IQWiG Reports – Commission No. A21-25

# Esketamine (major depressive disorder, psychiatric emergency) –

## Benefit assessment according to §35a Social Code Book V[1]

**Extract**

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Esketamin (Major Depression, psychiatrischer Notfall) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 May 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| eCRF | electronic case report form |
| ECT | electroconvulsive therapy |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MADRS | Montgomery-Åsberg Depression Rating Scale |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug esketamine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 4 March 2021.

### Research question

The aim of this report is to assess the added benefit of esketamine coadministered with oral antidepressant therapy in comparison with the appropriate comparator therapy (ACT) in adult patients with a moderate to severe episode of major depressive disorder when the regimen is used as acute short-term treatment for the rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency.

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment for esketamine coadministered with oral antidepressant therapy

| **Indication** | **ACT[a]** |
|---|---|
| As acute short-term treatment in adult patients with a moderate to severe episode of major depressive disorder so as to achieve a rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency | Therapy at the physician's discretion, selecting from[b]<br>▪ Crisis intervention / psychotherapy<br>▪ Pharmacological acute therapy of anxiety, insomnia, psychotic symptoms, restlessness<br>▪ Initiation of adequate antidepressant medication or optimization of the existing medication[c]<br>▪ Electroconvulsive therapy |
| a. Presented is the ACT specified by the G-BA.<br>b. In this context, the ACT defines the standard therapy for this treatment situation. It is therefore assumed that, within a study, patients in both study arms are adequately treated in accordance with the cited therapy selected upon the physician's discretion.<br>c. The potentially higher risk of suicide in the induction phase must be taken into consideration when selecting antidepressants.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

**Results**

The check for completeness of the study pool revealed no relevant studies for comparing esketamine versus the ACT. Contrary to this finding, the company used the SUI3001, SUI3002, and SUI2001 studies for the benefit assessment. The 3 studies are RCTs comparing esketamine with placebo in patients with a moderate to severe episode of major depressive disorder and current suicidal thoughts with intent, triggering the need for acute psychiatric hospitalization as per the physician's opinion. The studies submitted by the company are unsuitable for assessing any added benefit of esketamine since they do not compare esketamine with a therapy selected upon the physician's discretion as specified by the G-BA.

***Inadequate implementation of a therapy selected upon the physician's discretion in the studies submitted by the company, SUI3001, SUI3002, and SUI2001***

The ACT specified by the G-BA is therapy upon the physician's discretion. This includes crisis intervention / psychotherapy, pharmacological acute therapy (for the treatment of anxiety, insomnia, psychotic symptoms, and restlessness), initiation of adequate antidepressant medication or optimization of the existing medication, and electroconvulsive therapy (ECT). Hence, the ACT comprises both pharmacological and nonpharmacological treatment options.

In the studies submitted by the company, SUI3001, SUI3002, and SUI2001, patients received the study drug (esketamine or placebo) and additional antidepressant therapy (monotherapy or with augmentation therapy) and, where appropriate, comedication, e.g. with benzodiazepines. Hence, only the pharmacological options of the ACT were implemented. The nonpharmacological treatment options, in contrast, were not appropriately implemented.

For instance, the use of ECT was disallowed in all 3 studies despite the lack of an apparent medical rationale as to why ECT would not constitute a treatment option for the patients in the studies. The company merely stated that, while the use of ECT was a relevant treatment option in the present therapeutic indication, its use in the studies was infeasible. Overall, ECT can be assumed to represent a relevant and needed treatment option for patients in the SUI3001, SUI3002, and SUI2001 studies. Excluding this treatment option is therefore inappropriate with regard to the adequate implementation of the ACT.

Furthermore, the available data are unsuitable for evaluating the extent to which psychotherapeutic measures for crisis intervention or other measures for crisis intervention were appropriately implemented in the studies.

Due to the absence of ECT as a treatment option as well as the unclear implementation of crisis intervention / psychotherapy, the SUI3001, SUI3002, and SUI2001 studies do not permit comparing esketamine with the ACT specified by the G-BA. They are therefore unsuitable for deriving any added benefit of esketamine.

Consequently, no suitable data are available for assessing any added benefit of esketamine coadministered with oral antidepressant therapy versus the ACT in adult patients with a

moderate to severe episode of major depressive disorder when the regimen is used as acute short-term treatment for the rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency. This results in no hint of any added benefit of esketamine coadministered with oral antidepressant therapy in comparison with the ACT; an added benefit is therefore not proven.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]**

Table 3 presents a summary of the probability and extent of added benefit of esketamine coadministered with oral antidepressant therapy.

