Esketamine (reassessment after the deadline (depression, treatment-resistant, in combination with SSRI or SNRI)

Resolution of: 21 September 2023 valid until: unlimited
Entry into force on: 21 September 2023
Federal Gazette, BAnz AT 20 10 2023 B1

Therapeutic indication (according to the marketing authorisation of 18 December 2019):
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 September 2023):

See therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

- Lithium augmentation[1] or quetiapine extended release augmentation[1] or combination of two antidepressants

Extent and probability of the additional benefit of esketamine compared to quetiapine extended release

Hint for a considerable additional benefit

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

Study results according to endpoints:[2]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantages in response and remission, general depressive symptomatology, functional remission and health status.
Health-related quality of life	↑	Advantages in the mental and physical component summary scores of the SF-36v2.
Side effects	↑	Advantages for discontinuations due to AEs, in detail disadvantages for some of the specific AEs.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

ESCAPE-TRD study:

Esketamine + SSRI/SNRI vs quetiapine extended release + SSRI/SNRI
Study design: randomised, open-label (MADRS assessment blinded)

Mortality

Endpoint	Esketamine + SSRI/SNRI		Quetiapine extended release + SSRI/SNRI		Esketamine vs quetiapine extended release
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality (until week 32)	334	1 (0.3)	336	1 (0.3)	0.97 [0.07; 14.35]; 0.984

[2] Data from the dossier assessment of the IQWiG (A23-18) and from the addendum (A23-75), unless otherwise indicated.

Morbidity B

Endpoint	Esketamine + SSRI/SNRI		Quetiapine extended release + SSRI/SNRI		Esketamine vs quetiapine extended release
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Remission (MADRS)[b]					
Week 8	336	132 (39.3)	340	81 (23.8)	1.66 [1.31; 2.09]; < 0.001
Week 32	336	204 (60.7)	340	153 (45)	1.35 [1.17; 1.57]; < 0.001
Response (MADRS)[c]					
Week 8	336	180 (53.6)	340	130 (38.2)	1.41 [1.19; 1.66]; < 0.001
Week 32	336	232 (69.1)	340	181 (53.2)	1.30 [1.15; 1.47]; < 0.001
Functional remission (SDS)[d]					
Week 8	314	43 (13.7)	307	37 (12.1)	1.14 [0.75; 1.71]; 0.555[e]
Week 32	315	107 (34.0)	308	73 (23.7)	1.43 [1.11; 1.85]; 0.005[e]
General depressive symptomatology					
PHQ-9[f]					
Week 8	336	231 (68.8)	340	198 (58.2)	1.18 [1.05; 1.32]; 0.005
Week 32	336	232 (69.1)	340	192 (56.5)	1.23 [1.09; 1.38]; < 0.001
QLDS[g]					
Week 8	336	221 (65.8)	340	170 (50)	1.32 [1.16; 1.50]; < 0.001
Week 32	336	229 (68.2)	340	175 (51.5)	1.33 [1.17; 1.50]; < 0.001
Health status (EQ-5D VAS)[h] (percentage of patients with improvement)					
Week 8	336	183 (54.5)	340	145 (42.7)	1.28 [1.09; 1.50]; 0.002
Week 32	336	195 (58)	340	158 (46.5)	1.25 [1.08; 1.45]; 0.002

Endpoint	Esketamine + SSRI/SNRI		Quetiapine extended release + SSRI/SNRI		Esketamine vs quetiapine extended release
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Suicidality (C-SSRS)					
Suicidal thoughts[i]					
Week 8	311	25 (8)	291	19 (6.5)	1.24 [0.69; 2.21]; 0.472
Week 32	271	9 (3.3)	229	5 (2.2)	1.53 [0.53; 4.46]; 0.432
Suicidal behaviour[j]					
Week 8	311	0 (0)	291	1 (0.3)	n.d.
Week 32	271	0 (0)	229	1 (0.4)	n.d.

