Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Esketamine (depression, acute short-term treatment, combination therapy)

of 19 August 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient esketamine in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 March 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 27 February 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 1 June 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of esketamine compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements

submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of esketamine.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of esketamine (Spravato) in accordance with the product information

Spravato, co-administered with oral antidepressant therapy, is indicated 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.

Therapeutic indication of the resolution (resolution of 19 August 2021):

see therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Therapy according to doctor's instructions under consideration of

- crisis intervention/psychotherapy
- acute medicinal therapy for the treatment of anxiety, insomnia, psychotic symptoms, restlessness
- initiation of adequate antidepressant medication or optimisation of existing medication
- electroconvulsive therapy.

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. No medicinal products are explicitly approved for the rapid reduction of depressive symptoms that, according to clinical judgement, correspond to a psychiatric emergency. In principle, however, the medicinal products generally approved for depression are considered according to their therapeutic indication: Antidepressants of the substance classes non-selective monoamine reuptake inhibitors (imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, maprotiline, amitriptyline oxide), selective serotonin reuptake inhibitors (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram), serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine, milnacipran), monoamine oxidase inhibitors (tranylcypromine, moclobemide) and others (mianserin, trazodone, mirtazapine, bupropion, tianeptine, reboxetine, agomelatine, vortioxetine) are approved for moderate to severe depressive disorders.

The neuroleptic sulpiride is approved for depressive disorder when treatment with another antidepressant has been unsuccessful or is not feasible.

Quetiapine in its retarded form, is approved as add-on therapy in patients who have had an inadequate response to monotherapy with an antidepressant.

Lithium carbonate is approved for the treatment of certain acute depressions, e.g. in cases of treatment resistance or intolerance of antidepressants, in cases of the suspected changeover to mania, if necessary, in combination with antidepressants.

on 2. In the present therapeutic indication, acute psychotherapeutic treatment in the sense of crisis intervention is of importance. Electroconvulsive therapy (ECT) and sleep deprivation are other acute non-medicinal treatment options.

on 3. There are no G-BA resolutions in the therapeutic indication of the rapid reduction of depressive symptoms that correspond to a psychiatric emergency according to clinical

judgement. In the indication "Major Depressive Disorder in adults", a resolution on the benefit assessment of new medicinal products according to Section 35a SGB V, dated 15 October 2015, is available for the active ingredient vortioxetine. For the selective noradrenaline reuptake inhibitor reboxetine, there is a resolution of the G-BA of 16 September 2010 to exclude the prescription.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V".

Overall, the evidence base for the therapeutic indication is limited, but various therapeutic approaches are possible. The acute treatment recommended in the guidelines includes medicinal products therapy to influence symptoms such as anxiety, insomnia, psychotic symptoms and restlessness, as well as psychotherapeutic support in the sense of crisis intervention and electroconvulsive therapy (ECT). In contrast, there is insufficient evidence/guideline recommendation for sleep deprivation. In addition to acute therapeutic measures, it may be indicated to start or optimise medication for the underlying depressive episode. The various options mentioned can in principle be considered for all patients; in particular, no objectifiable criteria for patient-individual selection can be derived from the available evidence. The concrete procedure for selecting these options is thus left to the attending doctor.

Taking into account the written and oral statements, it is concluded that ECT may be a therapeutic option in the present therapeutic indication (psychiatric emergency). Even if ECT is rarely used in the present psychiatric emergency in current health care practice, the therapeutic indication nevertheless also includes patients who, according to medical assessment, can be treated promisingly with ECT. This could apply, for example, to patients with a long history of illness and experience of ECT therapy who require acute treatment. Therefore, not including ECT in the appropriate comparator therapy would not be adequate.

When selecting antidepressants, the possible increased risk of suicide in the initiation phase must be taken into account. The marketing authorisation of the antidepressants and the medicinal products used to treat the acute symptoms must be considered.

In this context, the designated appropriate comparator therapy defines the standard therapy in the therapeutic situation to be advised (the use of esketamine should be an add-on therapy in addition to the standard therapy) and should be part of both the intervention arm and the comparator arm (if necessary, replacement of esketamine with placebo to ensure blinding) within a study.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of esketamine is assessed as follows:

For 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, there is a hint of a minor additional benefit.