Table 3: Esketamine coadministered with oral antidepressant therapy – probability and extent of added benefit

| Indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| As acute short-term treatment in adult patients with a moderate to severe episode of major depressive disorder so as to achieve a rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency | Therapy upon the physician's discretion, selecting from[b.]<br>▪ Crisis intervention / psychotherapy<br>▪ Pharmacological acute therapy of anxiety, insomnia, psychotic symptoms, restlessness<br>▪ Initiation of adequate antidepressant medication or optimization of the existing medication[c]<br>▪ Electroconvulsive therapy | Added benefit not proven |
| a. Presented is the ACT specified by the G-BA.<br>b. In this context, the ACT defines the standard therapy for this treatment situation. Therefore, it is assumed that, within a study, patients in both study arms are adequately treated in accordance with the cited therapy selected upon the physician's discretion.<br>c. The potentially higher risk of suicide in the induction phase must be taken into consideration when selecting antidepressants.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

## 2.2 Research question

The aim of this report is to assess the added benefit of esketamine coadministered with oral antidepressant therapy in comparison with the ACT in adult patients with a moderate to severe episode of major depressive disorder when the regimen is used as acute short-term treatment for the rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency.

Table 4 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of esketamine coadministered with oral antidepressant therapy

| **Indication** | **ACT**[a] |
|---|---|
| As acute short-term treatment in adult patients with a moderate to severe episode of major depressive disorder so as to achieve a rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency | Therapy upon the physician's discretion, selecting from[b]<br>▪ Crisis intervention / psychotherapy<br>▪ Pharmacological acute therapy of anxiety, insomnia, psychotic symptoms, restlessness<br>▪ Initiation of adequate antidepressant medication or optimization of the existing medication[c]<br>▪ Electroconvulsive therapy |
| a. Presented is the ACT specified by the G-BA.<br>b. In this context, the ACT defines the standard therapy for this treatment situation. Therefore, it is assumed that within a study, patients in both study arms are adequately treated in accordance with the cited therapy selected upon the physician's discretion.<br>c. The potentially higher risk of suicide in the induction phase must be taken into consideration when selecting antidepressants.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs were used for the derivation of added benefit.

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on esketamine (as of 6 January 2021)
- Bibliographic literature search on esketamine (most recent search on 6 January 2021)
- Search in trial registries / study results databases on esketamine (most recent search on 4 January 2021)
- Search on the G-BA website on esketamine (most recent search on 22 January 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on esketamine (most recent search on 18 March 2021)

The check for completeness of the study pool revealed no relevant studies for comparing esketamine versus the ACT. Contrary to this finding, the company included in its benefit assessment the RCTs SUI3001 [3-6], SUI3002 [7-10], and SUI2001 [11-13].

The studies submitted by the company are unsuitable for assessing any added benefit of esketamine since they do not compare esketamine with a therapy selected upon the physician's discretion as specified by the G-BA. The SUI3001, SUI3002, and SUI2001 studies are described and their unsuitability for the benefit assessment explained in detail below.

**Studies SUI3001 and SUI3002**

SUI3001 and SUI3002 are twin studies sharing an identical study design but were conducted largely in different countries. They are randomized, double-blind, phase III studies comparing esketamine with placebo. The studies included patients with a moderate to severe episode of major depressive disorder (Montgomery-Åsberg Depression Rating Scale [MADRS] total score > 28) and current suicidal thoughts with intent, clinically warranting acute psychiatric hospitalization as judged by the physician. The studies excluded, among others, patients with psychotic symptoms. Patients had to agree to be hospitalized voluntarily for 5 days (or shorter/longer if warranted in the physician's opinion).

Alongside the study drug, patients in both treatment arms received antidepressant therapy upon the physician's discretion. This therapy included the initiation or optimization of antidepressant therapy in the form of antidepressant monotherapy or antidepressant plus augmentation therapy and was determined by the physician prior to randomization. Further concomitant therapies, e.g. benzodiazepines, were allowed. Conversely, the use of non-pharmacological therapy options was either disallowed (ECT) or not defined (crisis intervention / psychotherapy).

In total, 456 patients (SUI3001+SUI3002) were randomized in a 1:1 ratio and allocated to the 2 treatment arms. Randomization was stratified by both study centre and selected antidepressant medication (monotherapy or plus augmentation therapy). Esketamine or placebo was given 2 times per week for a period of 25 days, followed by a 65-day observation period (up to Day 90). Continuing the antidepressant therapy during the observation phase was allowed upon the physician's discretion. The primary outcome of both studies was change in depressive symptoms (MADRS).

