Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Esketamine (depression, acute short-term treatment, combination therapy)

of 19 August 2021

At its session on 19 August 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of esketamine in accordance with the resolution of 19 August 2021:

Benefit assessment procedure comprises several resolutions.
Please note the current version of the Pharmaceuticals Directive/Annex XII.

Courtesy translation – only the German version is legally binding.

Esketamine

Resolution of: 19 August 2021
Entry into force on: 19 August 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 4 February 2021):

Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

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

see therapeutic indication according to marketing authorisation.

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

Adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency

Appropriate comparator therapy:

Therapy according to doctor's instructions under consideration of

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

Extent and probability of the additional benefit of esketamine compared to the appropriate comparator therapy:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency

[1] Data from the dossier assessment of the IQWiG (A21-25) and from the amendment to the dossier assessment (A21-91), unless otherwise indicated.

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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	↑	Advantage in general depressive symptomatology and health status without reduction in the specific depressive symptomatology of suicidality.
Health-related quality of life	∅	There are no data.
Side effects	↔	No relevant differences overall for the benefit assessment. Disadvantages in individual specific AEs: Nervous system disorders, gastrointestinal tract disorders, psychiatric disorders and eye disorders.
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 ∅: there are no usable data for the benefit assessment. n.a.: not assessable		

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Studies: RCTs SUI3001 + SUI3002 and pooled analysis: Comparison of esketamine versus placebo, each in addition to antidepressant medicinal therapy.

Mortality

Endpoint; Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CII]; p-value
Overall mortality (until day 90)					
SUI3001	113	1 (0.9)	112	0 (0)	n.c.
SUI3002	114	0 (0)	113	0 (0)	n.c.
Total[a]	227	1 (0.4)	225	0 (0)	n.c.

a) Pooled analysis based on IPD.

IPD: individual patient data; CI: confidence interval; n: number of patients with event; N: number of patients evaluated; n.c.: not calculable; RR: relative risk

Morbidity

Endpoint Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p-value[a]
Responder analysis					
General depressive symptomatology (on day 25)					
Remission (MADRS)[b]					
SUI3001	114	46 (40.4)	112	38 (33.9)	1.21 [0.85; 1.71]; 0.295
SUI3002	115	49 (42.6)	115	31 (27.0)	1.56 [1.05; 2.30]; 0.027
Total[c]	229	95 (41.5)	227	69 (30.4)	1.36 [1.05; 1.77]; 0.020
Response (MADRS)[d]					
SUI3001	114	68 (59.6)	112	51 (45.5)	1.35 [1.05; 1.74]; 0.020
SUI3002	115	67 (58.3)	115	54 (47.0)	1.23 [0.94; 1.61]; 0.124
Total[c]	229	135 (59.0)	227	105 (46.3)	1.29 [1.07; 1.55]; 0.007

Please note the benefit assessment procedure comprises several resolutions of the Pharmaceuticals Directive

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Endpoint Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p-value[a]
Specific depressive symptomatology: Suicidality (SIBAT) (at day 25)					
Overall clinical impression of severity of suicidality (Module 7, CGI-SS-R score of 0 or 1)[e]					
SUI3001	114	71 (62.3)	112	57 (50.9)	1.24 [0.99; 1.55]; 0.064
SUI3002	115	69 (60.0)	115	66 (57.4)	1.05 [0.83; 1.32]; 0.670
Total[c]	229	140 (61.1)	227	123 (54.2)	1.14 [0.97; 1.34]; 0.125
Health status (EQ-5D VAS, until day 25)[f]					
SUI3001	114	68 (59.6)	112	49 (43.8)	1.35 [1.03; 1.79] 0.032
SUI3002	115	67 (58.3)	115	61 (53.0)	1.17 [0.91; 1.49]; 0.217
Total[c]	229	135 (59.0)	227	110 (48.5)	1.25 [1.04; 1.50]; 0.017

a) Cochran-Mantel-Haenszel method; stratified by centre and antidepressant therapy at randomisation (antidepressant monotherapy/antidepressant therapy plus augmentation).
b) Proportion of patients with remission, defined as MADRS total score ≤ 12; scale range 0 to 60 points.
c) Pooled analysis based on IPD.
d) Proportion of patients with response, defined as improvement in MADRS total score by ≥ 50% compared with baseline; scale range 0 to 60 points.
e) Scale from 0 to 6 points.
f) Proportion of patients with improvement, defined as an increase in score of ≥ 15 points from baseline; scale range: 0 to 100 points.

CGI-SS-R: Clinical Global Impression of Severity of Suicidality Revised Version; EQ-5D: EuroQoL 5 Dimensions; IPD: individual patient data; CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; n: number of patients with event; N: number of patients evaluated; RR: relative risk; SIBAT: Suicide Ideation and Behaviour Assessment Tool; VAS: visual analogue scale

