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, treatment-resistant, in combination with SSRI or SNRI)

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 to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the

benefit assessment prepared by the 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, 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.

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 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.

Therapy according to doctor's instructions under the selection of:

- augmentation with lithium[1Fehler! Textmarke nicht definiert.] or quetiapine retard[1]
- a combination with a second antidepressant[1Fehler! Textmarke nicht definiert.]
- electroconvulsive therapy
- a change from antidepressant monotherapy to another substance class.

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.

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

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. For moderate to severe depressive disorders, antidepressants of the substance classes non-selective monoamine reuptake inhibitors (imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, maprotiline, amitriptyline oxide), selective serotonin reuptake inhibitors (SSRI: Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram), serotonin-norepinephrine reuptake inhibitors (SNRI: duloxetine, venlafaxine, milnacipran), monoamine oxidase inhibitors (tranylcypromine, moclobemide), and others (mianserin, trazodone, mirtazapine, bupropion, tianeptine, reboxetine, agomelatine, vortioxetine) are approved. The marketing authorisation does not exclude the use in cases of treatment-resistant depression.

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

In its retarded form, quetiapine 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 suspected changeover to mania, if necessary in combination with antidepressants.

As a herbal medicine, St. John's wort has a marketing authorisation for moderately severe depressive episodes.

on 2. In the therapeutic indication, electroconvulsive therapy (ECT) and psychotherapy according to the psychotherapy guideline may be considered.

on 3. Resolutions on the benefit assessment according to Section 35a SGB V are not available in the therapeutic indication of treatment-resistant depression. There is a resolution regarding vortioxetine for the treatment of Major Depressive Disorder episodes in adults dated 15 October 2015. 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".

Evidence from meta-analyses and clinical guidelines is available for the therapeutic indication of treatment-resistant depression. The National Health Care Guideline (NVL) is particularly relevant for the German health care context[2]. Overall, the evidence base

[2] German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). S3 Guideline/National Health Care Guideline Unipolar Depression. 2nd Edition 2015. The guideline is currently under revision.

in the therapeutic indication "treatment-resistant depression" is limited, as the data is not based on studies with a high level of evidence (direct-comparative RCTs).

A prior antidepressant medicinal therapy is required for treatment-resistant Major Depressive Disorder.

In the NVL, a serum level control of the previous medicinal therapy and the maximum use of the possible dosages are initially recommended for treatment-resistant depression. The utilisation of the dosage (if tolerated) of antidepressant monotherapy compliant with marketing authorisation is undertaken before further therapy escalation. Since the use of esketamine therapy already represents such an escalation, the dose adjustment of the previous therapy is assumed and is not considered an appropriate comparator therapy.

The following options are suggested as therapeutic options for escalation: lithium augmentation or an atypical neuroleptic (in Germany, only quetiapine retard is approved for augmentation) to the last antidepressant monotherapy given, combined with a second antidepressant or a change of antidepressant monotherapy to another substance class.

Augmentation of existing antidepressant therapy with lithium or quetiapine is the recommended add-on therapy, analogous to the researched guidelines and meta-analyses.

In the case of existing treatment resistance, the combination of antidepressant monotherapy with another antidepressant can be carried out. According to the NVL, mianserin or mirtazapine can be used for this purpose.

Switching antidepressant monotherapy is also recommended; in this case, the substance class of the antidepressant previously used should also be changed when switching. On the basis of the guideline recommendations as well as the statements, this option is to be regarded as subordinate to the aforementioned augmentation or adjunctive therapies.

The marketing authorisation of the active ingredients used must be observed.

There is also evidence for the efficacy of electroconvulsive therapy (ECT) in the therapeutic indication of treatment-resistant depression. According to the S3 guideline, ECT may be considered an option after careful consideration, especially for severe depressive episodes or treatment-resistant depression. On the basis of the guideline recommendations as well as the statements, this option is to be regarded as subordinate to the above-mentioned augmentation or adjunctive therapies and is rarely performed in the reality of care compared to the other options. As ECT may be indicated for some subjects, it is identified as a possible option within the appropriate comparator therapy.