**SUI2001 study**

SUI2001 is a randomized, double-blind phase II study comparing esketamine with placebo; its design exhibits minor differences to SUI3001 and SUI3002. While the study similarly included patients with a moderate to severe episode of major depressive disorder, it did so already at a

MADRS total score ≥ 22, and the observation phase was 56 instead of 65 days. It randomized far fewer patients (N = 68) than the other two studies.

For further characteristics, see Table 10 and Table 11 in Appendix A of the full dossier assessment.

**Inadequate implementation of therapy upon the physician's discretion in the SUI3001, SUI3002, and SUI2001 studies**

The ACT specified by the G-BA is therapy upon the physician's discretion. This includes crisis intervention / psychotherapy, pharmacological acute therapy (for the treatment of anxiety, insomnia, psychotic symptoms, and restlessness), initiation of adequate antidepressant medication or optimization of the existing medication, and ECT. Hence, the ACT comprises both pharmacological and nonpharmacological treatment options. The studies submitted by the company, SUI3001, SUI3002, and SUI2001, implemented only the pharmacological options, such as antidepressant therapy and acute therapy with, e.g. benzodiazepines. The use of nonpharmacological options, in contrast, was either disallowed (ECT) or unclear (crisis intervention / psychotherapy). This approach does not constitute an adequate implementation of the ACT. A more detailed discussion is provided below.

***Electroconvulsive therapy***

In the SUI3001, SUI3002, and SUI2001 studies, the use of ECT was disallowed. There is no apparent medical rationale for not offering patients in these studies the option of ECT.

The S3 guideline for the treatment of unipolar depression recognizes ECT as an effective treatment for severe depressive disorders. It is to be taken into consideration as a treatment alternative, e.g., in case of severe, life-threatening depressive episodes [14]. ECT requires eligibility for short-acting anaesthesia; there are no absolute contraindications. Relative contraindications include some forms of brain tumours, recent myocardial or cerebral infarction, elevated intracranial pressure, and venous thrombosis with elevated risk of complications [14,15].

According to the inclusion criteria, all patients in the 3 studies submitted by the company had suicidal thoughts with intent at baseline and were therefore in a life-threatening condition. Patients who had diseases corresponding to the above-identified relative contraindications for ECT were already excluded from the studies. These exclusion criteria were, for instance, clinically significant cardiac disorders (including recent myocardial infarction), vascular disorders, neurological disorders, elevated intracranial pressure as well as a history of malignant disease within 5 years before screening.

The company's dossier fails to provide any medical rationale explaining why ECT would not constitute a treatment option for the patients. On the contrary, the company describes ECT as a relevant treatment option in the present therapeutic indication as per S3 guideline, but it suggests that its use would have been impossible in the studies. The company reasons that

inclusion of ECT as a treatment option in clinical studies is subject to restrictions because this treatment is conducted under short-acting anaesthesia, a muscle relaxant, and oxygen. Therefore, ECT requires a qualified specialist plus an anaesthesiologist, a comprehensive medical history, diagnostic clarification (e.g. as part of a cardiological consultation) as well as a detailed informed consent discussion, with written consent being provided by the patient or the patient's family. The company's rationale as to why ECT cannot be implemented is not convincing. Study settings, of all places, should be expected to have standard procedures addressing such framework conditions. Furthermore, according to the S3 guideline, ECT does not legally differ from other medical measures [14].

Overall, it can therefore be assumed that ECT would have been a relevant and necessary treatment option for the patients of the SUI3001, SUI3002, and SUI2001 studies; excluding this treatment option is therefore inappropriate with regard to the adequate implementation of the ACT. During the consultation, the G-BA likewise stated that generally withholding a medically necessary treatment option like ECT from patients without providing a medical rationale would fail to comply with the ACT [16].

Furthermore, the effects of esketamine presented in the company's dossier from studies SUI3001, SUI3002, and SUI2001 are not sufficiently large to suggest that an adequate implementation of the ACT in the studies could not influence them in a relevant way. For instance, in SUI3001 and SUI3002, remission of depressive symptoms (MADRS total score ≤ 12) within 90 days was found in 76.0% of patients in the intervention arm, with a median time to remission of about 15 days, compared to 69.6% in the comparator arm, at a median time to remission of approximately 22 days (HR [95% CI]: 1.34 [1.08; 1.67], pooled analysis of studies SUI3001 and SUI3002). According to the S3 guideline on unipolar depression, using ECT, remission is achieved in 60% to 80% of cases, with the maximum response found at 2 to 4 weeks [14]. Offering ECT in the studies might therefore have led to remission of depressive symptoms in a similar percentage of patients in the comparator arm within a short time period.

