinical added value in the therapeutic strategy (which includes ketamine) in the induction and maintenance of general anaesthesia, in anaesthesia and pain relief in emergency medicine and pain control in artificial ventilation.

Role in the care pathway?

- **<u>Induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics</u>**

Management in adults:
In adults, there is no specifically recommended single strategy for the induction and maintenance of anaesthesia, whether it is performed on a complete hospitalisation or outpatient basis. However, IV anaesthetics are preferred in adults. Anaesthetic strategies are the subject of guidelines (*Société Française d'Anesthésie et de Réanimation* (French Society of Anaesthesia and Intensive Care), SFAR); in particular, they depend on the type of patient and the type of surgery.
All the general anaesthetics administered by the IV route with an MA in this indication (i.e. propofol, etomidate, thiopental, midazolam and ketamine) may be used, alone or in combination.
Halogenated anaesthetics (sevoflurane, desflurane, isoflurane), administered as inhaled agents, also have an MA in this indication. Halothane is no longer used.
In general, depending on the patient and the procedure performed, it is recommended that short-acting anaesthetic agents be preferred, which is the case for most anaesthetic agents used today.
Curares, which are neuromuscular blocking agents, can be combined to facilitate intubation and surgery.

Management in children:
Inhalation is the most widely used method in paediatrics for the induction and maintenance of general anaesthesia:
- for induction, sevoflurane is the anaesthetic often used,
- for maintenance, several anaesthetic agents can be proposed, including sevoflurane or desflurane.

Depending on the type of surgery, its duration and the associated risks, IV anaesthesia is favoured. In this case propofol, etomidate, thiopental and ketamine can be used.

In adults and children, morphine derivatives are generally used to prevent perioperative and postoperative pain. The SFAR recommends the use of ketamine as a first-line analgesic, administered following anaesthetic induction and perioperatively as continuous administration. However, the safety profile of ketamine limits its use, in particular due to the risk of psychic reactions and prolongation of the awakening period.

Role of ESKETAMINE IDD (esketamine) in the care pathway:
For the induction and maintenance of general anaesthesia, ESKETAMINE IDD (esketamine) is a first-line treatment, to be used alone or in combination with other anaesthetics, in patients who are haemodynamically unstable or at risk of bronchospasm and in paediatrics.

- **<u>Supplementation of regional or local anaesthesia</u>**

Management in adults
Locoregional anaesthesia (LRA) is based on the use of local amino amide anaesthetics administered locally close to the peripheral nerves, by the epidural or intrathecal route. In adults lidocaine and mepivacaine are the most widely used anaesthetics for short surgical procedures. Ropivacaine and levobupivacaine are used for long procedures or those requiring postoperative analgesia.
At present, only fentanyl and sufentanil have an MA in this indication. The supplements most commonly used in clinical practice are morphine derivatives administered intrathecally, as well as clonidine administered intrathecally or as a peripheral nerve block, used off-label.
Midazolam and dexamethasone (IV) are used as LRA supplements.
Ketamine is not administered intrathecally since it does not have an MA and there is a risk of neurotoxicity.

Management in children
In paediatric medicine, as in adults, the local anaesthetics generally used for locoregional anaesthesia are amino amides. The use of bupivacaine is restricted to spinal anaesthesia.
As in adults, clonidine is used off-label, administered by the epidural or intrathecal route, as well as morphine derivatives (morphine, fentanyl and sufentanil) administered by the spinal or epidural route to obtain analgesia.
Role of ESKETAMINE IDD (esketamine) in the care pathway:
In regional or local anaesthesia, ESKETAMINE IDD (esketamine) has no role in the care pathway as a supplement to local anaesthetics in view of the available alternatives.

- **<u>Anaesthesia and pain relief (analgesia) in emergency medicine</u>**

Management in adults:

In an emergency context, several sedative and analgesic agents may be considered; however, treatments with rapid pharmacokinetics are favoured.

LRA is the favoured first-line method if the context allows it (localised pain accessible to anaesthetic block), although this is not the most usual situation. In this case, amino amide anaesthetic agents are proposed, in particular lidocaine, with or without adrenaline, and ropivacaine.

When LRA is contraindicated and/or use of analgesia by the systemic route is relevant, it is recommended to use the following:

- for mild to moderate pain, step 1 or 2 analgesics used alone or in combination with other treatments;
- in mild traumatology and for care-related pain, an equimolar mixture of oxygen and nitrous oxide (EMONO);
- in the event of failure of lower step analgesics and for intense pain, it is recommended to use intravenous morphine derivative titration from the outset, alone or as part of multimodal analgesia. However, their use remains limited: fentanyl and sufentanil are not recommended for analgesia in spontaneously breathing patients and remifentanil and alfentanil have not been adequately assessed in this context.

