HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
24 JUNE 2020

esketamine
SPRAVATO 28 mg nasal spray, solution

First assessment

Key points

Favourable opinion for reimbursement in combination with a SSRI or SNRI for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy.

Unfavourable opinion for reimbursement in the rest of the MA indication.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The treatment of resistant depression requires a specialist opinion and there is no current consensus in the guidelines concerning the therapeutic strategy to be adopted.
National guidelines formalised by the *Association Française de Psychiatrie Biologique et Neuropsychopharmacologie* (AFPBN - French Association for Biological Psychiatry and Neuropsychopharmacology) and the FondaMental foundation were published in 2017, for example, detailing the therapeutic strategy in the event of a lack of response to antidepressant therapy.

The resistant nature of a major depressive episode must be the subject of in-depth diagnosis by a specialist to rule out any pseudo-resistance and confirm the treatment strategy.
In the event of an inadequate response to first-line treatment, dosage optimisation with an increase in dose or change of antidepressant is recommended.
Augmentation of antidepressant therapy by the addition of lithium salts, triiodothyronine (T3) or antipsychotic medications (aripiprazole, quetiapine), in a context of off-label use, is also a therapeutic option in the event of a partial response to the initial treatment.
Combination with a second antidepressant treatment (in particular, alpha-2 agonists mirtazapine or mianserin) may also be envisaged in the event of a partial response to well-managed initial treatment, at an appropriate time, taking into account the potential interactions and contraindications.

The addition of psychotherapy to antidepressant treatment is also effective in the event of resistant moderate major depressive disorder.

Hospitalisation is recommended in the event of severe major depressive disorder.
In the event of severe treatment-resistant depression, non-medicinal salvage methods exist, such as electroconvulsive therapy or transcranial magnetic stimulation.

Role of the medicinal product in the care pathway:

SPRAVATO (esketamine), in combination with a SSRI or SNRI, is an alternative for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy.

In the other clinical situations covered by the MA, SPRAVATO (esketamine) has no role in the therapeutic strategy.

Special recommendations

Considering the risks of the development of adverse effects during the post-administration period with SPRAVATO 28 mg (esketamine), in particular sedation, dizziness and hypertension, the Committee reiterates that, in accordance with the SmPC, patients must be monitored adequately in the period immediately following the administration, which takes place in a hospital setting only. In particular, blood pressure should be reassessed approximately 40 minutes after administration and the healthcare professional should assess the clinical condition of patients until they are ready to leave the healthcare setting.

The Committee also reiterates the need to administer SPRAVATO (esketamine) in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available, for any patients with clinically significant or unstable cardiovascular or respiratory conditions (see SmPC).

Reason for assessment	**Inclusion in list**
Indication concerned	**"SPRAVATO (esketamine, nasal spray, solution), in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode."**
Clinical Benefit	**The clinical benefit of SPRAVATO (esketamine), in combination with a SSRI or SNRI, is:** **- Low in the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy;** **- Insufficient to justify public funding in the other MA situations.**
Clinical Added Value	**Considering:** **- demonstration of the superiority of esketamine compared to placebo, in combination with a newly initiated oral antidepressant in patients under the age of 65 years with a severe major depressive episode resistant to at least two oral antidepressants,** **• as an induction treatment after 4 weeks in terms of change in MADRS total score with a low effect size (difference of -3.5 points, $CI_{95\%}$ = [-6.7; -0.3] below the clinical relevance level);** **• as a maintenance treatment after 48 weeks or more in terms of time to relapse (median time not reached in the esketamine group *versus* 273 days in the placebo group, HR = 0.49; $CI_{95\%}$ = [0.29; 0.84]);** **- exploratory results relative to quality of life;** **- the safety profile, marked, in the short term, by cases of suicide/suicidal thoughts reported in clinical studies and compassionate use programme data, and by important identified risks, such as dissociative or perception disturbances and cardiovascular disorders;** **- and uncertainties with respect to long-term safety;** **the Committee deems that SPRAVATO (esketamine), in combination with a SSRI or SNRI, provides no clinical added value (CAV V) in the therapeutic strategy for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy.**
Public health impact	**SPRAVATO (esketamine) is unlikely to have an impact on public health.**
Role in the care pathway	**Considering:** **- the efficacy demonstrated *versus* placebo as induction treatment after 4 weeks and as maintenance treatment after 48 weeks, only in patients under the age of 65 years with a severe major depressive episode resistant to at least two oral antidepressants, with a low effect size;** **- the absence of any comparative studies *versus* clinically relevant comparators, meaning that esketamine cannot be positioned compared to these;** **- the safety profile, marked, in the short term, by cases of suicide/suicidal thoughts reported in clinical studies and compassionate use programme data, and by important identified risks, such as dissociative or perception disturbances and cardiovascular disorders;** **- the restriction related to this safety profile, requiring, in particular, treatment in structures with appropriate cardiopulmonary resuscitation equipment for at-risk patients*;** **- and in view of the potential benefit of this product in patients who could be eligible for ECT but do not have access to or refuse this therapy, or in the event of non-response/contraindication to this therapy, and although there are no comparative data with this intervention, but considering the medical need in this situation;**