***Crisis intervention / psychotherapy***

The concomitant use of nonpharmacological therapy options such as crisis intervention / psychotherapy was not defined in the study protocols (SUI3001, SUI3002, and SUI2001). The treatment plan merely stated that all patients had to agree to be hospitalized voluntarily for 5 days upon physician discretion, or for longer/shorter if warranted. As part of the study visits, patients were contacted twice weekly until Day 25 (end of treatment phase with esketamine or placebo) and thereafter at increasing intervals until Day 90 (SUI3001, SUI3002) or Day 81 (SUI2001).

For the initial treatment of suicidal patients, the S2k guideline on emergency psychiatry calls for counselling as a crisis intervention [17]. Once the emergency medical staff have completed the acute intervention, a psychiatric consult should be performed and treatment of the underlying disease initiated as quickly as possible. The S3 guideline can be applied to the treatment of unipolar depression [14]. Accordingly, crisis management in suicidal patients is to

include the development of a sustainable relationship as well as clarification of the current cause and the necessity of acute psychotherapeutic and pharmacotherapeutic measures [14]. The S3 guideline recommends that suicidal patients with a depressive episode be offered acute psychotherapy as crisis intervention, initially with a focus on suicidality.

At baseline, all patients in SUI3001, SUI3002, and SUI2001 had current suicidal thoughts with intent, and > 50% of patients had severe depressive disorder as measured by an MADRS total score ≥ 35. Information on the administration of psychotherapy over the course of the study was available only for SUI3002. Accordingly, only 4.8% of the 230 patients received psychotherapy within the 25-day treatment phase with esketamine or placebo [7]. It is unclear whether patients received psychotherapeutic or other measures as crisis intervention during the initial hospitalization or, if necessary, as part of the study visits.

The company's dossier does not discuss the extent to which the treatment option of crisis intervention / psychotherapy was implemented in the studies, despite the fact that all therapies deviating from the study medication (e.g. psychotherapy) had to be documented in the electronic case report form (eCRF). Hence, this information had to have been available to the company.

Consequently, it is impossible to evaluate the extent to which psychotherapeutic measures for crisis intervention or other measures for crisis intervention were appropriately implemented in the studies.

***Summary***

Due to the absence of ECT as a treatment option as well as the unclear implementation of crisis intervention / psychotherapy, SUI3001, SUI3002, and SUI2001 do not allow a comparison of esketamine with the ACT specified by the G-BA. They are therefore unsuitable for deriving any added benefit of esketamine.

## 2.4 Results

No suitable data are available for assessing any added benefit of esketamine coadministered with oral antidepressant therapy versus ACT in adult patients with a moderate to severe episode of major depressive disorder when the regimen is used as acute short-term treatment for the rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency This results in no hint of any added benefit of esketamine coadministered with oral antidepressant therapy in comparison with the ACT; an added benefit is therefore not proven.

## 2.5 Probability and extent of added benefit

Since no suitable data are available for assessing any added benefit in comparison with the ACT, there is no proof of added benefit of esketamine coadministered with oral antidepressant therapy in adult patients with a moderate to severe episode of major depressive disorder when

the regimen is used as acute short-term treatment for the rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency.

Table 5 summarizes the result of the assessment of added benefit of esketamine coadministered with oral antidepressant therapy in comparison with the ACT.

Table 5: Esketamine coadministered with oral antidepressant therapy – probability and extent of added benefit

| **Indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|
| As acute short-term treatment in adult patients with a moderate to severe episode of major depressive disorder so as to achieve a rapid reduction of depressive symptoms which have been clinically judged to constitute a psychiatric emergency | Therapy upon the physician's discretion, selecting from[b]<br>▪ Crisis intervention / psychotherapy<br>▪ Pharmacological acute therapy of anxiety, insomnia, psychotic symptoms, restlessness<br>▪ Initiation of adequate antidepressant medication or optimization of the existing medication[c]<br>▪ Electroconvulsive therapy | Added benefit not proven |
| a. Presented is the ACT specified by the G-BA.<br>b. In this context, the ACT defines the standard therapy for this treatment situation. Therefore, it is assumed that, within a study, patients in both study arms are adequately treated in accordance with the cited therapy upon the physician's discretion.<br>c. The potentially higher risk of suicide in the induction phase must be taken into consideration when selecting antidepressants.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

The above assessment departs from that by the company, which included the SUI3001 and SUI3002 studies and presented the SUI2001 study as supplementary information. Based on the results of the pooled analysis of SUI3001 and SUI3002, the company has derived proof of considerable added benefit for patients in the present therapeutic indication.

The G-BA decides on the added benefit.

**References for English extract**

Please see full dossier assessment for full reference list.

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