Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Esketamine (reassessment after the deadline (depression, treatment-resistant, in combination with SSRI or SNRI)

of 21 September 2023

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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 trials 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 benefit,
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. treatment costs for the statutory health insurance funds,
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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient esketamine (Spravato) to be assessed for the first time on 1 March 2021. The benefit assessment resolution was limited until 15 June 2023 against the background of expected further clinical data. At the pharmaceutical company's request, this limitation was shortened until 15 March 2023 by the resolution of the of 17 November 2022.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Spravato recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of

Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 14 March 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 15 June 2023, thus initiating the written statement procedure. 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 21.09.2023):

see the approved therapeutic indication

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

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy:

- Lithium augmentation[2] or quetiapine extended release augmentation or combination of two antidepressants

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 as 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 patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

[2] As an add-on to the last antidepressant monotherapy given.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. For treatment of moderate and severe depressive disorders, antidepressants of the substance classes non-selective monoamine reuptake inhibitors (imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, dosulepin, maprotiline, amitriptyline oxide), selective serotonin reuptake inhibitors (SSRI: fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram), serotonin-norepinephrine reuptake inhibitors (SNRI: duloxetine, venlafaxine, desvenlafaxine, 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 has been unsuccessful or is not feasible.

Quetiapine in its extended release dosage form is approved as an 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 present therapeutic indication, psychotherapeutic procedures according to the psychotherapy guideline as well as electroconvulsive therapy (ECT) in principle come into consideration.

on 3. In the therapeutic indication "treatment-resistant depression", the resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient esketamine of 19 August 2021 / 7 December 2021 / 17 November 2022 is available, which is replaced by the present resolution.

For the active ingredient esketamine, there is also a resolution in accordance with Section 35a SGB V dated 19 August 2021 / 7 December 2021 for the indication "for acute short-term treatment".

Furthermore, there is a resolution on the active ingredient 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 Section 35a SGB V”.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Evidence from meta-analyses and clinical guidelines is available for the treatment of depression. The National Health Care Guideline (NVL) Unipolar Depression is particularly relevant for the German healthcare context[3]. Overall, the evidence base on the therapeutic approach after multiple non-responses is to be considered limited.

The therapeutic indication presented here refers to treatment-resistant depression after non-response to at least two different treatments with antidepressants.

According to the NVL, if there is an insufficient response/ non-response to antidepressant medication, the causes should first be evaluated. This may include, in particular, an inappropriate dose of the antidepressant and a serum level that is too low. It is assumed that the dosage of the antidepressant therapy (if tolerated) is used to the full extent permitted by the marketing authorisation.

As evidence-based treatment options for escalation after non-response to antidepressant monotherapy, the current NVL mentions the following options in addition to combination with psychotherapy: lithium augmentation or a second-generation antipsychotic (in Germany, only quetiapine extended release is approved for augmentation) to the last antidepressant monotherapy given, combination with a second antidepressant or a change of antidepressant monotherapy to another substance class. According to the NVL, ECT may also be considered after multiple non-responses.

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 clinical study according to the psychotherapy guideline. The nature and extent of the psychotherapeutic measures shall be documented.

Among the pharmacotherapeutic options, augmentation of existing antidepressant therapy with lithium or quetiapine extended release and the combination of two antidepressants have the highest level of recommendation. For the latter option, according to the NVL, a combination of SSRIs, SNRIs or tri or tetracyclines (TCAs) with mianserin, mirtazapine or trazodone can be considered.

The change of antidepressant monotherapy (switch) is also mentioned in the NVL. However, based on the guideline recommendations, the underlying evidence and the written statements of the scientific-medical societies, this option is to be regarded as subordinate to the above-mentioned augmentations or combinations. In addition, a maximum of one switch with a change of product class is recommended. Against this background, a switch seems inappropriate, especially in the present therapeutic indication, after at least two non-responses to antidepressants. Therefore, the change of antidepressant is not determined as part of the appropriate comparator therapy.

[3] German Medical Association (BÄK), National Association of Statutory Health Insurance Physicians (KBV), Association of the Scientific-Medical Societies (AWMF). National Health Care Guideline Unipolar Depression - Long version, Version 3.2. 2022. DOI: 10.6101/AZQ/000505. register.awmf.org/de/leitlinien/detail/nvl-005

There is also evidence for the efficacy of electroconvulsive therapy (ECT) in the therapeutic indication of treatment-resistant depression. According to the NVL, ECT should be offered as an option for treatment-resistant depression, especially in older age or with psychotic symptoms.