	SPRAVATO (esketamine), in combination with a SSRI or SNRI, is an alternative for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy (ECT) or for patients who do not have access to or have refused this therapy. **In the other clinical situations covered by the MA, in particular in patients aged 65 years and over for whom the efficacy of SPRAVATO (esketamine) *versus* placebo has not been demonstrated, SPRAVATO (esketamine) has no role in the therapeutic strategy.**
Recommendations	◗ **Request for data** **The Committee wishes to implement monitoring of patients treated with SPRAVATO (esketamine) in France in order to:** - **describe their characteristics;** - **describe clinical practice and treatment use conditions;** - **observe the evolution of patients under treatment in terms of efficacy (particularly in terms of reduction in depression severity, time to relapse and remission), quality of life and safety.** **The Committee would like to obtain these data within a maximum period of 5 years with a view to reevaluation.** **Over this same period, the Committee would like to receive the results of the long-term safety studies (in particular SUSTAIN-3) requested in the context of granting of the MA.** ◗ **Other requests** **Considering the risks of the development of adverse effects during the post-administration period with SPRAVATO 28 mg (esketamine), in particular sedation, dizziness and hypertension, the Committee reiterates that, in accordance with the SmPC, patients must be monitored adequately in the period immediately after administration, which takes place in a hospital setting only. In particular, blood pressure should be reassessed approximately 40 minutes after administration and the healthcare professional should assess the clinical condition of patients until they are ready to leave the healthcare setting.** **The Committee also reiterates the need to administer SPRAVATO (esketamine) in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available, for any patients with clinically significant or unstable cardiovascular or respiratory conditions (see SmPC).**

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

◗ Major depressive disorder is defined as depressed mood or loss of interest or enjoyment in almost all activities. The level of functional impairment associated with major depression is variable, but there is distress and/or impairment of social or professional life, even in mild cases. The most serious consequences of major depressive disorder are suicide attempts and suicide.
◗ Esketamine is a symptomatic treatment for major depressive disorder.
◗ Considering:
- the superiority of esketamine *versus* placebo (in combination) demonstrated with a modest size effect only in patients under the age of 65 years with severe depression, as induction therapy and maintenance therapy;
- the safety profile, marked, in the short term, by reported cases of suicide/suicidal thoughts and by important identified risks (dissociative or perception disturbances and cardiovascular disorders);
- uncertainties with respect to long-term safety;

the efficacy/adverse effects ratio of SPRAVATO (esketamine), in combination with a SSRI or SNRI, is:
- low in adults under 65 years of age for the treatment of treatment-resistant depressive episodes in the context of severe depression,
- inadequately established in the other clinical situations covered by the MA wording.

◗ The therapeutic alternatives are other therapies indicated in the treatment of major depressive disorder at the same stage in the treatment strategy (see section 05 Clinically relevant comparators).
◗ SPRAVATO (esketamine), in combination with a SSRI or SNRI, is an alternative for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and presenting a contraindication or resistance to electroconvulsive therapy (ECT) or who do not have access to or have refused ECT.
In the other clinical situations covered by the MA, in particular in patients aged over 65 years for whom the efficacy of SPRAVATO (esketamine) *versus* placebo has not been demonstrated, SPRAVATO (esketamine) has no role in the therapeutic strategy.

Public health impact

Considering:
- the seriousness of the disease,
- its prevalence,
- the partially met medical need,
- the absence of robust quality of life data,
- the impact on the organisation of care given the specific administration conditions, which can be restrictive (administration frequency in hospital, supervision by a healthcare professional, structures with appropriate cardiopulmonary resuscitation equipment for at-risk patients),
- the lack of response to the identified need in view of the modest efficacy *versus* placebo demonstrated only in patients under the age of 65 years, as induction therapy and maintenance therapy, the short-term safety profile with cases of suicide/suicidal thoughts and important identified risks (dissociative and/or perception disturbances, cardiovascular disorders) and uncertainties with respect to long-term safety,

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

Considering all these elements, the Committee deems that the clinical benefit of SPRAVATO (esketamine), in combination with a SSRI or SNRI, is:
- **low in the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of**

contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy;
- **insufficient to justify public funding cover in the other MA situations.**

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the following indication: in combination with a SSRI or SNRI for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy, and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other MA situations.

01.2 Clinical Added Value

Considering:
- **demonstration of the superiority of esketamine compared to placebo, in combination with a newly initiated oral antidepressant in patients under the age of 65 years with a severe major depressive episode resistant to at least two oral antidepressants,**
  - **as an induction treatment after 4 weeks in terms of change in MADRS total score with a low effect size (difference of -3.5 points, $CI_{95\%}$ = [-6.7; -0.3] below the clinical relevance level);**
  - **as a maintenance treatment after 48 weeks or more in terms of time to relapse (median time not reached in the esketamine group *versus* 273 days in the placebo group, HR = 0.49; $CI_{95\%}$ = [0.29; 0.84]);**
- **exploratory results relative to quality of life;**
- **the safety profile, marked, in the short term, by cases of suicide/suicidal thoughts reported in clinical studies and compassionate use programme data, and by important identified risks, such as dissociative or perception disturbances and cardiovascular disorders;**
- **and uncertainties with respect to long-term safety;**

the Committee deems that SPRAVATO (esketamine), in combination with a SSRI or SNRI, provides no clinical added value (CAV V) in the therapeutic strategy for the treatment of treatment-resistant major depressive disorder in adults under 65 years of age who have not responded to at least two different treatments with antidepressants in the current severe depressive episode and in the event of contraindication or resistance to electroconvulsive therapy or for patients who do not have access to or have refused this therapy.