Treatment of treatment-resistant depression can basically be done with any of the above options. The decision is made according to the doctor's instructions. Previous medicinal and non-medicinal therapy is taken into account when selecting one of the therapeutic options mentioned.

In summary, for the present therapeutic indication, the appropriate comparator therapy is determined to be a therapy according to the doctor's instructions, selecting from:

- augmentation with lithium[1] or quetiapine retard[1]
- a combination with a second antidepressant[1]**Fehler! Textmarke nicht definiert.**
- electroconvulsive therapy

- a change from antidepressant monotherapy to another substance class.

Since none of the mentioned therapy options can be determined as a suitable therapy for the majority of patients, a single comparator study is usually not sufficient.

The basic therapy concept for the treatment of Major Depressive Disorder also includes psychotherapeutic procedures. Psychotherapy for treatment-resistant depression is consistently supported by evidence from meta-analyses and clinical guidelines. Therefore psychotherapeutic treatment should be offered to patients in both treatment arms of a study according to the psychotherapy guideline.

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

Change of the appropriate comparator therapy

Up to now, for adult patients with treatment-resistant moderate to severe depression, augmentation with lithium or quetiapine retard, combination with a second antidepressant, and a switch from antidepressant monotherapy to another substance class were considered equally appropriate treatment options of the appropriate comparative therapy.

In the opinion of the clinicians involved in the written statement procedure, this does not correspond to the current medical treatment situation of patients with treatment-resistant depression. In particular, switching monotherapy should be considered as a secondary option. In addition, electroconvulsive therapy may be considered for some patients. Therefore, the G-BA considers it appropriate to change the appropriate comparator therapy at this point in time and adapt it to the current state of medical knowledge. Accordingly, a therapy is determined as an appropriate comparator therapy according to the doctor's instructions.

2.1.3 Extent and probability of the additional benefit

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

The additional benefit is not proven for adults with treatment-resistant Major Depressive Disorder who have not responded to at least two different therapies with antidepressants in the current moderate to severe depressive episode.

Justification:

The pharmaceutical company identifies the two directly comparative, randomised clinical studies TRANSFORM-2 and TRANSFORM-3. Both studies investigate acute treatment with esketamine versus placebo, each with a newly initiated oral antidepressant from the substance classes SSRI or SNRI over a treatment duration of 28 days, plus screening and follow-up phases.

Study participants were required to have moderate to severe depression and a nonresponse (defined as ≤ 25% on the MADRS[3] total score) to at least one prior treatment with an oral antidepressant in the current episode and at least two weeks of therapy with another antidepressant that continued into the four-week screening period. Those study participants

3 Montgomery-Åsberg Depression Rating Scale

who did not respond even after the end of the screening phase were randomised to the two treatment arms. The patients examined thus corresponded to the therapeutic indication.

In the treatment phase, study participants received either esketamine or placebo along with a newly initiated antidepressant from the SSRI or SNRI substance classes.

The change of antidepressant (switch) corresponds to an option of the appropriate comparator therapy, but - as stated in the derivation of the ZVT - is recommended according to the NVL if a change of antidepressant monotherapy to another substance class is possible. However, the study also included patients who were already receiving combination therapies of two antidepressants or augmentations during the screening phase, for whom the option "change of antidepressant monotherapy" was not an option. Evaluations of study participants who were treated according to the appropriate comparator therapy are not available. The appropriate comparator therapy can therefore not be considered as adequately implemented.

In addition, the treatment duration of four weeks is not sufficient for a comprehensive assessment of the additional benefit in treatment-resistant depression. The therapeutic concept for the treatment of a depressive episode includes both acute therapy and remission maintenance. With the present randomised treatment phase of four weeks, effects of acute therapy could be assessed, if appropriate, for those patients in whom the titration phase has been completed and in whom the appropriate dose for the patient has been reached in the initiation phase, assuming adequate implementation of the appropriate comparator therapy.