Even if ECT represents a relevant therapy option for some of the patients in the therapeutic indication, this option is to be regarded as subordinate to the above-mentioned augmentations or add-on therapies on the basis of the guideline recommendations and the reality of care, as well as taking into account the written and oral statements.

Change of the appropriate comparator therapy

Up to now, the appropriate comparator therapy for adults with treatment-resistant depression has been considered to be therapy according to doctor's instructions, selecting the following options: Lithium augmentation or quetiapine extended release augmentation, combination with a second antidepressant, change of antidepressant monotherapy to another substance class (switch) and ECT.

On the basis of the current evidence-based recommendations of the National Health Care Guideline on Unipolar Depression published in September 2022[3] and against the background of the statements received, the G-BA considers it necessary to change the appropriate comparator therapy and to adapt it to the current state of medical knowledge.

The National Health Care Guideline sees the change of antidepressant as a secondary therapeutic alternative in the case of non-response to an antidepressant and also recommends a maximum of one change to another product class. Against this background, a switch as an optimisation option after at least two different therapy attempts with antidepressants further appears to be inappropriate.

According to the assessment of the clinical experts involved in the written statement procedure, the pharmacotherapeutic options of lithium augmentation or quetiapine extended release augmentation as well as the combination of two antidepressants have the highest value in the treatment of treatment-resistant depression. The options mentioned are to be regarded as equivalent; a differential therapy recommendation or criteria for the selection of one of these treatment options are not available. Thus, lithium augmentation or quetiapine extended release augmentation as well as the combination of two antidepressants are to be regarded as equally appropriate therapy options, taking into account the evidence and medical treatment practice.

Although ECT may be indicated in some subjects, it is not considered to be an equivalent therapeutic option to pharmacotherapeutic strategies in the therapeutic indication of treatment-resistant depression for the reasons stated above and is therefore not designated as part of the appropriate comparator therapy.

In summary, the G-BA therefore considers it justified to determine lithium augmentation or quetiapine extended release augmentation or the combination of two antidepressants as the appropriate comparator therapy in the present therapeutic indication.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of esketamine is assessed 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

Hint for a considerable additional benefit

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits the randomised open-label multicentre ESCAPE-TRD study, in which esketamine is compared with quetiapine extended release, in each case in combination with an SSRI or SNRI.

According to inclusion criteria, adults aged < 75 years with moderate to severe Major Depressive Disorder (IDS-C30 total score of > 34) without psychotic features were enrolled in the study. Patients had to show a non-response (improvement of symptoms by less than 25%) to current antidepressant treatment with an SSRI or SNRI. To be enrolled in the study, patients also had to show signs of minimal clinical improvement (via a qualified psychiatric interview by an experienced clinician) at the time of screening.

The current antidepressant treatment must have been preceded by a non-response to at least one, and at most five, different consecutive antidepressant treatments within the current depressive episode. At least two antidepressant product classes must have been used.

A total of 676 patients were enrolled in the study. There was a 1:1 randomisation to the intervention arm with esketamine or the control arm with quetiapine extended release, each in combination with an SSRI or SNRI.
Treatment with esketamine in the intervention arm or quetiapine extended release in the control arm was carried out according to the specifications in the product information. The initiation and continuation of psychotherapy were allowed in both study arms.

The primary endpoint was defined as remission of depression at week 8, operationalised as a total score ≤ 10 points on the Montgomery-Åsberg Depression Rating Scale (MADRS). Secondary endpoints were assessed using further measurement tools in the areas of morbidity, quality of life and side effects at weeks 8 and 32.

Extent and probability of the additional benefit

Mortality

By week 32, one subject had died in each of the intervention and control arms. For the endpoint of overall mortality, there is no statistically significant difference between the treatment arms.

Morbidity

Remission and response using Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) is an established and validated instrument for assessing depressive sympomatology. In the ESCAPE-TRD study, response (MADRS total score improvement of ≥ 50%) and remission (MADRS total score ≤ 12) of depressive sympomatology were assessed at weeks 8 and 32 respectively.

For the endpoints of remission and response, there were statistically significant differences between the treatment arms to the advantage of esketamine at both week 8 and week 32.

There is an effect modification for the response at week 32 depending on the substance class of the existing antidepressant (SNRI vs SSRI). A statistically significant advantage of esketamine is shown for patients whose existing antidepressant was an SNRI, but not for those with existing SSRI treatment.

Time to permanent remission and relapse using Montgomery-Åsberg Depression Rating Scale (MADRS)

The analyses on permanent remission presented in the dossier are not taken into account in the benefit assessment, as the study duration of 32 weeks is too short to allow a statement on permanent remission.

