SUMMARY

esketamine

SPRAVATO 28 mg

nasal spray solution

Modification of the listing conditions

Original French opinion adopted by the Transparency Committee on 17 July 2024

The legally binding text is the original French opinion version

Summary of opinion

Favourable opinion for maintenance of reimbursement in combination with a SSRI or SNRI only 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.

As a reminder, the clinical benefit is insufficient in the other situations of the MA.

Transparency Committee's conclusions

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.
- This medicinal product 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;
  - new comparative efficacy data from a study having demonstrated a superiority versus quetiapine LP, both in combination with a SSRI or SNRI, on the primary endpoint of remission at 8 weeks (MADRS ≤10) and the limitations associated with this study (open-label study, non-optimal comparator with an insufficient clinical benefit, low representativity of the severe population, short duration);
  - 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, confirmed in the longer term with a mean exposure duration of 42.9 months (up to 79 months);

the efficacy/adverse effects ratio of SPRAVATO (esketamine), in combination with a SSRI or SNRI, is moderate only 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. It remains inadequately established in the other clinical situations covered by the MA wording.

➔ SPRAVATO (esketamine), in combination with a SSRI or SNRI, represents 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.

➔ Public health benefit

Considering:

- the seriousness of the disease and its prevalence,
- the partially met medical need,
- the lack of response to the identified need considering:
  - the lack of evidence of an additional impact on morbidity and mortality in situations of treatment-resistant major depressive disorder not having responded to at least two different treatments with antidepressants in the current severe depressive episode,
  - the lack of evidence of an additional impact on quality of life,
  - 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),

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 moderate only 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.

The Committee issues a favourable opinion for maintenance of inclusion of SPRAVATO (esketamine) in the list of covered drugs for inpatients approved for use only within the scope retained and at the MA dosages.

Clinical Added Value

Considering:

- the initial data having demonstrated 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, with a low size effect, in terms of change in MADRS total score (difference of -3.5 points, 95% CI = [-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; 95% CI = [0.29; 0.84]);
- new comparative data from a study having demonstrated a superiority *versus* quetiapine LP, both in combination with a SSRI or SNRI, on the primary endpoint of remission at 8 weeks (MADRS ≤10) and the limitations associated with this study (open-label study, non-optimal comparator with an insufficient clinical benefit, low representativity of the severe population, short duration);
- 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, confirmed in the longer term with a mean exposure duration of 42.9 months (up to 79 months);
- the absence of robust quality of life data;

the Committee deems that SPRAVATO (esketamine), in combination with a SSRI or SNRI, provides no clinical added value **(CAV V)** in the care pathway 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.