HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 FEBRUARY 2022

The legally binding text is the original French opinion version

isoflurane
CEDACONDA 100% V/V liquid inhalation vapour

First assessment

Key points

Favourable opinion for reimbursement in the sedation of ventilated adult patients during intensive care.

What therapeutic improvement?

No clinical added value compared to propofol.

Role in the care pathway?

The purpose of sedation-analgesia during intensive care is to ensure the patient is pain-free and easily awakened. It reduces the risks of extubation and ablation of catheters or drains.

It is necessary to identify any organ dysfunctions that may affect the pharmacokinetics and pharmacodynamics of the sedatives and analgesics used.

Failure to recognise these dysfunctions may lead to an accumulation of medicinal products, resulting in excessive sedation and/or analgesia that may unnecessarily prolong mechanical ventilation and the patient's stay in the intensive care unit. Conversely, if sedation is too light, there is a risk of self-extubation and the resulting detrimental myocardial consequences, particularly in coronary patients.

The adverse effects of excessive sedation include loss of contact with the patient, a risk of apnoea on disconnection of the ventilator or accidental extubation, prolongation of mechanical ventilation and hypotension. The current reference treatments are propofol and midazolam. They are administered either alone or, more usually, in combination with a morphine-based medicinal product since they have no analgesic action. There are no guidelines for choosing one over the other.

The guidelines of the *Société Française d'Anesthésie et de Réanimation* (SFAR - French Society of Anaesthesia and Intensive Care) / *Société de Réanimation de Langue Française* (SRLF - French-language Society for Intensive Care), and the American Society of Critical Care Medicine specified the current management of sedation for ventilated patients in the resuscitation room/ICU.
Various hypnotic agents are used in ventilated patients during intensive care:

- by the intravenous route (IV): propofol, midazolam, clonidine, dexmedetomidine and ketamine;

- by the inhaled route, halogenated agents: isoflurane, sevoflurane and desflurane.

Halogenated agents are agents with a rapid action onset that are rapidly eliminated, enabling the achievement of light to deep target sedation levels. However, their method of administration requires continuous monitoring of their concentration in expired gases and their adsorption on filters to prevent an atmospheric pollution effect. Halogenated agents can be a backup solution and require suitable equipment and consumables (SEDACONDA, MIRUS devices). When they are used, it is necessary to ensure that the rules relative to their use and training of nursing personnel are followed.

Medicinal products containing clonidine, ketamine, sevoflurane and desflurane have no MA in this indication.

Moreover, the use of multimodal analgesia (combination of morphine derivatives (morphine, fentanyl, sufentanil, alfentanil and remifentanil) with other substances, in particular paracetamol, nefopam and ketamine) is recommended during intensive care to reduce the adverse effects of morphine derivatives.

However, the SFAR points out that analgesia - including with morphine derivatives if necessary - should be favoured, in order to reduce exposure to sedatives.

Role of CEDACONDA (isoflurane) in the care pathway:

CEDACONDA (isoflurane) is a first-line halogenated agent for the sedation of ventilated patients during intensive care, like medicinal products containing propofol, dexmedetomidine and midazolam.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Ventilated patients requiring sedation during intensive care can have life-threatening conditions.
◗ The proprietary medicinal product CEDACONDA (isoflurane) is a symptomatic medicinal product.
◗ The efficacy/adverse effects ratio is high.
◗ There are other medicinal products used in ventilated adult patients during intensive care (see 05 Clinically relevant comparators).
◗ This is a first-line treatment, like medicinal products containing propofol, dexmedetomidine and midazolam.

Public health impact
Considering:

- the seriousness of the clinical situation of ventilated patients requiring sedation during intensive care,
- the incidence of these situations,
- the met medical need,
- the lack of additional response to the identified need in the absence of an additional impact of CEDACONDA (isoflurane) on morbidity and mortality,
- the absence of data supporting an impact on the care pathway,

CEDACONDA (isoflurane) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of CEDACONDA (isoflurane) is substantial in the MA indication.

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

Clinical Added Value

Considering:

- demonstration of the non-inferiority of isoflurane versus propofol in a phase III study in ventilated adult patients having undergone sedation during intensive care, on the primary endpoint, i.e. the proportion of time spent at the target sedation depth (RASS -1 to -4), with a mean difference observed between isoflurane and propofol of -0.45%, 95% CI [-2.99; 2.09] (non-inferiority limit set at -13.67%);

but in view of:

- the absence of robust comparative data between the two groups, particularly with respect to the time to awakening after the discontinuation of sedation;
- the medical need already met by various alternatives administered by the IV or inhaled route;

The Committee considers that CEDACONDA (isoflurane) provides no clinical added value (CAV V) compared to propofol in the sedation of ventilated adults during intensive care.