The evaluations on relapse are based, among other things, on the operationalisation MADRS total score ≥ 22. It is questionable to what extent patients who were previously in remission (i.e. MADRS ≤ 12) can actually be considered relapse-free with a MADRS total score of 21 or less. Thus, there is no suitable operationalisation for the endpoint of relapse, so that it is not used to derive an additional benefit.

Functional remission using the Sheehan Disability Scale (SDS)

The SDS is a self-assessment tool for examining functional impairment in the life domains of work, social life and family life in patients with mental illness.

The endpoint of functional remission was assessed by responder analyses on the SDS total score ≤ 6 (each item at least ≤ 2 points). There is no statistically significant difference at week 8 between the treatment arms, but there is a statistically significant advantage of esketamine over quetiapine extended release at week 32.

General depressive sympomatology by means of Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 is a self-assessment tool to assess depressive sympomatology. In the responder analysis (improvement of the PHQ-9 total score by ≥ 5 points), there are statistically significant advantages of esketamine over quetiapine extended release at both week 8 and week 32.

General depressive sympomatology by means of Quality of Life in Depression Scale (QLDS)

The QLDS is a validated self-assessment tool for recording the sympomatology of patients with depression.

At both week 8 and week 32, there are statistically significant differences between the treatment arms to the advantage of esketamine.

In a subgroup analysis, the advantage of esketamine at week 8 is confirmed for those patients with an existing SNRI treatment, but not for those whose existing antidepressant was an SSRI.

Health status using European Quality of Life Questionnaire 5-Dimensions (EQ-5D)

The EQ-5D-VAS represents an independent visual analogue scale for self-assessment of one's own current health status and is assigned to the category of morbidity.

For the endpoint of health status, measured by improvement of ≥ 15 points on the EQ-5D visual analogue scale (VAS), there are statistically significant advantages of esketamine over quetiapine extended release at both week 8 and week 32.

Suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a standardised clinical interview for the systematic assessment of suicidal thoughts and behaviour. The endpoint suicidality was operationalised as a "yes" response at any time during treatment to one of the five questions on suicidal thoughts (categories 1 to 5) in the C-SSRS (suicidal thoughts) or a "yes" response at any time during treatment to one of the five questions on suicidal behaviour (categories 6 to 10) in the C-SSRS (suicidal behaviour).

There were no statistically significant differences between the treatment arms at week 8 or week 32 for the endpoint aspects of suicidal thoughts and suicidal behaviour.

Quality of life

Health-related quality of life using Short Form-36 Health Survey Version 2 (SF-36v2)

Health-related quality of life was assessed in the ESCAPE-TRD study using the SF-36v2. The pharmaceutical company submits evaluations of responder analyses related to an improvement of the physical or mental component summary score compared to the start of the study.

For the physical component summary (PCS) score of the SF-36v2 (responder analysis for improvement of the PCS by ≥ 9.4 points), there is a statistically significant difference between the treatment arms to the advantage of esketamine at week 32, but not at week 8.

In terms of the mental component summary (MCS) score of the SF-36v2 (responder analysis for improvement of MCS by ≥ 9.6 points), there are statistically significant advantages of esketamine over quetiapine extended release at week 8 and week 32 respectively.

For the result at week 32, there is an effect modification depending on the product class of the existing antidepressant: Statistically significant advantages in favour of esketamine can only be derived for the combination with an existing SNRI, but not that with an SSRI.

Side effects

The overall rate of AEs is only presented additionally.

SAEs and therapy discontinuations due to AEs (until week 32)

There is no statistically significant difference between treatment arms for the endpoint of SAEs, whereas for the endpoint of therapy discontinuation due to AEs, there is a statistically significant advantage of esketamine over quetiapine extended release.

Specific adverse effects (until week 32)

For the endpoints of psychiatric disorders (SOC, AEs) and nervous system disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), nausea (PT, AEs) and vomiting (PT, AEs), there were statistically significant differences between the treatment arms to the disadvantage of esketamine.

Transience of the AEs

The pharmaceutical company shall submit evaluations of AEs whose onset and end were documented on the same day (transient) or not on the same day (non-transient) and which occurred in at least 5% of the patients. The dossier argues that the AEs typical of esketamine are of short duration and thus, less significant for the burden on patients than, for example, therapy discontinuations due to AEs.

For the following reasons, the transience of events is not taken into account in the benefit assessment: Esketamine was administered in the study sites under controlled conditions that allowed systematic observation, while patients in the comparator arm took quetiapine extended release independently outside the study site. This may lead to inaccurate recording of the duration of adverse events during treatment with quetiapine extended release. In addition, transient AEs, especially due to frequent occurrence or recurrence, can also lead to patient-relevant burdens.