Justification:

For the benefit assessment of esketamine in adult patients 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 considered by physicians to correspond to a psychiatric emergency, the pharmaceutical company submits the randomised, controlled phase III studies SUI3001 and SUI3002 (including a pooled analysis of the two studies), as well as the supporting phase II study SUI2001.

The two RCTs SUI3001 and SUI3002 included patients with a moderate to severe episode of Major Depressive Disorder and current suicidal ideation with intent to act, which from a physician's perspective indicates the need for acute psychiatric hospitalisation. All included subjects received antidepressant drug therapy and were also randomised to additional treatment with esketamine or placebo, such that the studies compared esketamine + antidepressant therapy with placebo + antidepressant therapy.

The current depressive episode was severe on average (MADRS total score of approximately 40 points, although the exact proportion of study participants with moderate or severe depression is unclear) and had already lasted for a period of approximately 42 months. More than half of the patients were considered by physicians to be at significant or massive risk of suicide, as measured by the Clinical Global Impression of Severity of Suicidality Revised Version [CGI-SS-R] of the Suicide Ideation and Behaviour Assessment Tool (SIBAT). 60% of the SUI3001 and 65% of the SUI3002 study population had made a prior suicide attempt.

The supporting study SUI2001 is a Phase II study comparing esketamine with placebo in addition to medicinal antidepressant therapy. Suicidal patients with a moderate to severe episode of Major Depressive Disorder were also included, but from a MADRS total score ≥ 22, and the observation phase was 56 instead of 65 days. Compared with the two RCTs SUI3001 and SUI3002, significantly fewer patients were randomised (N = 68). Overall, this study was not included because higher-quality evidence was available with the evaluation of the two phase III studies, including a pooled analysis.

Implementation of the appropriate comparator therapy

For the present therapeutic indication, the G-BA has defined a therapy according to doctor's instructions taking into account crisis intervention/psychotherapy, acute medicinal therapy (for the treatment of anxiety, insomnia, psychotic symptoms, restlessness), initiation of adequate antidepressant medication or optimisation of existing medication and electroconvulsive therapy (ECT) as appropriate comparator therapy.

In the studies SUI3001 and SUI3002 submitted by the company, the patients received, in addition to the study medication (esketamine or placebo), antidepressant therapy (monotherapy or monotherapy plus augmentation therapy) and, if necessary, concomitant therapy (e.g. with benzodiazepines). In particular, due to two aspects of the study conduct, the appropriate comparator therapy is assessed as not fully implemented.

First, the use of ECT was not allowed in either study.

Although ECT is difficult to perform in the clinical emergency situation described above, it is also subject to institutional conditions (equipment, possibility of short-term anaesthesia under the supervision of a specialist anaesthetist), which are not always available in clinical care. It is also questionable to what extent patients in the designated clinical emergency situation can be adequately informed about the intervention to be performed. Nevertheless,

it can be assumed that for a sub-population in the studies SUI3001, and SUI3002, ECT could have been a relevant and necessary treatment option. Therefore, the exclusion of this therapy option is not appropriate with regard to an adequate implementation of the appropriate comparator therapy.

Second, it remains unclear to what extent psychotherapeutic measures in the sense of crisis intervention or other crisis intervention measures were adequately implemented in the studies. According to the S3 guideline, crisis management in cases of suicidality should include establishing a sustainable relationship, clarifying the current cause, and the need for acute psycho- and pharmacotherapeutic measures. Suicidal subjects with a depressive episode should be offered psychotherapy that initially focuses on suicidality. Although it can be assumed in principle that crisis intervention psychotherapeutic measures are also taken during inpatient admission in the emergency situation described, the accompanying use of crisis intervention/psychotherapy was not defined in the study protocols. Furthermore, the available data do not allow an assessment of the extent to which psychotherapeutic measures in the sense of crisis intervention or other crisis intervention measures were adequately implemented in the studies

Despite these uncertainties, the antidepressant therapy used in the studies can be considered a sufficient approximation of the implementation of the appropriate comparator therapy. The studies can therefore be used for the benefit assessment.