In summary, the studies TRANSFORM-2 and TRANSFORM-3 cannot be used to derive the additional benefit due to the lack of implementation of the appropriate comparator therapy.

For long-term treatment, the pharmaceutical company identifies the single-arm study SUSTAIN-2 and compares its results with the data of a prospective European cohort study. In the cohort study, there is no documentation of adverse events, which are necessary for assessing the additional benefit. The comparison made is therefore not suitable for the assessment of the additional benefit.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of esketamine in the therapeutic indication treatment-resistant depression finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

The data from the study programme available to date cannot be used to assess the additional benefit. The pharmaceutical company is currently conducting another study with the active ingredient esketamine versus augmentation with quetiapine (retard). According to the pharmaceutical company, the study is expected to be completed in December 2022.

Since more clinical data are expected that are relevant for the benefit assessment of the medicinal product, it is justified to limit the resolution's validity until further scientific knowledge is available for the assessment of the additional benefit of esketamine. The time limit enables the inclusion of the expected results from the phase ESCAPE-TRD study in the benefit assessment of the drug according to Section 35a SGB V. For this purpose, a time limit of the resolution until 15 June 2023 is considered appropriate.

Conditions of the limitation:

For the new benefit assessment after the expiry of the deadline, the results on all patient-relevant outcomes used for the proof of an additional benefit, including the results of the ESCAPE-TRD study, are to be presented in the dossier. A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long. In accordance with Section 3 paragraph 1, number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of esketamine recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of esketamine (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for esketamine can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2 VerfO and Chapter 5, Section 12, No. 2 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The assessment is for esketamine (nasal spray) in combination with an SSRI or SNRI in the therapeutic indication "in 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."

The appropriate comparator therapy was determined as a therapy according to the doctor's instructions (taking into account lithium augmentation or quetiapine retard, a combination with a second antidepressant, an electroconvulsive therapy, a change from antidepressant monotherapy to another substance class).

There are no studies of esketamine in comparison with the appropriate comparator therapy. The additional benefit is therefore not proven.

Based on the background that further clinical data are expected which may be relevant for the assessment of the benefit of the medicinal product, the resolution is limited until 15.06.2023.

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

According to the therapeutic indication, esketamine nasal spray can be used to treat both hospitalised and non-hospitalised patients with treatment-resistant depression. The resolution of 15 October 2015 on vortioxetine reported a total of 2,795,000 to 2,922,000 patients with moderate to severe depression. According to IQWiG's assessment, one-third of treatment-resistant patients can be assumed, although this figure is subject to uncertainty. This results in the patient number of approximately 932,000 - 974,000.

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 product information as well as the information in the LAUER-TAXE® (last revised: 1 August 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs. Dose adjustments in elderly patients are only considered if there are specific dosage guidelines in the respective product information.

In general, initial induction regimens are not taken into account for the cost representation since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

If an active ingredient was available in several dosage forms, a solid oral dosage form was used as an example for the cost calculation.

Tranylcypromine should only be used as a reserve antidepressant, according to the product information (Jatrosom, last revised April 2021), and a combination with tricyclic antidepressants is only indicated in individual cases.

Electroconvulsive therapy:

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 a total duration of at least 6 months and gradually increasing treatment intervals from once a week to once a month.[4] For the calculation of costs, an average of 10 treatment days can be used for acute therapy. Maintenance treatment varies and is therefore not quantifiable.

4 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].