Overall assessment

The assessment of the additional benefit of esketamine is based on the open-label, randomised, controlled, multicentre ESCAPE-TRD study, which compared esketamine with quetiapine extended release, each in combination with an SSRI or SNRI. Results are available for endpoints in the categories of mortality, morbidity, health-related quality of life and safety over an observation period of 8 and 32 weeks.

In the study, one death occurred in each of the intervention and control arms. For the endpoint of overall mortality, an additional benefit is not proven; no relevant difference for the benefit assessment was shown.

In the morbidity category, remission and response are highly relevant and were investigated in the present study using MADRS. There were advantages of esketamine over quetiapine extended release at weeks 8 and 32 for both remission and response. For general depressive sympomatology (assessed using the PHQ-9 and the QLDS) and health status (assessed using the EQ-5D visual analogue scale), there are advantages of esketamine over quetiapine extended release, in each case in combination with an SSRI or SNRI. With regard to functional remission (represented by the SDS), there is a difference to the advantage of esketamine at week 32, but not at week 8. No statistically significant differences can be found for the endpoint of suicidality (assessed by C-SSRS).

The analyses of quality of life using SF-36v2 show advantages of esketamine over quetiapine extended release at week 32 (physical component summary score) and weeks 8 and 32 (mental component summary score).

In terms of side effects, there is an advantage of esketamine in terms of therapy discontinuations due to adverse events. The overall rates of serious adverse events do not show statistically significant differences. In detail, the specific adverse events show disadvantages of esketamine compared to quetiapine extended release. In summary, there are advantages of esketamine in terms of side effects.

In the overall analysis, the G-BA comes to the conclusion that there is a considerable additional benefit of esketamine compared to quetiapine extended release in the treatment of adult patients with treatment-resistant major depressive disorder.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the open-label, randomised, controlled ESCAPE-TRD study.

The unblinded study design poses a high risk of bias at the endpoint level, which limits the reliability of data of the results:
Since most of the endpoints relevant to the benefit assessment were recorded using self-assessment tools, a blinded survey is not possible for these.
The endpoints of remission and response using MADRS were assessed by blinded study personnel. The patients who answered questions about their symptoms during the MADRS assessment, however, were informed about their respective inclusion in the intervention or control arm, so that a high risk of bias can also be assumed for the endpoints recorded by means of the MADRS due to the (partly) subjective survey.

Furthermore, the reliability of data of the evaluations relevant for the benefit assessment is considered limited due to the high percentage of replaced values, which is partly discrepant between the study arms

Overall, the available data basis is subject to uncertainties for the reasons mentioned. In the overall assessment, the G-BA classifies the reliability of data for the additional benefit in the "hint" category.

2.1.4 Summary of the assessment

This assessment is a reassessment after the deadline due to the availability of new clinical data from the ESCAPE-TRD study.

The therapeutic indication assessed here is as follows:

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.

The G-BA has determined lithium augmentation or quetiapine extended release augmentation (in each case as an add-on to the last antidepressant monotherapy given) or a combination of two antidepressants to be the appropriate comparator therapy for esketamine in combination with an SSRI or SNRI in adults with treatment-resistant Major Depressive Disorder who have not responded to at least two different antidepressant therapies in the current moderate to severe depressive episode.

The assessment of the additional benefit of esketamine over quetiapine extended release is based on the open-label, randomised, controlled, multicentre ESCAPE-TRD study.

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

In the morbidity category, advantages of esketamine can be observed for remission and response (assessed by MADRS), general depressive sympomatology (assessed by PHQ-9 and QLDS), health status (assessed by EQ-5D-VAS) and functional remission at week 32 (assessed by SDS). No relevant differences were found for the endpoint of suicidality (assessed by C-SSRS).

In the quality of life category, the evaluations of the SF-36v2 endpoints show advantages of esketamine over quetiapine extended release at week 32 (physical component summary score) and at weeks 8 and 32 (mental component summary score).

In terms of side effects, there are advantages of esketamine in terms of therapy discontinuations due to adverse events and disadvantages, in detail, for the specific adverse events.

The reliability of data of the evidence is categorised as a "hint", which is due to the high risk of bias in the open-label study design and subjective endpoint assessment as well as the high percentage of values replaced after study discontinuation.

In summary, hint for a considerable additional benefit of esketamine over quetiapine extended release is determined.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the patient numbers specified by the pharmaceutical company.