Mortality

Until day 90, 1 subject had died in the intervention arm and none in the control arm. Thus, no advantage or disadvantage of esketamine + antidepressant therapy over placebo + antidepressant therapy can be determined for the endpoint of overall mortality.

Morbidity

The study assessed general and specific depressive symptomatology.

General depressive symptomatology

Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) is an established and validated instrument for assessing depressive symptomatology. Studies assessed response (MADRS total score improvement of ≥ 50%) and remission (MADRS total score ≤ 12) of depressive symptomatology.

Here, an advantage of esketamine + antidepressant therapy over placebo + antidepressant therapy is seen in remission and response in both the responder evaluation at day 25 and the time-to-event analysis until day 90.

Beck Hopelessness Scale(BHS)

The "Beck Hopelessness Scale" is an instrument in which the patients assess the aspect of hopelessness. In the endpoint BBB (analysis of continuous data), there were no statistically

significant differences between the treatment groups in the individual studies as well as in the pooled analysis.

Quality of Life in Depression Scale (QLDS)

For the QLDS, although the pooled analysis shows a statistically significant advantage of esketamine + antidepressant therapy over placebo + antidepressant therapy at day 25, the 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the effect is clinically relevant.

It is currently being discussed within the G-BA whether the assignment of the QLDS to the category of morbidity or to the category of health-related quality of life is appropriate. As the lack of clinical relevance of the observed effect does not affect the assessment of the additional benefit, this benefit assessment refrains from a final assignment to an endpoint category.

Specific depressive symptomatology: Suicidality

Suicide Ideation and Behaviour Assessment Tool(SIBAT)

The specific depressive symptomatology of suicidality was assessed with the Suicide Ideation and Behaviour Assessment Tool (SIBAT). Here, pooled analyses of the continuous data show no statistically significant difference at day 25 or day 90 between treatment groups for either the patient-reported (self-assessments of risk/protective factors, suicidal ideation, desire to die, suicidal intent, frequency of suicidal ideation, and likelihood of suicide) or physician-assessed modules (overall clinical impression of frequency of suicidal ideation, acute suicide risk, and long-term suicide risk).

Health status (EQ-5D VAS)

For the health status endpoint, as measured by improvement of ≥ 15 points on the EQ-5D visual analogue scale (VAS), the pooled analysis showed a statistically significant advantage to the benefit of esketamine + antidepressant therapy versus placebo + antidepressant therapy in both the responder evaluation until day 25 and the time-to-event analysis until day 90.

Health-related quality of life

No endpoints were collected in this category. For the classification of the QLDS see above.

Side effects

Overall rates of SAEs and discontinuations due to AEs

For the endpoints SAEs and discontinuation due to AEs, there was no statistically significant difference between the treatment groups in the pooled analysis.

Nervous system disorders, psychiatric disorders, gastrointestinal disorders, eye disorders (SOC, AE)

There was a statistically significant disadvantage of esketamine + antidepressant therapy versus placebo + antidepressant therapy in the pooled analysis with respect to several SOCs (nervous system disorders, psychiatric disorders, gastrointestinal disorders, eye disorders).

Overall assessment

Results on mortality, morbidity and side effects from two RCTs and a pooled analysis are available. For the endpoint "general depressive symptomatology", assessed using the MADRS, BHS and QLDS, the pooled analysis showed statistically significant and relevant differences favouring esketamine only when considering the MADRS. In contrast, there is no advantage or disadvantage for esketamine in the specific depressive symptomatology suicidality (measured by SIBAT). In the endpoint "health status" (EQ-5D VAS) there is a statistically significant advantage of esketamine.

In terms of side effects, there are no statistically significant disadvantages for esketamine in the overall rates, but there are statistically significant disadvantages for esketamine in individual-specific adverse events (SOC).

For "General depressive symptomatology", an overall advantage can be found as the MADRS is an established and comprehensive standard in the assessment of depression. For the other instruments (BHS, QLDS, SIBAT), no effect in favour of esketamine could be detected. For the assessment in the present therapeutic indication, however, it must be taken into account in the overall consideration that no advantage is found in the specific depressive symptomatology suicidality (measured via SIBAT), which, however, would have been of importance in the present emergency indication.