Treatment duration:

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	Once every 7 or 14 days	26.1 - 52.1	1	26.1 - 52.1
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	1 x day	365	1	365
Escitalopram	1 x day	365	1	365
Fluoxetine	1 x day	365	1	365
Fluvoxamine	1-3 x day	365	1	365
Paroxetine	1 x day	365	1	365
Sertraline	1 x day	365	1	365
Serotonin-norepinephrine reuptake inhibitors (SNRIs)				
Venlafaxine	1 x day	365	1	365
Duloxetine	1 x day	365	1	365
Milnacipran	2 x day	365	1	365
Appropriate comparator therapy				
Lithium augmentation				
Lithium	1-2 x day	365	1	365
plus antidepressant				
Augmentation with quetiapine retard				
Quetiapine	1 x day	365	1	365
plus antidepressant				
Antidepressants				
Tri- and tetracyclic antidepressants (TCAs) - non-selective monoamine reuptake inhibitors (NSMRIs)				
Amitriptyline oxide	1 x day	365	1	365
Amitriptyline	1 x day	365	1	365
Clomipramine	1 x day	365	1	365

Designation of the therapy	Treatment method	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Doxepin	1 x day	365	1	365
Imipramine	1 x day	365	1	365
Maprotiline	1 x day	365	1	365
Nortriptyline	3-4 x day	365	1	365
Trimipramine	Once to several times a day	365	1	365
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	1 x day	365	1	365
Escitalopram	1 x day	365	1	365
Fluoxetine	1 x day	365	1	365
Fluvoxamine	1-3 x day	365	1	365
Paroxetine	1 x day	365	1	365
Sertraline	1 x day	365	1	365
Monoamine oxidase inhibitors (MAOIs)				
Moclobemide	several times a day, after meals	365	1	365
Tranylcypromine	1-3 x day	365	1	365
Serotonin-norepinephrine reuptake inhibitors (SNRIs)				
Venlafaxine	1 x day	365	1	365
Duloxetine	1 x day	365	1	365
Milnacipran	2 x day	365	1	365
Other antidepressants				
Mianserin	1-3 x day	365	1	365
Mirtazapine	1 x day	365	1	365
Bupropion	1 x day	365	1	365
Agomelatine	1 x day	365	1	365
Tianeptine	3 x day	365	1	365

Designation of the therapy	Treatment method	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Trazodone	Once to several times a day	365	1	365
Electroconvulsive therapy				
Electroconvulsive therapy - acute therapy	1	10	1	10
Electroconvulsive therapy - maintenance treatment	Patient-individual			

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 (< 65 years)	56 mg - 84 mg	56 mg - 84 mg	2 x 28 mg - 3 x 28 mg	26,1 - 52.1	52.2 x 28 mg - 156.3 x 28 mg
Esketamine (≥ 65 years)	28 mg - 84 mg	28 mg - 84 mg	1 x 28 mg - 3 x 28 mg	26,1 - 52.1	26.1 x 28 mg - 156.3 x 28 mg
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365	365 x 20 mg - 365 x 40 mg
Citalopram (> 65 years)	10 mg - 20 mg	10 mg - 20 mg	1x 10 mg 1x 20 mg	365 365	365x 10 mg - 365x 20 mg
Escitalopram	10 mg - 20 mg	10 mg - 20 mg	1 x 10 mg - 1 x 20 mg	365	365 x 10 mg - 365 x 20 mg
Escitalopram (> 65 years)	5 mg -	5 mg -	1 x 5 mg -	365	365 x 5 mg -

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
	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Fluoxetine	20 mg - 60 mg	20 mg - 60 mg	1 x 20 mg - 1 x 40 mg + 1 x 20 mg	365	365 x 20 mg - 365 x 40 mg + 365 x 20 mg
Fluvoxamine	100 mg -	100 mg - 300 mg	1 x 100 mg - 3 x 100 mg	365	365 x 100 mg - 1095 x 100 mg
Paroxetine	20 mg - 50 mg	20 mg - 50 mg	1 x 20 mg - 1 x 40 mg + 1 x 10 mg	365	365 x 20 mg - 365 x 40 mg + 365 x 10 mg
Paroxetine (elderly patients)	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365	365 x 20 mg - 365 x 40 mg
Sertraline	50 mg - 200 mg	50 mg - 200 mg	1 x 50 mg - 1 x 200 mg	365	365 x 50 mg - 365 x 200 mg
Serotonin-norepinephrine reuptake inhibitors (SNRIs)					
Venlafaxine	75 mg - 375 mg	75 mg - 375 mg	1 x 75 mg - 1 x 300 mg + 1 x 75 mg	365	365 x 75 mg - 365 x 300 mg + 365 x 75 mg
Duloxetine	60 mg - 120 mg	60 mg - 120 mg	1 x 60 mg - 2 x 60 mg	365	365 x 60 mg - 730 x 60 mg
Milnacipran	50 mg	100 mg	2 x 50 mg	365	730 x 50 mg
Appropriate comparator therapy					
Lithium augmentation					
Lithium	on the basis of lithium serum level	18 mmol - 36 mmol	1.5 x 12.2 mmol - 3 x 12.2 mmol	365	547.5 x 12.2 mmol - 1095 x 12.2 mmol