The information provided by the pharmaceutical company is based on an analysis of treatment data and a literature search. Both approaches are subject to uncertainties.
The analysis of the treatment data is limited by, among other things, the use of opipramol prescriptions and the restriction to at least three consecutive prescriptions as well as at least two previous antidepressant therapies with a change of substance class in each case.
The derivations from the literature search are of uncertain significance due to inconsistent definitions of treatment resistance, lack of restriction to moderate and severe depression, exclusion of comorbidities and other aspects.

In summary, the lower limit can be considered a plausible approximation of patient numbers, the upper limit is subject to uncertainties.

In past benefit assessment procedures, the number of patients was estimated to be between 932,000 and 974,000. This calculation was based on the assumption that the percentage of treatment resistance among depressive patients is one third, which results in considerable uncertainties. The current estimate is a more valid approximation.

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: 1 September 2023):

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

The initiation and monitoring of treatment with Spravato must be done only by a psychiatrist. Spravato is intended for use by the patient under the direct supervision of a healthcare professional.

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 (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients.

The training material contains, in particular, information on the need for monitoring before and after the use of Spravato, as well as information on side effects and signs of abuse and dependence.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2023).

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 varies

from patient to patient 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 co-morbidities) 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.

Tranylcypromine should only be used as a reserve antidepressant, according to the product information (Tranylcypromine neuraxpharm®, as of December 2021).

Sulpiride is an antipsychotic, but is approved in the treatment of depressive disorders when treatment with another antidepressant has been unsuccessful or infeasible.

Treatment period:

Designation of the therapy	**Treatment mode**	**Number of treatments/ patient/ year**	**Treatment duration/ treatment (days)**	**Treatment days/ patient/ year**
Medicinal product to be assessed				
Esketamine	1 x every 7 or every 14 days	26.1 - 52.1	1	26.1 - 52.1
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	1 x daily	365	1	365
Escitalopram	1 x daily	365	1	365
Fluoxetine	1 x daily	365	1	365
Fluvoxamine	1-3 x day	365	1	365
Paroxetine	1 x daily	365	1	365
Sertraline	1 x daily	365	1	365
Serotonin-norepinephrine reuptake inhibitors (SNRIs)				
Desvenlafaxine	1 x daily	365	1	365
Duloxetine	1 x daily	365	1	365
Milnacipran	2 x daily	365	1	365
Venlafaxine	1 x daily	365	1	365
Appropriate comparator therapy				
Lithium augmentation or quetiapine extended release augmentation *(in each case as an add-on to the last antidepressant monotherapy given)* or combination of two antidepressants				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lithium augmentation				
Lithium carbonate	1-2 x day	365	1	365
plus antidepressant				
Quetiapine extended release augmentation				
Quetiapine extended release	1 x daily	365	1	365
plus antidepressant				
Antidepressants				
Tri and tetracyclic antidepressants (TCAs) - non-selective monoamine reuptake inhibitors (NSMRIs)				
Amitriptyline oxide	1 x daily	365	1	365
Amitriptyline	1 x daily	365	1	365
Clomipramine	1 x daily	365	1	365
Doxepin	1 x daily	365	1	365
Imipramine	1 x daily	365	1	365
Maprotiline	1 x daily	365	1	365
Nortriptyline	3-4 times a day	365	1	365
Trimipramine	1 - several times a day	365	1	365
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	1 x daily	365	1	365
Escitalopram	1 x daily	365	1	365
Fluoxetine	1 x daily	365	1	365
Fluvoxamine	1-3 x day	365	1	365
Paroxetine	1 x daily	365	1	365
Sertraline	1 x daily	365	1	365
Serotonin-norepinephrine reuptake inhibitors (SNRIs)				
Desvenlafaxine	1 x daily	365	1	365
Duloxetine	1 x daily	365	1	365
Milnacipran	2 x daily	365	1	365
Venlafaxine	1 x daily	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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Other antidepressants				
Agomelatine	1 x daily	365	1	365
Bupropion	1 x daily	365	1	365
Mianserin	1-3 x day	365	1	365
Mirtazapine	1 x daily	365	1	365
Sulpiride	3 x daily	365	1	365
Tianeptine	3 x daily	365	1	365
Trazodone	1 - several times a day	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	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	1 x 10 mg - 1 x 20 mg	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 x 5 mg - 365 x 10 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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 - 300 mg	100 mg - 300 mg	1 x 100 mg - 3 x 100 mg	365	365 x 100 mg - 1,095 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)					
Desvenlafaxine	50 mg - 200 mg	50 mg - 200 mg	1 x 50 mg - 2 x 100 mg	365	365 x 50 mg - 730 x 100 mg
Duloxetine	60 mg - 120 mg	60 mg - 120 mg	1 x 60 mg - 1 x 120 mg	365	365 x 60 mg - 365 x 120 mg
Milnacipran	50 mg	100 mg	2 x 50 mg	365	730 x 50 mg
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
Appropriate comparator therapy					
Lithium augmentation or quetiapine extended release augmentation *(in each case as an add-on to the last antidepressant monotherapy given)* or combination of two antidepressants					
Lithium augmentation					
Lithium carbonate	on the basis of lithium serum level dose; target value: 0.5 to 1.2 mmol/l	18.3 mmol - 36.6 mmol	1.5 x 12.2 mmol - 3 x 12.2 mmol	365	547.5 x 12.2 mmol - 1095 x 12.2 mmol
plus antidepressant					
Quetiapine extended release augmentation					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Quetiapine extended release	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					
Antidepressants					
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	0.5 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
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 -	10 mg -	1x 10 mg -	365	365 x 10 mg -