Morphine is the most widely used product in this context.

For spontaneously breathing patients, the French guidelines recommend analgesic combinations in the context of multimodal analgesia in the following situations:

- EMONO, ketamine, nefopam and/or LRA in combination with morphine for the treatment of pain in traumatology;
- nefopam and/or ketamine in combination with the usual analgesics for the treatment of neuropathic pain;
- midazolam in the event of persistent agitation despite well managed analgesia;
- co-analgesia combining ketamine, along with locoregional analgesia, in addition to morphine titration in patients on long-term morphine treatment and in addicts.

The SFAR recommends the administration of intravenous ketamine off-label for analgesia in spontaneously breathing patients.

Management in children:

In a paediatric emergency context, analgesia - and, if necessary sedation - should be systematically initiated in the presence of pain or when an invasive procedure needs to be performed.

As in adults, the treatment of pain is based first of all on LRA using lidocaine.

If systemic analgesia is required, it is recommended to use the following:

- for mild or moderate pain, paracetamol by the oral or IV route and/or codeine by the oral route,
- in the event of failure of lower step analgesics or in the event of severe pain from the outset, it is recommended to use a step 3 analgesic (e.g. morphine) directly, to obtain rapid efficacy,
- for analgesia before the performance of short procedures: ketamine by the slow IV or intramuscular route.

Role of ESKETAMINE IDD (esketamine) in the care pathway:

For anaesthesia and pain relief in emergency medicine, ESKETAMINE IDD (esketamine) is:

- a first-line treatment for analgesia enabling the performance of short invasive procedures;
- a second-line treatment for anaesthesia and analgesia in the event of severe pain, following NSAID or opiate treatment, or in the event of failure of lower step analgesics for mild or moderate pain.

ESKETAMINE IDD (esketamine) can be used alone or in combination with analgesics, in particular opiates.

- **Pain control in artificial respiration (intubation)**

Management in adults:

In ventilated patients, in emergency departments or ICU, it is recommended to begin sedation immediately following tracheal intubation.

In its 2010 guidelines, the SFAR cited the following as some of the most suitable treatments for the sedation of ventilated patients: midazolam and propofol for hypnotics, fentanyl and sufentanil for morphine derivatives. In 2018, the SFAR also recommended the off-label intravenous administration of ketamine for co-analgesia in combination with a morphine derivative.

Management in children:

The main objectives of sedation and/or analgesia in intubated and ventilated children is to ensure their comfort, to enable correct adjustment of artificial ventilation and to facilitate their transport and mobilisation.

Several products can be used in children:

- benzodiazepines, which remain the most widely used sedatives in children, particularly midazolam;
- ketamine,
- morphine derivatives (fentanyl or sufentanil).

Midazolam + fentanyl or midazolam + sufentanil as continuous infusion are the combinations recommended for sedation and analgesia in intubated and ventilated children.

Role of ESKETAMINE IDD (esketamine) in the care pathway:

As pain control in artificial respiration, ESKETAMINE IDD (esketamine) is a first-line treatment that can be used alone or in combination with opiates, after opiates alone, in intubated and ventilated adult and paediatric patients.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

Induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics

◗ ESKETAMINE IDD (esketamine) is intended for use in the context of any anaesthesia technique inducing partial or total loss of sensitivity of the body for the performance of a surgical, medical or obstetric procedure.
◗ This proprietary medicinal product is a symptomatic treatment.
◗ ESKETAMINE IDD (esketamine) has a high efficacy/adverse effects ratio.
◗ There are therapeutic alternatives (see chapter 5 Clinically relevant comparators).
ESKETAMINE IDD (esketamine) is a first-line treatment.

Public health impact
Considering:
- the high incidence of patients requiring general anaesthesia,
- the met identified medical need,
- the lack of response to the identified need in the absence of any demonstrated impact on morbidity and mortality, quality of life or the care pathway,

ESKETAMINE IDD (esketamine) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of ESKETAMINE IDD (esketamine) is substantial in the induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics.

Supplementation of regional or local anaesthesia

◗ ESKETAMINE IDD (esketamine) is used in the context of any anaesthesia technique inducing partial or total loss of sensitivity of the body for the performance of a surgical, medical or obstetric procedure.
◗ This proprietary medicinal product is a symptomatic treatment.
◗ The efficacy/adverse effects ratio of ESKETAMINE IDD (esketamine) is inadequately established due to a lack of robust data.
◗ There are therapeutic alternatives (see chapter 5 Clinically relevant comparators).
◗ ESKETAMINE IDD (esketamine) has no role in the care pathway as a supplement to local anaesthetics in view of the available alternatives.