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
	dose; target value: 0.5 to 1.2 mmol/l				
plus antidepressant					
Augmentation with quetiapine retard					
Quetiapine	150 mg - 300 mg	150 mg - 300 mg	1 x 150 mg - 1 x 300 mg	365	365 x 150 mg - 365 x 300 mg
plus antidepressant					
Tri- and tetracyclic antidepressants (TCAs) - non-selective monoamine reuptake inhibitors (NSMRIs)					
Amitriptyline oxide	90 mg- 150 mg	90 mg- 150 mg	1 x 90 mg - 1 x 90 mg + 1 x 60 mg	365	365 x 90 mg - 365 x 90 mg + 365 x 60 mg
Amitriptyline	50 mg - 150 mg	50 mg - 150 mg	1 x 50 mg - 1 x 100 mg + 1 x 50 mg	365	365 x 50 mg - 365 x 100 mg + 365 x 50 mg
Clomipramine	37.5 mg - 150 mg	37.5 mg - 150 mg	1/2 x 75 mg - 2 x 75 mg	365	182.5 x 75 mg - 730 x 75 mg
Doxepin	50 mg - 150 mg	50 mg - 150 mg	1 x 50 mg - 1 x 100 mg + 1 x 50 mg	365	365 x 50 mg - 365 x 100 mg + 365 x 50 mg
Imipramine	50 mg - 150 mg	50 mg - 150 mg	2 x 25 mg - 1 x 100 mg + 2 x 25 mg	365	730 x 25 mg - 365 x 100 mg + 730 x 25 mg
Maprotiline	25 mg - 150 mg	25 mg - 150 mg	1 x 25 mg - 2 x 75 mg	365	365 x 25 mg - 730 x 75 mg

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
Nortriptyline	25 mg - 150 mg	25 mg - 150 mg	1 x 25 mg - 6 x 25 mg	365	365 x 25 mg - 2190 x 25 mg
Trimipramine	100 mg - 400 mg	100 mg - 400 mg	1 x 100 mg - 4 x 100 mg	365	365 x 100 mg - 1460 x 100 mg
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365	365 x 20 mg - 365 x 40 mg
Citalopram (> 65 years)	10 mg - 20 mg	10 mg - 20 mg	1x 10 mg - 1x 20 mg	365 365	365 x 10 mg - 365 x 20 mg
Escitalopram	10 mg - 20 mg	10 mg - 20 mg	1 x 10 mg - 1 x 20 mg	365	365 x 10 mg - 365 x 20 mg
Escitalopram (> 65 years)	5 mg - 10 mg	5 mg - 10 mg	1 x 5 mg - 1 x 10 mg	365 365	365 x 5 mg - 365 x 10 mg
Fluoxetine	20 mg - 60 mg	20 mg - 60 mg	1 x 20 mg - 1 x 40 mg + 1 x 20 mg	365	365 x 20 mg - 365 x 40 mg + 365 x 20 mg
Fluvoxamine	100 mg -	100 mg - 300 mg	1 x 100 mg - 3 x 100 mg	365	365 x 100 mg - 1095 x 100 mg
Paroxetine	20 mg - 50 mg	20 mg - 50 mg	1 x 20 mg - 1 x 40 mg + 1 x 10 mg	365	365 x 20 mg - 365 x 40 mg + 365 x 10 mg
Paroxetine (elderly patients)	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365	365 x 20 mg - 365 x 40 mg
Sertraline	50 mg -	50 mg -	1 x 50 mg -	365	365 x 50 mg -