Health-related quality of life

Endpoint	Esketamine + SSRI/SNRI		Quetiapine extended release + SSRI/SNRI		Esketamine vs quetiapine extended release
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
SF-36v2					
Physical Component Summary (PCS) score[k]					
Week 8	336	47 (14)	340	40 (11.8)	1.20 [0.80; 1.78]; 0.379
Week 32	336	72 (21.4)	340	52 (15.3)	1.41 [1.02; 1.95]; 0.037
Mental Component Summary (MCS) score[l]					
Week 8	336	180 (53.6)	340	138 (40.6)	1.32 [1.12; 1.55]; < 0.001
Week 32	336	195 (58)	340	150 (44.1)	1.32 [1.14; 1.53]; < 0.001

Side effects

Endpoint	Esketamine + SSRI/SNRI		Quetiapine extended release + SSRI/SNRI		Esketamine vs quetiapine extended release
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Adverse events in total					
AEs (presented additionally)	334	307 (91.9)	336	262 (78.0)	–
Serious adverse events (SAE)					
SAEs	334	19 (5.7)	336	17 (5.1)	1.11 [0.59; 2.09]; 0.746
Therapy discontinuation due to adverse events					
Discontinuation due to AEs	334	14 (4.2)	336	37 (11)	0.38 [0.21; 0.69]; 0.002
Specific adverse events					
Nervous system disorders (SOC, AEs)[m]	334	231 (69.2)	336	161 (47.9)	1.44 [1.26; 1.65]; < 0.001
Psychiatric disorders (SOC, AEs)[n]	334	156 (46.7)	336	44 (13.1)	3.58 [2.65; 4.82]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs)[o]	334	54 (16.2)	336	10 (3.0)	5.43 [2.81; 10.48]; < 0.001
Nausea (PT, AEs)	334	98 (29.3)	336	12 (3.6)	8.17 [4.58; 14.58]; < 0.001
Vomiting (PT, AEs)	334	36 (10.8)	336	5 (1.5)	7.14 [2.84; 17.93]; < 0.001

a. Cochran-Mantel-Haenszel method; stratified by age and number of prior therapies to which patients did not respond.
b. Defined as MADRS total score ≤ 12
c. Defined as improvement in MADRS total score by ≥ 50% compared to the start of the study (scale range 0 to 60 points)
d. Defined as SDS total score ≤ 6, with each item scoring at least ≤ 2 points
e. IQWiG's calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ method).
f. Percentage of patients with improvement, defined as a decrease in score by ≥ 5 points compared to the start of the study (corresponds to 15% of the scale range: 0 to 27 points)

g. Percentage of patients with improvement, defined as a decrease in score by ≥ 6 points compared to the start of the study (corresponds to 15% of the scale range: 0 to 34 points)
h. Percentage of patients with improvement, defined as an increase in score by ≥ 15 points compared to the start of the study; scale range: 0 to 100 points
i. Operationalised as a "yes" response at any time during treatment to 1 of the 5 questions on suicidal thoughts (categories 1 to 5) in the C-SSRS (suicidal thoughts)
j. Operationalised as a "yes" response at any time during treatment to 1 of the 5 suicidal behaviour questions (categories 6 to 10) in the C-SSRS (suicidal behaviour)
k. Percentage of patients with improvement: increase in PCS score by ≥ 9.4 points compared to start of the study (corresponds to 15% of the scale range; normalised scale with a minimum of approximately 7 and a maximum of approximately 70)
l. Percentage of patients with improvement: increase in MCS score by ≥ 9.6 points compared to start of the study (corresponds to 15% of the scale range; normalised scale with a minimum of approximately 6 and a maximum of approximately 70)
m. including, among others, the PTs dizziness, headache, dysgeusia and paraesthesia
n. including, among others, the PTs dissociation and state of confusion
o. including, among others, the PTs sneezing, rhinalgia and throat irritation