Overall, therefore, only a minor additional benefit can be determined on the basis of the morbidity data. The observed benefit in general health status, assessed by the EQ-5D VAS, emphasises the additional benefit. Disadvantages are only evident in specific AEs, but not in the overall rates so that a relevant disadvantage is not assumed here in the overall assessment. Overall, there is a minor additional benefit.

Reliability of data (probability of additional benefit)

In the studies SUI3001 and SUI3002, the uncertainties with regard to the adequate implementation of the appropriate comparator therapy lead to limitations in the reliability of data.

Psychotherapeutic measures in the sense of crisis intervention are an integral part of the care practice for patients in the present therapeutic indication in Germany. It remains unclear in the studies whether or to what extent psychotherapeutic measures were used in the sense of crisis intervention. In addition, electroconvulsive therapy was excluded as an option.

Furthermore, due to these uncertainties, the transferability to the German health care context cannot be adequately assessed.

The uncertainties described lead to a limitation of the reliability of data. Overall, the reliability of data is rated as a hint.

2.1.4 Summary of the assessment

The assessment of esketamine (nasal spray) is done co-administered with oral antidepressant therapy the therapeutic indication "adult patients 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. "

A therapy according to doctor's instructions (taking into account crisis intervention/psychotherapy, acute medicinal therapy for the treatment of anxiety, insomnia, psychotic symptoms, restlessness, initiation of adequate antidepressant medication or optimisation of existing medication and electroconvulsive therapy) was defined as the appropriate comparator therapy.

The two SUI studies, SUI3001 and SUI 3002, as well as a pooled analysis, are taken into account in the assessment. Esketamine was compared with placebo, in each case in addition to medicinal antidepressant therapy.

There were no differences in mortality that were relevant for the benefit assessment.

In the morbidity category, there were statistically significant advantages for esketamine in the general depressive symptomatology (assessed by MADRS in response and remission) and in health status (assessed by EQ-5D-VAS), but not in the specific depressive symptomatology of suicidality (assessed by SIBAT).

Data on quality of life were not collected.

Disadvantages are only evident in specific AEs, but not in the overall rates so that a relevant disadvantage is not assumed.

For the evaluation in the present therapeutic indication, the overall assessment has to consider that there is no advantage in the specific depressive symptomatology of suicidality, which would have been of importance in the present emergency indication.

Overall, therefore, only a minor additional benefit can be determined on the basis of the morbidity data, since the significance of which is classified as a hint due to uncertainties in the implementation of the appropriate comparator therapy.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The presentation of patient numbers (approx. 49,100 - 69,200 patients) follows the information provided by the pharmaceutical company. Only inpatients are taken into account in the calculation. There are uncertainties due to the data basis, which is based on a study of a psychiatric hospital. The transferability of the proportion of suicidal subjects from this study to the totality of all inpatient adults with moderate to severe depression is questionable. In addition, due to the survey methodology used, the sample's representativeness drawn within the study is uncertain. The transferability of the ratio of the number of admissions to the number of patients with suicidal ideation with intent to act to the analysis population and subsequently to the total number of patients is also questionable.

Overall, the number of patients is subject to uncertainty due to the methodological limitations mentioned above.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Spravato (active ingredient: esketamine) at the following publicly accessible link (last access: 25 May 2021):

https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_de.pdf

Treatment with Spravato may only be initiated and monitored by a psychiatrist.

The use of Spravato and subsequent follow-up must take place in an appropriate medical setting.

Spravato must not be used if increased blood pressure or increased intracranial pressure poses a serious risk.

Patients with clinically significant or unstable cardiovascular or respiratory disease require additional precautions. For these patients, Spravato must be used in a setting where appropriate resuscitation equipment and healthcare professionals trained in cardiopulmonary resuscitation are available.

In accordance with the European Medicines Agency, the pharmaceutical company must provide training material and a patient guideline. The following training material must be made available to healthcare professionals: Guideline for healthcare professionals with information on specific risks and a checklist for healthcare professionals.

The patient guideline has to be made available to patients.

2.4 Treatment costs

The treatment costs are based on the information in the product information.