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
	200 mg	200 mg	1 x 200 mg		365 x 200 mg
Monoamine oxidase inhibitors (MAOIs)					
Moclobemide	75 mg - 300 mg	150 mg - 600 mg	2 x 0.5 x 150 mg - 2 x 300 mg	365	365 x 150 mg - 730 x 300 mg
Tranylcypromine	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg - 2 x 20 mg	365	365 x 10 mg - 730 x 20 mg
Serotonin-norepinephrine reuptake inhibitors (SNRIs)					
Venlafaxine	75 mg - 375 mg	75 mg - 375 mg	1 x 75 mg - 1 x 300 mg + 1 x 75 mg	365	365 x 75 mg - 365 x 300 mg + 365 x 75 mg
Duloxetine	60 mg - 120 mg	60 mg - 120 mg	1 x 60 mg - 2 x 60 mg	365	365 x 60 mg - 730 x 60 mg
Milnacipran	50 mg	100 mg	2 x 50 mg	365	730 x 50 mg
Other antidepressants					
Mianserin	30 mg - 90 mg	30 mg - 90 mg	1 x 30 mg - 1 x 60 mg + 1 x 30 mg	365	365 x 30 mg - 365 x 60 mg + 365 x 30 mg
Mirtazapine	15 mg - 45 mg	15 mg - 45 mg	1 x 15 mg - 1 x 45 mg	365	365 x 15 mg - 365 x 45 mg
Bupropion	150 mg- 300 mg	150 mg- 300 mg	1 x 150 mg- 1 x 300 mg	365	365 x 150 mg- 365 x 300 mg
Agomelatine	25 mg - 50 mg	25 mg - 50 mg	1 x 25 mg - 2 x 25 mg	365	365 x 25 mg - 730 x 25 mg
Tianeptine	12.5 mg	37.5 mg	3 x 12.5 mg	365	1095 x 12.5 mg
Tianeptine (> 70 years)	12.5 mg	25 mg	2 x 12.5 mg	365	730 x 12.5 mg

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
Trazodone	200 mg	200 mg - 400 mg	2 x 100 mg - 4 x 100 mg	365	730 x 100 mg - 1460 x 100 mg
Trazodone (elderly patients)	100 mg	100 mg - 300 mg	1 x 100 mg - 3 x 100 mg	365	365 x 100 mg - 1095 x 100 mg
Electroconvulsive therapy					
Electroconvulsive therapy - acute therapy	–				
Electroconvulsive therapy - maintenance treatment	–				

Costs:

