HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
22 SEPTEMBER 2021

The legally binding text is the original French opinion version

esketamine
SPRAVATO 28 mg nasal spray, solution
New indication

Key points

Unfavourable opinion for reimbursementco-administered with an oral antidepressant therapy, in adults with a moderate to severe episode of major depressive disorder, as an acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

Role in the care pathway?

The management of depressive disorder varies depending on the severity of the episode:- mild episode: supportive psychotherapy as first-line treatment, with reassessment of treatment after 4 to 8 weeks;- moderate episode: supportive psychotherapy as first-line treatment, combined with antidepressant (AD) therapy if necessary, with reassessment of treatment after 4 to 8 weeks;- severe episode: immediate initiation of AD therapy with prompt referral to a psychiatrist for treatment combining psychotherapy and AD therapy. Treatment efficacy should be assessed after 4 to 8 weeks.

Several AD classes with specific pharmacological mechanisms of action are currently available in France, with no difference in clinical efficacy having been demonstrated between them. The choice of first-line AD therapy is primarily based on the safety profile, with a selective serotonin reuptake inhibitor (SSRI),

serotonin and noradrenaline reuptake inhibitor (SNRI) or a medicinal product belonging to the “other AD therapies” class, with the exception of tianeptine and agomelatine, recommended as first-line therapy.

In clinical practice, hospital admission is the most frequent consequencein a psychiatric emergency. In the context of the guidelines for the first-line management of depression, the latest HAS recommendations (October 2017) specify that hospitalisation should be considered either immediately or during the course of a major depressive episode in the following situations:

- patient with an imminent suicide plan
- patient with an immediate risk of self-harm;
- patient with a potential for violence;
- certain severe forms of depression, in the event of associated severe psychotic or somatic symptoms;
- presence of marked anxious agitation with lack of emotional control of impulsiveness;
- withdrawal from a psychoactive substance;
- wherever the specific situation requires it.

According to the 2017 national consensus of the AFPBN (French Association for Biological Psychiatry and Neuropsychopharmacology) and the FondaMental foundation, no expert consensus has been reached with respect to the use of adjuvant treatment along with antidepressant therapy in the event of the risk of self-harm. The medicinal options cited by way of example by the experts are: hydroxyzine, a benzodiazepine, a second-generation antipsychotic or lithium, in the context of off-label use. The antidepressants cited as first-line treatment in the event of a high suicide risk are SSRIs and SNRIs.

Electroconvulsive therapy (ECT) is an alternative to medicinal treatments in the event of a severe clinical profile combined with a suicide risk.

Role of SPRAVATO (esketamine) in the care pathway:

SPRAVATO (esketamine) in combination with an AD alone or with a potentiation agent was evaluated in two randomised, double-blind, placebo-controlled studies having included adult patients (<65 years) with severe depression and hospitalised for a psychiatric emergency (either due to a suicide attempt or an imminent suicide risk).

Considering:

- the modest effect size for the change in MADRS score at 24 hours versus placebo (primary endpoint);
- the absence of difference between SPRAVATO (esketamine) and placebo, on the reduction of risk of suicide 24h after administration of the first dose, a ranked secondary endpoint that is relevant in this psychiatric emergency context;
- the absence of robust efficacy data in terms of reduction in severity after 4 weeks (25 days) in the absence of ranking of this endpoint, despite the fact that this treatment duration corresponds to the posology currently referred to in the SPC for SPRAVATO (esketamine);
- the absence of a comparative study versus clinically relevant comparators, meaning that it is not possible to determine the position of esketamine compared to the latter (in particular ECT)
- safety data for esketamine reporting a high frequency of “psychiatric disorder”-type SAEs (suicide attempt, suicidal depression, suicidal thoughts, depression) in both treatment groups (11.9% and 11.6% respectively) and a suicide in the esketamine group during the follow-up phase, whereas no deaths were reported in the placebo group; this death having been considered, by the investigator, not to be causally related to the treatment.

the Committee deems that SPRAVATO (esketamine) has no role in the care pathway, when co-administered with oral antidepressant therapy, in adults with a moderate to severe episode of major depressive disorder, as an acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

In addition, the Committee highlights various aspects relative to integration of SPRAVATO (esketamine) in the current management of patients in situations of psychiatric emergency, with:

- the need for a psychiatrist to prescribe SPRAVATO (esketamine);

- the need for a clinical 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.

COMMITTEE'S CONCLUSIONS

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

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.

◗ The proprietary medicinal product SPRAVATO (esketamine) is a preventive treatment.

◗ The available clinical data does not enable the clinical benefit of SPRAVATO (esketamine) to be determined given (see Section 08.4 Summary and Discussion):

- the modest effect size for the change in MADRS score 24 hours after administration of the first dose (absolute between-group difference of -3.8 points on a scale of 0 to 60),
- the absence of robust efficacy data in terms of reduction in depression severity after 4 weeks (25 days) in the absence of ranking of this endpoint, despite the fact that this is considered to be clinically relevant since it corresponds to the posology currently referred to inthe SPC for SPRAVATO (esketamine),
- the absence of a demonstrated difference between SPRAVATO (esketamine) and placebo on the reduction of risk of suicide between baseline and 24h after administration of the first dose, an endpoint considered to be relevant in this psychiatric emergency context,
- safety data for esketamine reporting a high frequency of "psychiatric disorder"-type SAEs and a suicide in this group,

consequently, its efficacy/adverse effects ratio has not been adequately established in the indication extension concerned.

◗ There are medicinal and non-medicinal alternatives.

◗ SPRAVATO (esketamine) has no role in the care pathway, when co-administered with an oral antidepressant therapy, in adults with a moderate to severe episode of major depressive disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency (see section "09 Role in the care pathway").

Public health impact

Considering:

- the seriousness of the disease,
- its prevalence,
- the partially met medical need,
- the lack of response to the identified need, with the absence of an expected impact on morbidity, and the absence of a demonstrated impact on the reduction of depression and suicide risk after 4 weeks, as well as a lack of demonstrated impact on quality of life,
- the potential impact on the organisation of care given the specific administration conditions in a psychiatric emergency, which can be restrictive (mandatory prescription by a psychiatrist and in structures with appropriate cardiopulmonary resuscitation equipment for at-risk patients).

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) is insufficient to justify public funding coverage, when co-administered with an oral antidepressant therapy, in adults with a moderate to severe episode of major depressive disorder, as an acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication, when co-administered with an oral antidepressant therapy, in adults with a moderate to severe episode of major depressive disorder, as an acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.