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	20 mg	20 mg	1 x 20 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 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 - 300 mg	100 mg - 300 mg	1 x 100 mg - 3 x 100 mg	365	365 x 100 mg - 1,095 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)					
Desvenlafaxine	50 mg - 200 mg	50 mg - 200 mg	1 x 50 mg - 2 x 100 mg	365	365 x 50 mg - 730 x 100 mg
Duloxetine	60 mg - 120 mg	60 mg - 120 mg	1 x 60 mg - 1 x 120 mg	365	365 x 60 mg - 365 x 120 mg
Milnacipran	50 mg	100 mg	2 x 50 mg	365	730 x 50 mg
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
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	20 mg -	20 mg -	1 x 20 mg -	365	365 x 20 mg -

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	40 mg	40 mg	1 x 40 mg		365 x 40 mg
Other antidepressants					
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
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
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
Sulpiride	150 mg - 300 mg	150 mg - 300 mg	3 x 50 mg- 3 x 100 mg	365	1,095 x 50 mg - 1,095 x 100 mg
Tianeptine	12.5 mg	37.5 mg	3 x 12.5 mg	365	1,095 x 12.5 mg
Tianeptine (> 70 years)	12.5 mg	25 mg	2 x 12.5 mg	365	730 x 12.5 mg
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 - 1,095 x 100 mg

Costs:

Costs of the medicinal products

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Esketamine 28 mg	12 NAS	€ 3,278.05	€ 2.00	€ 133.30	€ 3,142.75

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Citalopram 10 mg[4]	100 FCT	€ 18.81	€ 2.00	€ 0.59	€ 16.22
Citalopram 20 mg[4]	100 FCT	€ 25.86	€ 2.00	€ 1.15	€ 22.71
Citalopram 40 mg[4]	100 FCT	€ 45.16	€ 2.00	€ 2.68	€ 40.48
Desvenlafaxine 50 mg	100 SRT	€ 85.97	€ 2.00	€ 3.54	€ 80.43
Desvenlafaxine 100 mg	100 SRT	€ 158.00	€ 2.00	€ 6.96	€ 149.04
Duloxetine 60 mg[4]	100 HGC	€ 85.24	€ 2.00	€ 5.85	€ 77.39
Duloxetine 120 mg[4]	98 HGC	€ 86.11	€ 2.00	€ 5.92	€ 78.19
Escitalopram 5 mg[4]	100 FCT	€ 17.12	€ 2.00	€ 0.46	€ 14.66
Escitalopram 10 mg[4]	100 FCT	€ 22.25	€ 2.00	€ 0.86	€ 19.39
Escitalopram 20 mg[4]	100 FCT	€ 35.28	€ 2.00	€ 1.90	€ 31.38
Fluoxetine 20mg[4]	100 FCT	€ 27.36	€ 2.00	€ 1.27	€ 24.09
Fluoxetine 40mg[4]	100 FCT	€ 41.13	€ 2.00	€ 2.36	€ 36.77
Fluvoxamine 100 mg[4]	100 FCT	€ 22.42	€ 2.00	€ 0.88	€ 19.54
Milnacipran 50 mg	100 HC	€ 80.15	€ 2.00	€ 3.27	€ 74.88
Paroxetine 10 mg[4]	100 FCT	€ 19.93	€ 2.00	€ 0.68	€ 17.25
Paroxetine 20 mg[4]	100 FCT	€ 27.36	€ 2.00	€ 1.27	€ 24.09
Paroxetine 40 mg[4]	100 TAB	€ 41.13	€ 2.00	€ 2.36	€ 36.77
Sertraline 50 mg[4]	100 FCT	€ 28.89	€ 2.00	€ 1.39	€ 25.50
Sertraline 200 mg[4]	100 FCT	€ 59.05	€ 2.00	€ 0.00	€ 57.05
Venlafaxine 75 mg[4]	100 TAB	€ 31.44	€ 2.00	€ 1.59	€ 27.85
Venlafaxine 300 mg[4]	100 SRT	€ 63.86	€ 2.00	€ 0.00	€ 61.86
Appropriate comparator therapy					
Lithium augmentation or quetiapine extended release augmentation *(in each case as an add-on to the last antidepressant monotherapy given)* or combination of two antidepressants					
Agomelatine 25 mg[4]	98 FCT	€ 70.81	€ 2.00	€ 4.71	€ 64.10
Amitriptyline 50 mg[4]	100 TAB	€ 23.87	€ 2.00	€ 0.99	€ 20.88
Amitriptyline 100 mg[4]	100 TAB	€ 35.31	€ 2.00	€ 1.90	€ 31.41
Amitriptyline oxide 60 mg[4]	100 TAB	€ 17.56	€ 2.00	€ 0.00	€ 15.56
Amitriptyline oxide 90 mg[4]	100 TAB	€ 20.30	€ 2.00	€ 0.00	€ 18.30

[4] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Bupropion 150 mg[4]	90 MRT	€ 94.33	€ 2.00	€ 6.57	€ 85.76
Bupropion 300 mg[4]	90 MRT	€ 137.50	€ 2.00	€ 9.98	€ 125.52
Citalopram 10 mg[4]	100 FCT	€ 18.81	€ 2.00	€ 0.59	€ 16.22
Citalopram 20 mg[4]	100 FCT	€ 25.86	€ 2.00	€ 1.15	€ 22.71
Citalopram 40 mg[4]	100 FCT	€ 45.16	€ 2.00	€ 2.68	€ 40.48
Clomipramine 75 mg[4]	100 SRT	€ 66.49	€ 2.00	€ 4.36	€ 60.13
Desvenlafaxine 50 mg	100 SRT	€ 85.97	€ 2.00	€ 3.54	€ 80.43
Desvenlafaxine 100 mg	100 SRT	€ 158.03	€ 2.00	€ 6.96	€ 149.07
Doxepin 50 mg[4]	100 FCT	€ 21.12	€ 2.00	€ 0.78	€ 18.34
Doxepin 100 mg[4]	100 FCT	€ 29.13	€ 2.00	€ 1.41	€ 25.72
Duloxetine 60 mg[4]	100 HGC	€ 85.24	€ 2.00	€ 5.85	€ 77.39
Duloxetine 120 mg[4]	98 HGC	€ 86.11	€ 2.00	€ 5.92	€ 78.19
Escitalopram 5 mg[4]	100 FCT	€ 17.12	€ 2.00	€ 0.46	€ 14.66
Escitalopram 10 mg[4]	100 FCT	€ 22.25	€ 2.00	€ 0.86	€ 19.39
Escitalopram 20 mg[4]	100 FCT	€ 35.28	€ 2.00	€ 1.90	€ 31.38
Fluoxetine 20mg[4]	100 FCT	€ 27.36	€ 2.00	€ 1.27	€ 24.09
Fluoxetine 40mg[4]	100 FCT	€ 41.13	€ 2.00	€ 2.36	€ 36.77
Fluvoxamine 100 mg[4]	100 FCT	€ 22.42	€ 2.00	€ 0.88	€ 19.54
Imipramine 25 mg[4]	100 FCT	€ 16.67	€ 2.00	€ 0.00	€ 14.67
Imipramine 100 mg[4]	100 FCT	€ 29.13	€ 2.00	€ 0.00	€ 27.13
Lithium carbonate 450 mg	100 SRT	€ 45.67	€ 2.00	€ 14.26	€ 29.41
Maprotiline 25 mg[4]	100 FCT	€ 17.61	€ 2.00	€ 0.00	€ 15.61
Maprotiline 75 mg[4]	100 FCT	€ 31.76	€ 2.00	€ 1.62	€ 28.14
Mianserin 30 mg[4]	100 FCT	€ 53.45	€ 2.00	€ 3.33	€ 48.12
Mianserin 60 mg[4]	100 FCT	€ 94.44	€ 2.00	€ 0.00	€ 92.44
Milnacipran 50 mg	100 HC	€ 80.15	€ 2.00	€ 3.27	€ 74.88
Mirtazapine 15 mg[4]	100 FCT	€ 25.81	€ 2.00	€ 1.15	€ 22.66
Mirtazapine 45 mg[4]	96 ODT	€ 61.62	€ 2.00	€ 3.98	€ 55.64
Moclobemide 150 mg[4]	100 FCT	€ 56.85	€ 2.00	€ 3.60	€ 51.25
Moclobemide 300 mg[4]	100 FCT	€ 91.48	€ 2.00	€ 6.34	€ 83.14

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Nortriptyline 25 mg[4]	100 FCT	€ 17.29	€ 2.00	€ 0.00	€ 15.29
Paroxetine 10 mg[4]	100 FCT	€ 19.93	€ 2.00	€ 0.68	€ 17.25
Paroxetine 20 mg[4]	100 FCT	€ 27.36	€ 2.00	€ 1.27	€ 24.09
Paroxetine 40 mg[4]	100 TAB	€ 41.13	€ 2.00	€ 2.36	€ 36.77
Quetiapine 150 mg extended release[4]	100 SRT	€ 47.34	€ 2.00	€ 2.85	€ 42.49
Quetiapine 300 mg extended release[4]	100 SRT	€ 78.48	€ 2.00	€ 5.31	€ 71.17
Sertraline 50 mg[4]	100 FCT	€ 28.89	€ 2.00	€ 1.39	€ 25.50
Sertraline 200 mg[4]	100 FCT	€ 59.05	€ 2.00	€ 0.00	€ 57.05
Sulpiride 50 mg[4]	100 TAB	€ 19.30	€ 2.00	€ 0.63	€ 16.67
Sulpiride 100 mg[4]	100 TAB	€ 25.62	€ 2.00	€ 1.13	€ 22.49
Tianeptine 12.5 mg	300 FCT	€ 116.19	€ 2.00	€ 4.98	€ 109.21
Tranylcypromine 20 mg	100 FCT	€ 223.30	€ 2.00	€ 13.27	€ 208.03
Tranylcypromine 40 mg	100 FCT	€ 435.31	€ 2.00	€ 27.39	€ 405.92
Trazodone 100 mg[4]	100 TAB	€ 53.45	€ 2.00	€ 3.33	€ 48.12
Trimipramine 100 mg[4]	100 FCT	€ 29.13	€ 2.00	€ 1.41	€ 25.72
Venlafaxine 75 mg[4]	100 TAB	€ 31.44	€ 2.00	€ 1.59	€ 27.85
Venlafaxine 300 mg[4]	100 SRT	€ 63.86	€ 2.00	€ 0.00	€ 61.86
Abbreviations: FCT = film-coated tablets; HGC = hard gastro-resistant capsule; HC= hard capsules; NAS = nasal spray; SRT = sustained-release tablets; ODT = orally disintegrating tablet; TAB = tablets; MRT = modified-release tablet					

LAUER-TAXE® last revised: 1 September 2023

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 taken into account 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 the standard expenditure in the course of the treatment are not shown.

On 18 August 2023, the assessment committee communicated a need for adjustment in the Uniform Value Scale (EBM); however, specific information was not available at the time of adoption of the resolution.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

According to Section 4.1. Spravato product information, esketamine is approved for the treatment of adults with treatment-resistant Major Depressive Disorder in combination with an SSRI or SNRI. Since vortioxetine belongs neither to the SSRI nor the SNRI product class, but - according to feedback from the BfArM - to the "serotonin modulators and stimulators" (SMS), the combination of esketamine and vortioxetine for the treatment of adults with therapy-resistant Major Depressive Disorder cannot therefore be considered to be covered by the marketing authorisation. Therefore, vortioxetine (Brintellix) is not designated as a medicinal product that can be used in combination therapy with esketamine (Spravato) according to Section 35a, paragraph 3, sentence 4 SGB V.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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.

Process sequence

At its session on 6 November 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy. On 23 May 2023, this was amended in a meeting of the Subcommittee on Medicinal Products.

On 14 March 2023, 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 5 VerfO.

By letter dated 16 March 2023 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 12 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 June 2023. The deadline for submitting statements was 6 July 2023.

The oral hearing was held on 24 July 2023.

By letter dated 25 July 2023, the IQWiG was commissioned with a supplementary assessment of the ESCAPE-TRD study as well as the data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 11 August 2023.

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 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 was discussed at the sessions of the subcommittee on 29 August 2023 and on 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 November 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 May 2023	Change of the appropriate comparator therapy
Working group Section 35a	18 July 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	24 July 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 August 2023 15 August 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	29 August 2023 12 September 2023	Concluding discussion of the draft resolution

Plenum	21 September 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 21 September 2023

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

Prof. Hecken