Public health impact

Considering:

- the high incidence of patients requiring locoregional anaesthesia,
- the met identified medical need,
- the lack of response to the identified need in the absence of any demonstrated impact on morbidity and mortality, quality of life or the care pathway,

ESKETAMINE IDD (esketamine) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ESKETAMINE IDD (esketamine) is insufficient to justify public funding cover in the supplementation of regional or local anaesthesia in view of the available alternatives.

Anaesthesia and pain relief (analgesia) in emergency medicine

- In emergency medicine, the rapid treatment of pain is a priority.
- This proprietary medicinal product is a symptomatic treatment.
- ESKETAMINE IDD (esketamine) has a high efficacy/adverse effects ratio.
- There are therapeutic alternatives (see chapter 5 Clinically relevant comparators).
- ESKETAMINE IDD (esketamine) is a first-line or second-line treatment.

Public health impact

Considering:

- the high incidence of patients requiring anaesthesia and/or pain relief (analgesia) in emergency medicine,
- the met identified medical need,
- the lack of response to the identified need in the absence of any demonstrated impact on morbidity and mortality, quality of life or the care pathway,

ESKETAMINE IDD (esketamine) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ESKETAMINE IDD (esketamine) is substantial in anaesthesia and pain relief (analgesia) in emergency medicine.

Pain control in artificial respiration (intubation)

◗ Pain control is necessary when initiating and maintaining artificial ventilation, but pain is not systematic in all conscious intubated and ventilated patients.
◗ This proprietary medicinal product is a symptomatic treatment.
◗ The efficacy/adverse effects ratio of ESKETAMINE IDD (esketamine) is substantial, despite the absence of data in this indication specifically but in view of the efficacy/adverse effects ratio of the overall general anaesthesia indication, which requires intubation.
◗ There are therapeutic alternatives (see chapter 5 Clinically relevant comparators).
◗ ESKETAMINE IDD (esketamine) is a second-line treatment.

Public health impact

Considering:

- the high incidence of ventilated patients,
- the met identified medical need,
- the lack of response to the identified need in the absence of any demonstrated impact on morbidity and mortality, quality of life or the care pathway,

ESKETAMINE IDD (esketamine) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ESKETAMINE IDD (esketamine) is substantial in pain control in artificial respiration (intubation).

The Committee issues a favourable opinion for inclusion of ESKETAMINE IDD (esketamine) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indications "induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics, in anaesthesia and pain relief (analgesia) in emergency medicine, and pain control in artificial respiration (intubation)" and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion of ESKETAMINE IDD (esketamine) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication "supplementation of regional or local anaesthesia".

Clinical Added Value

Induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics

Considering:
- **demonstration of the efficacy of esketamine in comparison with placebo in a study, in terms of the reduction in cumulative postoperative morphine use (primary endpoint) in patients having undergone lumbar arthrodesis;**

but taking into account:
- **the absence of a statistically significant difference between esketamine and placebo in terms of reduction in oxycodone use in a study having included adults having undergone lumbar surgery;**
- **the absence of robust data demonstrating an advantage of esketamine in terms of efficacy or safety compared to the available alternatives;**
- **the medical need met by these alternatives;**

the Transparency Committee considers that ESKETAMINE IDD (esketamine) provides no clinical added value (CAV V) in the therapeutic strategy (which includes ketamine) in the induction and maintenance of general anaesthesia, as the only anaesthetic or in combination with hypnotics.

Anaesthesia and pain relief (analgesia) in emergency medicine

Considering:
- **the absence of robust data enabling demonstration of an advantage in terms of efficacy and safety compared to the alternatives, this data being obtained from non-comparative, descriptive observational studies;**
- **the medical need met by the existing alternatives;**

the Transparency Committee considers that ESKETAMINE IDD (esketamine) provides no clinical added value (CAV V) in the therapeutic strategy (which includes ketamine) in anaesthesia and pain relief in emergency medicine.

Pain control in artificial respiration (intubation)

Considering:
- **the absence of data having assessed the efficacy and safety of esketamine, but only of ketamine, in pain control in artificial respiration;**
- **the medical need met by the available alternatives;**

the Transparency Committee considers that ESKETAMINE IDD (esketamine) provides no clinical added value (CAV V) in the therapeutic strategy (which includes ketamine) in pain control in artificial respiration.