Abbreviations used:
C-SSRS: Columbia Suicide Severity Rating Scale; n.d.: no data; CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; n: number of patients with (at least 1) event; N: number of patients evaluated; PHQ-9: Patient Health Questionnaire - 9-item; PT: preferred term; QLDS: Quality of Life in Depression Scale; RCT: randomised controlled trial; RR: relative risk; SDS: Sheehan Disability Scale; SF-36v2: Short Form-36 Health Survey Version 2; SNRI: serotonin-norepinephrine reuptake inhibitors; SOC: system organ class; SSRI: selective serotonin reuptake inhibitor; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

2. Number of patients or demarcation of patient groups eligible for treatment

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

Approx. 317,000 to 505,000 patients

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.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Esketamine	€ 6,835.48 - € 40,934.32
Selective serotonin reuptake inhibitors (SSRIs)	
Citalopram	€ 59.20 - € 147.75
Escitalopram	€ 53.51 - € 114.54
Fluoxetine	€ 87.93 - € 222.14
Fluvoxamine	€ 71.32 - € 213.96
Paroxetine	€ 87.93 - € 197.17
Sertraline	€ 93.08 - € 208.23
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	
Desvenlafaxine	€ 293.57 - € 1,088.21
Duloxetine	€ 282.47 - € 291.22
Milnacipran	€ 546.62
Venlafaxine	€ 101.65 - € 327.44
Total: Esketamine + SSRI or SNRI	€ 6,888.99 - € 42,022.53
Appropriate comparator therapy:	
Lithium augmentation	
Lithium carbonate	€ 161.02 - € 322.04

Designation of the therapy	Annual treatment costs/ patient
Antidepressant*	€ 53.51 - € 1,088.21[3]
Total:	€ 214.53 - € 1,410.25
Quetiapine extended release augmentation	
Quetiapine extended release	€ 155.09 - € 259.77
Antidepressant*	€ 53.51 - € 1,088.21[3]
Total:	€ 208.60 - € 1,347.98
Combination of two antidepressants	
SSRI or SNRI or TCA	€ 53.51 - € 1,088.21
Mirtazapine or mianserin or trazodone	€ 82.71 - € 702.55
Total:	€ 136.22 - € 1,790.76
*) Antidepressants	
Tri- and tetracyclic antidepressants (TCA) / non-selective monoamine reuptake inhibitors (NSMRI)	
Amitriptyline oxide	€ 56.79 - € 123.59
Amitriptyline	€ 76.21 - € 190.86
Clomipramine	€ 109.74 - € 438.95
Doxepin	€ 66.94 - € 160.82
Imipramine	€ 107.09 - € 206.12
Maprotiline	€ 56.98 - € 205.42
Nortriptyline	€ 55.81 - € 334.85
Trimipramine	€ 93.88 - € 375.51
Selective serotonin reuptake inhibitors (SSRIs)	
Citalopram	€ 59.20 - € 147.75
Escitalopram	€ 53.51 - € 114.54
Fluoxetine	€ 87.93 - € 222.14
Fluvoxamine	€ 71.32 - € 213.96
Paroxetine	€ 87.93 - € 197.17
Sertraline	€ 93.08 - € 208.23
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	
Desvenlafaxine	€ 293.57 - € 1,088.21
Duloxetine	€ 282.47 - € 291.22
Milnacipran	€ 546.62

[3] The range is composed of the lower limit for escitalopram and the upper limit for desvenlafaxine. Tranylcypromine is only to be used as a reserve antidepressant according to the product information (Tranylcypromine neuraxpharm®, as of December 2021), and is therefore not considered here.

Designation of the therapy	Annual treatment costs/ patient
Venlafaxine	€ 101.65 - € 327.44
Monoamine oxidase inhibitors (MAOIs)	
Moclobemide	€ 187.06 - € 606.92
Tranylcypromine	€ 759.31 – 1,481.61
Other antidepressants	
Agomelatine	€ 238.74 - € 477.48
Bupropion	€ 347.80 - € 509.05
Mianserin	€ 175.64 - € 513.04
Mirtazapine	€ 82.71 - € 211.55
Sulpiride	€ 182.54 - € 246.27
Tianeptine	€ 265.74 - € 398.62
Trazodone	€ 175.64 - € 702.55

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2023

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.