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Esketamine is listed in LAUER-TAXE® as a clinic pack only. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung), and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic package plus 19 % value-added tax - in deviation from the LAUER-TAXE® data usually taken into account. In Module 3, the company specifies a hospital pharmacy purchase price of € 8,280.00 excluding value-added tax.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Esketamine	24 x 28 mg NAS	-			€ 9,853.20[5]
Citalopram 10 mg	100 FCT6	€ 18.53	€ 1.77	€ 0.59	€ 16.17
Citalopram 20 mg	100 FCT[6]	€ 25,59	€ 1.77	€ 1.15	€ 22.67
Citalopram 40 mg	100 FCT[6]	€ 44,89	€ 1.77	€ 2.68	€ 40.44
Escitalopram 5 mg	100 FCT[6]	€ 16.85	€ 1.77	€ 0.46	€ 14.62
Escitalopram 10 mg	100 FCT[6]	€ 21,98	€ 1.77	€ 0.87	€ 19.34
Escitalopram 20 mg	100 FCT[6]	€ 35,01	€ 1.77	€ 1.90	€ 31.34
Fluoxetine 20mg	100 TAB[6]	€ 27,08	€ 1.77	€ 1.27	€ 24.04
Fluoxetine 40mg	100 TAB[6]	€ 40.85	€ 1.77	€ 2.36	€ 36.72
Fluvoxamine 100 mg	100 TAB[6]	€ 22,15	€ 1.77	€ 0.88	€ 19.50
Milnacipran 50 mg	100 HC	€ 79.87	€ 1.77	€ 3.27	€ 74.83
Paroxetine 20mg	100 FCT[6]	€ 27,08	€ 1.77	€ 1.27	€ 24.04
Paroxetine 40mg	100 FCT[6]	€ 40,85	€ 1.77	€ 2.36	€ 36.72
Paroxetine 10mg	100 FCT[6]	€ 19,66	€ 1.77	€ 0.68	€ 17.21
Venlafaxine 75 mg	100 RET[6]	€ 39,88	€ 1.77	€ 2.28	€ 35.83
Venlafaxine 300 mg	100 RET[6]	€ 83,16	€ 1.77	€ 0.00	€ 81.39
Duloxetine 60 mg	100 ECC[6]	€ 84.97	€ 1.77	€ 5.85	€ 77.35
Sertraline 50 mg	100 FCT[6]	€ 31,76	€ 1.77	€ 1.64	€ 28.35
Sertraline 200 mg	100 FCT[6]	€ 63,94	€ 1.77	€ 0.00	€ 62.17
Appropriate comparator therapy					
Agomelatine 25 mg	98 FCT[6]	€ 70.53	€ 1.77	€ 4.70	€ 64.06
Amitriptyline 50 mg	100 FCT[6]	€ 23,60	€ 1.77	€ 0.99	€ 20.84
Amitriptyline 100 mg	100 FCT[6]	€ 35,03	€ 1.77	€ 1.90	€ 31.36
Amitriptyline oxide 90 mg	100 TAB[6]	€ 20,03	€ 1.77	€ 0.00	€ 18.26
Amitriptyline oxide 60 mg	100 TAB[6]	€ 17,29	€ 1.77	€ 0.00	€ 15.52
Bupropion 150 mg	90 MRT	€ 86,35	€ 1.77	€ 3.57	€ 81.01
Bupropion 300 mg	90 MRT	€ 74,27	€ 1.77	€ 3.00	€ 69.50
Citalopram 10 mg	100 FCT[6]	€ 18.53	€ 1.77	€ 0.59	€ 16.17
Citalopram 20 mg	100 FCT[6]	€ 25,59	€ 1.77	€ 1.15	€ 22.67
Citalopram 40 mg	100 FCT[6]	€ 44,89	€ 1.77	€ 2.68	€ 40.44
Clomipramine 75 mg	100 RET[6]	€ 66,21	€ 1.77	€ 4.37	€ 60.07