For the cost calculation, it is assumed that, according to the recommendations of the S3 guideline for unipolar depression in the present therapeutic indication of the psychiatric emergency in patients with a moderate to severe episode of Major Depressive Disorder, mainly an inpatient treatment is considered.

Billing is based on the flat-rate remuneration system for psychiatric and psychosomatic facilities (PEPP) and varies according to diagnosis, additional diagnosis, pre-structural category (e.g. increased care requirements) and length of stay. Since the costs for the inpatient stay are incurred equally for the medicinal product to be assessed and the appropriate comparative therapy, these are not quantified in the present cost calculation.

The oral antidepressant basic therapy is provided equally for the medicinal product to be evaluated, and the appropriate comparator therapy is continued after the emergency treatment. The PEPP flat rate covers the costs of the medicinal product during the inpatient

stay. For these reasons, a detailed list of medicinal therapies and costs was not presented. The same applies to acute medicinal therapy for the treatment of anxiety, insomnia, psychotic symptoms or restlessness.

Treatment duration:

According to the S3 guideline, electroconvulsive therapy (ECT) as an acute treatment consists of an average of 10 individual treatments, which are usually carried out two to three times a week, weighing up the effects and side effects. This should be followed by maintenance treatment with ECT, usually for at least 6 months and gradually increasing treatment intervals from once a week to once a month.[2] Only the acute therapy of an average of 10 treatment days is used for the cost calculation.

Designation of the therapy	Treatment method	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Esketamine	2x a week	4 weeks	2	8
Inpatient stay[3]	Patient-individual			
Appropriate comparator therapy				
Inpatient stay[3]	Patient-individual			
Electroconvulsive therapy (ECT)	1	10	1	10

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Esketamine	84 mg	84 mg	3 x 28 mg	8	24 x 28 mg
Inpatient stay[3]	-				
Appropriate comparator therapy					
Inpatient stay[3]	-				

2 DGPPN, BÄK, AWMF, KBV: S3 Guideline/National Health Care Guideline Unipolar Depression, Version 5, 2nd edition, 2015. https://www.awmf.org/leitlinien/detail/ll/nvl-005.html [last accessed 08/07/2021; the guideline is currently under revision].
3 Includes crisis intervention/psychotherapy, acute medicinal therapy and initiation of adequate antidepressant medication or optimization of existing medication.

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Electroconvulsive therapy	-				

Costs:

Costs of the medicinal products:

Esketamine meets the criteria of the NUB-PEPP agreement. Therefore, in accordance with Section 1, paragraph 1 of the New examination and treatment methods - Flat-rate remuneration system for psychiatric and psychosomatic facilities (NUB-PEPP) agreement for the year 2021, the stipulation of a hospital-specific fee pursuant to Section 6, paragraph 4 BPflV (German National Hospital Rate Ordinance) is admissible for esketamine.

For electroconvulsive therapy (ECT), specific additional rates are calculated for the basic service and the therapy session.

Designation of the therapy	Packaging size	Cost/performance
Medicinal product to be assessed		
Esketamine	24 x 28 mg NAS	hospital-specific fee according to New examination and treatment methods (NUB) agreement
Inpatient stay[3]		case-specific flat-rate remuneration system for psychiatric and psychosomatic facilities (PEPP)
Appropriate comparator therapy		
Inpatient stay[3]		case-specific flat-rate remuneration system for psychiatric and psychosomatic facilities (PEPP)
Electroconvulsive therapy:		
ZP73.01 Basic service		€ 394.58
ZP73.02 Therapy session		€ 298.23

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be considered as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 6 November 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of esketamine to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 01 March 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient esketamine.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 June 2021. The deadline for submitting written statements was 22 June 2021.

The oral hearing was held on 5 July 2021.

By letter dated 6 July 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by IQWiG was submitted to the G-BA on 30 July 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 10 August 2021, and the proposed resolution was approved.

At its session on 19 August 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	26 June 2018	Determination of the appropriate comparator therapy
Working group Section 35a	29 June 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 July 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 July 2021 20 July 2021 3 August 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	10 August 2021	Concluding consultation of the draft resolution
Plenum	19 August 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 August 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken