Esketamine
(treatment-resistant major depression)

Benefit assessment according to §35a SGB V[1]
(expiry of the decision)

EXTRACT

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how she/he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECT	electroconvulsive therapy
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IDS-C_{30}	Inventory of Depressive Symptoms-Clinician rated, 30-item
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MADRS	Montgomery-Åsberg Depression Rating Scale
NVL	Nationale VersorgungsLeitlinie (German National Care Guideline)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SNRI	serotonin-noradrenaline reuptake inhibitor
SPC	Summary of Product Characteristics
SSRI	selective serotonin reuptake inhibitor

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug esketamine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 16 March 2023.

At the time of the first assessment, the ESCAPE-TRD study with esketamine versus quetiapine retard augmentation, each in combination with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI), was still ongoing and no results were available. For the reassessment after expiry, it was therefore requested that the results on all patient-relevant outcomes used for the proof of an added benefit be presented in the dossier, including the results of the ESCAPE-TRD study.

Research question

The aim of this report is to assess the added benefit of esketamine in combination with an SSRI or an SNRI versus treatment of physician's choice as an appropriate comparator therapy (ACT) in adult patients with treatment-resistant major depression who have not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode.

The G-BA's specification of the ACT resulted in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of esketamine in combination with an SSRI or SNRI

Therapeutic indication	**ACT[a, b]**
Adults with treatment-resistant major depression, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	Treatment of physician's choice choosing from[c]: ▪ augmentation with lithium[d] or quetiapine retard[d] ▪ a combination with a second antidepressant[d] ▪ electroconvulsive therapy (ECT) ▪ a switch from antidepressant monotherapy to another substance class.
a. Presented is the ACT specified by the G-BA. b. The therapy concept for the treatment of major depression also includes psychotherapeutic procedures. According to the psychotherapy guideline [1], psychotherapeutic treatment should therefore be offered to patients in both treatment arms of a study. c. Since none of the mentioned treatment options can be determined as suitable therapy for the majority of patients, a single-comparator study is usually not sufficient. d. As an add-on to the last antidepressant monotherapy administered. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor	

The company basically followed the specification of the G-BA by designating a therapy according to physician's choice choosing from augmentation with lithium or quetiapine retard, combination with a second antidepressant, electroconvulsive therapy (ECT) as well as a switch from antidepressant monotherapy to another substance class as ACT. However, it argued that augmentation with quetiapine retard is a representative and meaningful treatment option in the therapeutic indication.

Overall, the company's justification on the suitability of a single-comparator study with augmentation with quetiapine retard as comparator therapy is not sufficient. The present benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit. In doing so, it must be taken into account that the therapy concept for the treatment of an episode of treatment-resistant major depression includes both acute treatment and maintenance treatment (remission maintenance or relapse prevention). The required minimum study duration for the present research question is 6 weeks for acute treatment and 24 weeks for maintenance treatment.

Results

The company included the RCT ESCAPE-TRD comparing esketamine with quetiapine retard, each in combination with an SSRI or SNRI, and used it for the assessment.

Deviating from the company's approach, the RCT ESCAPE-TRD was not used for the benefit assessment of esketamine because the ACT specified by the G-BA was not implemented.

Evidence presented by the company – ESCAPE-TRD study

The ESCAPE-TRD study is a randomized, open-label study comparing esketamine with quetiapine retard each at flexible doses and in combination with an SSRI or SNRI. The study design of the ESCPAPE-TRD study includes a 2-week screening phase followed by a treatment phase consisting of 8 weeks of acute treatment and 24 weeks of maintenance treatment and a 2-week follow-up phase.

Adults aged < 75 years with moderate to severe major depression without psychotic features were included. At the time of screening, patients also had to have had a non-response to current antidepressant treatment with an SSRI or SNRI. In their current depressive episode, patients had to have received at least 1 but no more than 5 previous antidepressant therapies in addition to their current treatment, and patients had to have been treated with ≥ 2 antidepressant drug classes.

A total of 676 patients were randomly assigned in a 1:1 ratio to treatment with either esketamine (N = 336) or quetiapine retard (N = 340), each in combination with an SSRI or SNRI.

In the ESCAPE-TRD study, esketamine and quetiapine retard were administered in accordance with the respective Summary of Product Characteristics (SPC). Treatment with SSRIs and SNRIs was to be continued in accordance with the respective SPC. Patients were supposed to receive psychotherapeutic support or continue their existing psychotherapy.

The primary outcome of the ESCAPE-TRD study was disease remission at week 8, operationalized as a total score of ≤ 10 points on the Montgomery-Åsberg Depression Rating Scale (MADRS). Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

ACT not implemented in the ESCAPE-TRD study

The G-BA specified a treatment of physician's choice choosing from augmentation with lithium or quetiapine retard, a combination with a second antidepressant, ECT and a switch from antidepressant monotherapy to another substance class for adult patients with treatment-resistant major depression who had not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode.

In Module 4 A, the company argues that augmentation with quetiapine retard is a representative and meaningful treatment option in the therapeutic indication. The company's reasoning is not appropriate. In the following, we will first describe to what extent the therapy options named by the G-BA represent possible therapy options for the patients in the ESCAPE-TRD study.

Augmentation with (lithium or) quetiapine retard or a combination with a second antidepressant

According to the National Health Care Guideline (NVL), among the possible treatment options, augmentation with lithium or quetiapine as well as the combination with a second antidepressant (mirtazapine, mianserin or trazodone) are considered the first-choice therapies for treatment-resistant depression if patients do not respond to monotherapy, and they are also named as options in later lines of treatment. However, due to the increased risk of side effects, the NVL makes a weakened recommendation for the two therapy options.

The ESCAPE-TRD study only included patients who had already been treated with ≥ 2 drug classes, including SSRIs and/or SNRIs. The study documents show that only few patients had already received treatment with lithium or quetiapine before and a small proportion had not responded to mirtazapine, trazodone or mianserin. From the information provided, it is not clear whether or how many patients actually received augmentation therapy (lithium and quetiapine) or combination therapy (mirtazapine, trazodone and mianserin). However, due to

the low use of these therapies, it can be assumed that, besides augmentation with lithium or quetiapine retard a combination of 2 antidepressants represents a possible treatment option for a relevant proportion of patients within the framework of a treatment of physician's choice. Moreover, neither the inclusion and exclusion criteria of the study nor the patient characteristics provide information on why augmentation with quetiapine retard would be preferable for the patients included in the ESCAPE-TRD study compared to the other treatment options according to physician's choice (in particular compared to the combination with a second antidepressant) named by the G-BA as an ACT.

ECT

In treatment-resistant depressive episodes, the NVL makes a strong recommendation for ECT, especially for older patients or patients with psychotic disorders. Due to the inclusion criteria, the proportion of patients for whom ECT is particularly recommended according to the NVL was small In the ESCAPE-TRD study. Nevertheless, it is not clear from the recommendations of the NVL that ECT is exclusively indicated for patients with a psychotic disorder and/or for older patients. For example, when screening for the ESCAPE-TRD study, the physician had to specify in the electronic case report form (eCRF) whether ECT would also have been an option for the patients if they had not been included in the study. Information on the number of patients in the ESCAPE-TRD study for whom this would have been the case is not available. To be included in the ESCAPE-TRD study, patients were also not allowed to have depressive symptoms that had not previously responded to ECT, and ECT was part of the standard treatment for patients who discontinued the therapy. However, the company did not provide any information on how many patients received ECT as part of a standard treatment after discontinuation of the therapy.

Overall, it can therefore be assumed that for the patients included in the ESCAPE-TRD study, ECT is a possible treatment option besides augmentation and a combination of 2 antidepressants.

Change of antidepressant monotherapy

According to the NVL, a one-time change of antidepressant seems acceptable, but not a successive trying out of several antidepressants. Moreover, the change of antidepressant monotherapy is assigned a subordinate importance. As the patients in the ESCAPE-TRD study already had to be pretreated with ≥ 2 drug classes, the change of the antidepressant monotherapy is not considered a suitable treatment option for the patients in the study.

Psychotherapeutic support

According to the G-BA's specification of the ACT, the therapy concept for the treatment of major depression also includes psychotherapeutic procedures. The NVL also strongly recommends a combination with psychotherapy in cases of non-response to drug therapy.

Guideline-compliant care of patients was basically envisaged included in the ESCAPE-TRD study. However, the utilization of psychotherapeutic support by patients was dependent on availability and local capacities. The company did not provide any data on the extent to which provision of psychotherapeutic support was guaranteed to patients in the ESCAPE-TRD study and whether there were differences between the two treatment arms in this respect.

Summary

In summary, it cannot be inferred from the available information whether augmentation with quetiapine retard used for all patients in the ESCAPE-TRD study represents an adequate implementation of the treatment of physician's choice specified by the G-BA. Moreover, it is not clear from the available information whether and to what extent psychotherapy or psychotherapeutic measures were used to support the drug therapy. Therefore, the ACT was not implemented in the ESCAPE-TRD study.

Results on added benefit

As for the present research question no suitable data are available to assess the added benefit over the ACT, there is no hint of an added benefit of esketamine in combination with an SSRI or SNRI versus the ACT; an added benefit is therefore not proven.

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

Table 3 presents a summary of the probability and extent of added benefit of esketamine.

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

Table 3: Esketamine in combination with SSRI or SNRI – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adults with treatment-resistant major depression, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	Treatment of physician's choice choosing from[c]: ▪ augmentation with lithium[d] or quetiapine retard[d], ▪ combination with a second antidepressant[d], ▪ ECT, ▪ a switch from antidepressant monotherapy to another substance class.	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The therapy concept for the treatment of major depression also includes psychotherapeutic procedures. According to the psychotherapy guideline [1], psychotherapeutic treatment should therefore be offered to patients in both treatment arms of a study.
c. Since none of the mentioned treatment options can be determined as suitable therapy for the majority of patients, a single-comparator study is usually not sufficient.
d. As an add-on to the last antidepressant monotherapy administered.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of esketamine in combination with an SSRI or an SNRI versus treatment of physician's choice as an ACT in adult patients with treatment-resistant major depression who have not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of esketamine in combination with an SSRI or SNRI

Therapeutic indication	**ACT[a, b]**
Adults with treatment-resistant major depression, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	Treatment of physician's choice choosing from[c]: ▪ augmentation with lithium[d] or quetiapine retard[d], ▪ combination with a second antidepressant[d], ▪ ECT, ▪ a switch from antidepressant monotherapy to another substance class.
a. Presented is the ACT specified by the G-BA. b. The therapy concept for the treatment of major depression also includes psychotherapeutic procedures. According to the psychotherapy guideline [1], psychotherapeutic treatment should therefore be offered to patients in both treatment arms of a study. c. Since none of the mentioned treatment options can be determined as suitable therapy for the majority of patients, a single-comparator study is usually not sufficient. d. As an add-on to the last antidepressant monotherapy administered. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor	

The company basically followed the specification of the G-BA by designating a therapy according to physician's choice choosing from augmentation with lithium or quetiapine retard, combination with a second antidepressant, ECT as well as a switch from antidepressant monotherapy to another substance class as ACT. However, it argued that augmentation with quetiapine retard is a representative and meaningful treatment option in the therapeutic indication.

Overall, the company's justification on the suitability of a single-comparator study with augmentation with quetiapine retard as comparator therapy is not sufficient (see Chapter I 3). The present benefit assessment is conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs were used for the derivation of the added benefit. In doing so, it must be taken into account that the therapy concept for the treatment

of an episode of treatment-resistant major depression includes both acute treatment and maintenance treatment (remission maintenance or relapse prevention) [4]. The required minimum study duration for the present research question is 6 weeks for acute treatment and 24 weeks for maintenance treatment. This is in accordance with the guidelines of the European Medicines Agency (EMA) [5]. This deviates from the company's inclusion criteria, which included RCTs with a minimum study duration of 8 weeks. However, this has no consequences for the present benefit assessment, as the check of the completeness of the study pool identified no additional relevant studies (see Chapter I 3).

Regardless of the suitable minimum study duration, an event-driven study to confirm definitive remission is also conceivable for the present research question.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on esketamine (status: 19 December 2022)
- bibliographical literature search on esketamine (last search on 19 December 2022)
- search in trial registries/trial results databases for studies on esketamine (last search on 23 February 2023)
- search on the G-BA website for esketamine (last search on 23 February 2023)

To check the completeness of the study pool:

- search in trial registries for studies on esketamine (last search on 30 March 2023); for search strategies, see Appendix I A of the full dossier assessment

The check of the completeness of the study pool identified no relevant RCTs on the comparison of esketamine in combination with an SSRI or SNRI versus treatment of physician's choice choosing from augmentation with lithium or quetiapine retard, combination with a second antidepressant, ECT as well as a switch from antidepressant monotherapy to another substance class as ACT.

This deviates from the approach of the company, which included the RCT ESCAPE-TRD [6-8] comparing esketamine with quetiapine retard, each in combination with an SSRI or SNRI, in its study pool and used it for the assessment.

The RCT ESCAPE-TRD was not used for the benefit assessment of esketamine because the study failed to implement the ACT specified by the G-BA. This is explained below.

Evidence presented by the company – ESCAPE-TRD study

The ESCAPE-TRD study is a randomized, open-label study comparing esketamine with quetiapine retard each at flexible doses and in combination with an SSRI or SNRI. The study design of the ESCPAPE-TRD study includes a 2-week screening phase followed by a treatment phase consisting of 8 weeks of acute treatment and 24 weeks of maintenance treatment and a 2-week follow-up phase.

Included were adults aged < 75 years with major depression (according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition [DSM-V]) without psychotic features and an Inventory of Depressive Symptoms-Clinician rated, 30-item (IDS-C_{30}) total score of > 34, corresponding to moderate to severe depression. At the time of screening, patients also had

to have had a non-response (defined as < 25% improvement of the symptoms) to current antidepressant treatment with an SSRI or SNRI. However, patients had to show signs of minimal clinical improvement during screening and patients without signs of clinical improvement were excluded from the study. In their current depressive episode, patients had to have received at least 1 but no more than 5 previous antidepressant therapies in addition to their current treatment, and patients had to have been treated with ≥ 2 antidepressant drug classes. All therapies, including the current therapy with an SSRI or SNRI, had to have been administered in adequate dosage and for a duration of ≥ 6 weeks. Patients who were using a combination of antidepressants and/or supplementary substances at the time of screening had to discontinue these therapies (with the exception of the SSRI/SNRI to be continued) prior to randomization on the day of treatment initiation in accordance with the applicable SPC.

A total of 676 patients were randomly assigned in a 1:1 ratio to treatment with either esketamine (N = 336) or quetiapine retard (N = 340), each in combination with an SSRI or SNRI. Stratification was by age (18 to 64 years vs. 65 to 74 years) and number of prior therapies to which the patients had not responded (2 vs. ≥ 3).

In the ESCAPE-TRD study, esketamine and quetiapine retard were administered in accordance with the respective SPC [9,10]. Treatment with SSRIs and SNRIs was to be continued in accordance with the respective SPC. In addition to drug therapy, patients were also planned to receive psychotherapeutic support or continue their ongoing psychotherapy, if they requested so and after medical consultation.

In the intervention arm, a clinical assessment was made by the treating physician after 4 weeks. If there was no therapeutic benefit, the treatment could be discontinued in consultation with the patient. In addition, in both study arms, the investigator regularly assessed whether the treatment should be continued from week 8 onwards. If treatment was discontinued, patients were to switch to standard therapy. According to the study design, all patient- and physician-recorded instruments on efficacy, morbidity and health-related quality of life were to be collected up to week 32 and side effects up to 2 weeks after discontinuation.

The primary outcome of the ESCAPE-TRD study was disease remission at week 8, operationalized as a total score of ≤ 10 points on the MADRS. The MADRS was recorded in a blinded fashion. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Further information on the characteristics of the ESCAPE-TRD study, the interventions used and the included patients can be found in I Appendix B.1 of this benefit assessment.

ACT not implemented in the ESCAPE-TRD study

The G-BA specified a treatment of physician's choice choosing from augmentation with lithium or quetiapine retard, a combination with a second antidepressant, ECT and a switch from antidepressant monotherapy to another substance class for adult patients with treatment-resistant major depression who had not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode. In its information on the ACT, the G-BA described that none of the mentioned treatment options can be determined as suitable therapy for the majority of patients and that a single-comparator study is usually not sufficient. Only an augmentation with quetiapine retard was used in the comparator arm of the ESCAPE-TRD study presented by the company; a multi-comparator study on the comparison of several treatment options is not available.

In Module 4 A, the company argues that augmentation with quetiapine retard is a representative and meaningful treatment option in the therapeutic indication. The subordinate position according to the NVL [4] would speak against a change of antidepressant monotherapy, and the low quality of evidence according to the NVL as well as the subordinate position according to the justification on the G-BA's decision of 19 August 2021 [11,12], with which the change of the appropriate therapy took place, would speak against the ECT. Augmentation with lithium or quetiapine as well as a combination with a second antidepressant, on the other hand, were to be assessed as first-choice treatment according to the NVL and thus of equal importance. Moreover, the NVL does not mention any criteria for choosing the appropriate therapy from these three options. Thus, the comparison with augmentation therapy with quetiapine retard in the context of a single-comparator study was justified. The company's reasoning is not appropriate. In the following, we will first describe to what extent the therapy options named by the G-BA represent possible or suitable therapy options for the patients in the ESCAPE-TRD study.

Augmentation with (lithium or) quetiapine retard or a combination with a second antidepressant

According to the NVL [4], among the possible treatment options, augmentation with lithium or quetiapine as well as the combination with a second antidepressant are considered the first-choice therapies for treatment-resistant depression if patients do not respond to monotherapy, and they are also named as options in later lines of treatment. According to the NVL, SSRIs, SNRIs or tri-/tetracyclic antidepressants should be combined with mianserin on the one hand, or mirtazapine or trazodone on the other, in case of a combination therapy of 2 antidepressants. However, due to the increased risk of side effects, the NVL makes a weakened recommendation for the two therapy options. Moreover, there are no criteria in the recommendations according to which augmentation or combination therapy should be preferred.

The ESCAPE-TRD study only included patients who had already been treated with ≥ 2 drug classes, including SSRIs and/or SNRIs. Approx. 60% of the randomized patients had not responded to 2 therapies and the remaining patients had not responded to ≥ 3 therapies. The study documents show that only few patients had already received treatment with lithium or quetiapine (< 5% each). Non-response to quetiapine was retrospectively determined in 3.1% of the patients. The data also show that 18% of patients had not responded to mirtazapine, 7% had not responded to trazodone and 1% had not responded to mianserin. However, from the information provided, it is not clear whether or how many patients received the named therapies as part of an augmentation (lithium and quetiapine) or as part of a combination therapy (mirtazapine, trazodone and mianserin). However, due to the low use of these therapies, it can be assumed that, besides augmentation with lithium or quetiapine retard a combination of 2 antidepressants represents a possible treatment option for a relevant proportion of patients within the framework of a treatment of physician's choice. Moreover, neither the inclusion and exclusion criteria of the study nor the patient characteristics provide information on why augmentation with quetiapine retard would be preferable for the patients included in the ESCAPE-TRD study compared to the other treatment options according to physician's choice (in particular compared to the combination with a second antidepressant) named by the G-BA as an ACT.

ECT

In treatment-resistant depressive episodes, the NVL makes a strong recommendation for ECT, especially for older patients or patients with psychotic disorders. In accordance with the inclusion criteria, patients with psychotic disorder were excluded from the ESCAPE-TRD study. In addition, no patients aged ≥ 75 years were included. As a result, only about 5% of the patients in the ESCAPE-TRD study were 65 to 74 years old. Thus, the proportion of patients for whom ECT is particularly recommended according to the NVL was small In the study. Nevertheless, it is not clear from the recommendations of the NVL that ECT is exclusively indicated for patients with a psychotic disorder and/or for older patients. For example, when screening for the ESCAPE-TRD study, the physician had to specify in the eCRF whether ECT would also have been an option for the patients if they had not been included in the study. Information on the number of patients in the ESCAPE-TRD study for whom this would have been the case is not available. However, the regulatory documents for esketamine show that in the approval studies TRD3001 [13] and TRD3002 [14], ECT was also reported as a possible treatment option for 48% and 29% of patients, respectively. Patients with a psychotic disorder and patients ≥ 65 years were also excluded in these studies.

Moreover, to be included in the ESCAPE-TRD study, patients were not allowed to have depressive symptoms that had not previously responded to ECT. In addition, in the ESCAPE-TRD study, ECT was part of the standard treatment for patients who discontinued therapy. However, the company did not provide any information on how many patients received ECT

as part of a standard treatment after discontinuation of the therapy. During the treatment phase, the use of ECT was not allowed.

Overall, it can therefore be assumed that for the patients included in the ESCAPE-TRD study, ECT is a possible treatment option besides augmentation and a combination of 2 antidepressants.

Change of antidepressant monotherapy

According to the NVL, a one-time change of antidepressant seems acceptable, but not a successive trying out of several antidepressants. Moreover, the change of antidepressant monotherapy is assigned a subordinate importance. As, according to the inclusion criteria, the patients in the ESCAPE-TRD study already had to be pretreated with ≥ 2 drug classes, the change of the antidepressant monotherapy in line with the approach of the company is not considered a suitable treatment option for the patients in the study.

Psychotherapeutic support

According to the G-BA's specification of the ACT, the therapy concept for the treatment of major depression also includes psychotherapeutic procedures. The NVL also strongly recommends a combination with psychotherapy in cases of non-response to drug therapy. According to the study documents, the ESCAPE-TRD study envisaged that patients would receive psychotherapeutic support in addition to drug therapy. For this purpose, the physicians should discuss possible psychotherapeutic options such as psychotherapy, psychoeducation and/or psychological counselling with the patients before randomization. Before randomization, the patients had to specify whether and which psychotherapeutic measure they wanted to make use of. Patients with ongoing psychotherapeutic support could continue this during the study. Thus, guideline-compliant care of patients was generally envisaged in the ESCAPE-TRD study. However, the utilization of psychotherapeutic support by patients was dependent on availability and local capacities. In the dossier, the company does not provide any information on which psychotherapeutic measures were used and to what extent. Thus, it remains unclear to what extent the provision of psychotherapeutic support was guaranteed to patients in the ESCAPE-TRD study and whether there were differences between the two treatment arms in this respect.

Summary

In summary, it cannot be inferred from the available information whether augmentation with quetiapine retard used for all patients in the ESCAPE-TRD study represents an adequate implementation of the treatment of physician’s choice specified by the G-BA. The company did not provide sufficient information on how many patients have already had a combination therapy with a second antidepressant or for how many patients ECT had also been considered a suitable therapy option by the physician before randomization. In addition, there is a lack of

general criteria that can be used to assess which therapy option would be most suitable. Moreover, it is not clear from the available information whether and to what extent psychotherapy or psychotherapeutic measures were used to support the drug therapy. Therefore, the ACT was not implemented in the ESCAPE-TRD study.

A supplementary presentation of the results of the ESCAPE-TRD study can be found in I Appendix B.2 (excluding results on subgroups, common adverse events [AEs], common serious AEs [SAEs], discontinuations due to AEs and specific AEs based on the AEs that occurred in the study).

I 4 Results on added benefit

There are no suitable data for the assessment of the added benefit of esketamine in combination with an SSRI or an SNRI versus treatment of physician's choice as an ACT in patients with treatment-resistant major depression who have not responded to at least 2 different therapies with antidepressants in the current moderate to severe depressive episode. There is no hint of an added benefit of esketamine in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for esketamine in comparison with the ACT.

Table 5: Esketamine in combination with SSRI or SNRI – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adults with treatment-resistant major depression, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode	Treatment of physician's choice choosing from[c]: ▪ augmentation with lithium[d] or quetiapine retard[d], ▪ combination with a second antidepressant[d], ▪ ECT, ▪ a switch from antidepressant monotherapy to another substance class.	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The therapy concept for the treatment of major depression also includes psychotherapeutic procedures. According to the psychotherapy guideline [1], psychotherapeutic treatment should therefore be offered to patients in both treatment arms of a study.
c. Since none of the mentioned treatment options can be determined as suitable therapy for the majority of patients, a single-comparator study is usually not sufficient.
d. As an add-on to the last antidepressant monotherapy administered.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SNRI: serotonin-noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

The assessment described above deviates from the company's assessment, which derived a hint of considerable added benefit on the basis of the results of the ESCAPE-TRD study (comparison of esketamine + SSRI/SNRI with quetiapine retard + SSRI/SNRI) .

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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