5 Hospital pharmacy purchase price according to the information provided by the contractor in module 3 plus 19 % value added tax.
6 Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Doxepin 560 mg	100 FCT[6]	€ 20,85	€ 1.77	€ 0.78	€ 18.30
Doxepin 100 mg	100 FCT[6]	€ 28,86	€ 1.77	€ 1.41	€ 25.68
Duloxetine 60 mg	100 ECC[6]	€ 84,97	€ 1.77	€ 5.85	€ 77.35
Escitalopram 5 mg	100 FCT[6]	€ 16.85	€ 1.77	€ 0.46	€ 14.62
Escitalopram 10 mg	100 FCT[6]	€ 21,98	€ 1.77	€ 0.86	€ 19.35
Escitalopram 20 mg	100 FCT[6]	€ 35,01	€ 1.77	€ 1.90	€ 31.34
Fluoxetine 20mg	100 TAB[6]	€ 27,08	€ 1.77	€ 1.27	€ 24.04
Fluoxetine 40mg	100 TAB[6]	€ 40.85	€ 1.77	€ 2.36	€ 36.72
Fluvoxamine 100 mg	100 TAB[6]	€ 22,15	€ 1.77	€ 0.88	€ 19.50
Imipramine 25 mg	100 FCT[6]	€ 16,40	€ 1.77	€ 0.00	€ 14.63
Lithium carbonate 450 mg	100 RET[6]	€ 30,81	€ 1.77	€ 0.00	€ 29.04
Maprotiline 25 mg	100 FCT[6]	€ 17,33	€ 1.77	€ 0.00	€ 15.56
Maprotiline 75 mg	100 FCT[6]	€ 31,49	€ 1.77	€ 1.62	€ 28.10
Mianserin 30 mg	100 FCT[6]	€ 53,18	€ 1.77	€ 3.34	€ 48.07
Mianserin 60 mg	100 FCT[6]	€ 94,16	€ 1.77	€ 6.57	€ 85.82
Milnacipran 50 mg	100 HC	€ 79,87	€ 1.77	€ 3.27	€ 74.83
Mirtazapine 15 mg	100 FCT[6]	€ 25,54	€ 1.77	€ 1.15	€ 22.62
Mirtazapine 45 mg	100 FCT[6]	€ 63,93	€ 1.77	€ 4.18	€ 57.98
Moclobemide 150 mg	100 FCT[6]	€ 56,57	€ 1.77	€ 3.61	€ 51.19
Moclobemide 300 mg	100 FCT[6]	€ 91,20	€ 1.77	€ 6.34	€ 83.09
Nortriptyline 25 mg	100 FCT[6]	€ 17,02	€ 1.77	€ 0.00	€ 15.25
Paroxetine 20mg	100 TAB[6]	€ 27,08	€ 1.77	€ 1.27	€ 24.04
Paroxetine 40mg	100 TAB[6]	€ 40,85	€ 1.77	€ 2.36	€ 36.72
Paroxetine 10mg	100 TAB[6]	€ 19,66	€ 1.77	€ 0.68	€ 17.21
Quetiapine 150 mg	100 RET[6]	€ 51,28	€ 1.77	€ 3.18	€ 46.33
Quetiapine 300 mg	100 RET[6]	€ 84,92	€ 1.77	€ 5.84	€ 77.31
Sertraline 50 mg	100 FCT[6]	€ 31,76	€ 1.77	€ 1.64	€ 28.35
Sertraline 200 mg	100 FCT[6]	€ 63,94	€ 1.77	€ 0.00	€ 62.17
Tianeptine 12.5 mg	300 FCT	€ 145,10	€ 1.77	€ 6.36	€ 136.97
Tranylcypromine 10 mg	100 FCT	€ 119,44	€ 1.77	€ 5.14	€ 112.53
Tranylcypromine 20 mg	100 FCT	€ 227,90	€ 1.77	€ 10.29	€ 215.84
Trazodone 100 mg	100 TAB[6]	€ 53,18	€ 1.77	€ 3.34	€ 48.07
Trimipramine 100 mg	100 FCT[6]	€ 28,86	€ 1.77	€ 1.41	€ 25.68
Venlafaxine 75 mg	100 RET[6]	€ 39,88	€ 1.77	€ 2.28	€ 35.83
Venlafaxine 300 mg	100 RET[6]	€ 83,16	€ 1.77	€ 0.00	€ 81.39

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Abbreviations: FCT = film-coated tablets, ECC = enteric-coated hard capsules, HC = hard capsules, NAS = nasal spray, RET = sustained-release tablets, MRT = modified-release tablet					

LAUER-TAXE® last revised: 1 August 2021

Electroconvulsive therapy:

Electroconvulsive therapy (ECT) is mainly performed on an inpatient basis. In the process, specific additional charges are calculated for the basic service and the therapy session as well as case-specific PEPP flat rates for the length of stay in the hospital.

Designation of the therapy	Cost/performance
Appropriate comparator therapy	
Electroconvulsive therapy:	
ZP73.01 Basic service	€ 394.58
ZP73.02 Therapy session	€ 298.23
Inpatient stay in ECT therapy	case-specific flat-rate remuneration system for psychiatric and psychosomatic facilities (PEPP)

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 26 June 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 1 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.

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,

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