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Endpoint; Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Median time to event / days [95% CI] Patients with event n (%)	N	Median time to event / days [95% CI] Patients with event n (%)	HR [95 % CI]; p-value[a]
Time-to-event analysis					
General depressive symptomatology (until day 90)					
Remission (MADRS)[b]					
SUI3001	114	17.1 [11.9; 21.9] 90 (78.9)	112	25.0 [17.1; 39.0] 72 (64.3)	1.48 [1.08; 2.02]; 0.014
SUI3002	115	14.9 [10.0; 21.0] 84 (73.0)	115	18.0 [11.0; 23.1] 86 (74.8)	1.23 [0.91; 1.66]; 0.181
Total[c]	229	14.9 [11.9; 18.0] 174 (76.0)	227	21.9 [14.9; 25.0] 158 (69.6)	1.34 [1.08; 1.67] 0.007
Response (MADRS)[d]					
SUI3001	114	4.9 [2.1; 7.9] 100 (87.7)	112	7.9 [4.9; 14.0] 92 (82.1)	1.26 [0.95; 1.67]; 0.113
SUI3002	115	4.9 [2.1; 7.9] 97 (84.3)	115	7.9 [4.9; 11.0] 99 (86.1)	1.23 [0.93; 1.62]; 0.156
Total[c]	229	4.9 [2.1; 7.9] 197 (86.0)	227	7.9 [7.0; 10.0] 191 (84.1)	1.24 [1.02; 1.52]; 0.032
Specific depressive symptomatology: Suicidality (SIBAT, until day 90)					
Overall clinical impression of severity of suicidality (Module 7, CGI-SS-R score of 0 or 1)[e]					
SUI3001	114	4.9 [2.1; 7.9] 100 (87.7)	112	7.9 [4.0; 14.0] 96 (85.7)	1.21 [0.91; 1.60]; 0.183
SUI3002	115	4.0 [2.1; 6.1] 103 (89.6)	115	4.9 [3.0; 7.9] 101 (87.8)	1.22 [0.93; 1.61]; 0.156
Total[c]	229	4.0 [2.1; 7.0] 203 (88.6)	227	7.0 [4.0; 10.0] 197 (86.8)	1.21 [0.99; 1.47]; 0.058
Health status (EQ-5D VAS[f], until day 90)					
SUI3001	114	10.0 [10.0; 11.9] 79 (69.3)	112	24.1 [11.9; 27.1] 76 (67.9)	1.22 [0.89; 1.67]; 0.218
SUI3002	115	11.0 [10.0; 11.9] 87 (75.7)	115	11.9 [11.0; 24.1] 78 (67.8)	1.32 [0.97; 1.79]; 0.078
Total[c]	229	11.0 [10.0; 11.9] 166 (72.5)	227	13.1 [11.9; 24.1] 154 (67.8)	1.26 [1.01; 1.57]; 0.036

a) Cox-Proportional-Hazards-Model, unstratified; health status: stratified by centre and antidepressant therapy at randomisation (antidepressant monotherapy/antidepressant therapy plus augmentation)
b) Time to remission defined as MADRS total score ≤ 12; scale range 0 to 60 points.

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Endpoint; Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Median time to event / days [95% CI] Patients with event n (%)	N	Median time to event / days [95% CI] Patients with event n (%)	HR [95 % CI]; p-value[a]

c) Pooled analysis based on IPD.
d) Time to response defined as improvement in MADRS total score by ≥ 50% from baseline; scale range 0 to 60 points.
e) Scale from 0 to 6 points.
f) Time to improvement; defined as an increase in score of ≥ 15 points from baseline; scale range: 0 to 100 points.

CGI-SS-R: Clinical Global Impression of Severity of Suicidality Revised Version; EQ-5D: EuroQoL 5 Dimensions; IPD: individual patient data; CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; n: number of patients with event; N: number of patients evaluated; RR: relative risk; SIBAT: Suicide Ideation and Behaviour Assessment Tool; VAS: visual analogue scale

Endpoint; Study	Esketamine + antidepressant therapy			Placebo + antidepressant therapy			Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N[a]	Values at start of study MV (SD)	Change at the time of evaluation MV[b] (SE)	N[a]	Values at start of study MV (SD)	Change at the time of evaluation MV[b] (SE)	MD [95% CI]; p-value[b]
Analysis of continuous data							
General depressive symptomatology							
BHS (to day 25)[c]							
SUI3001	105	15.2 (4.3)	-7.1 (0.6)	98	15.9 (4.6)	-6.0 (0.6)	-1.07 [-2.75; 0.61]; 0.211
SUI3002	91	15.5 (4.2)	-7.5 (0.7)	96	15.6 (4.0)	-6.6 (0.7)	-0.86 [-2.64; 0.91]; 0.338
Total[d]	196	15.4 (4.2)	-7.4 (0.5)	194	15.8 (4.3)	-6.3 (0.5)	-1.01 [-2.23; 0.21]; 0.103
BHS (to day 90)[c]							
SUI3001	84	15.2 (4.3)	-7.5 (0.7)	79	15.9 (4.6)	-7.1 (0.7)	-0.36 [-2.27; 1.56]; 0.712
SUI3002	78	15.5 (4.2)	-8.6 (0.7)	86	15.6 (4.0)	-7.7 (0.7)	-0.83 [-2.69; 1.03]; 0.381

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Endpoint; Study	Esketamine + antidepressant therapy			Placebo + antidepressant therapy			Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N[a]	Values at start of study MV (SD)	Change at the time of evaluation MV[b] (SE)	N[a]	Values at start of study MV (SD)	Change at the time of evaluation MV[b] (SE)	MD [95% CI]; p-value[b]
Total[d]	162	15.4 (4.2)	-8.1 (0.5)	165	15.8 (4.3)	-7.5 (0.5)	-0.65 [-1.98; 0.67]; 0.330
QLDS (at day 25)[e]							
SUI3001	104	27.3 (6.3)	-14.1 (1.1)	97	27.1 (6.5)	-11.3 (1.1)	-2.83 [-5.72; 0.06]; 0.055
SUI3002	92	26.7 (6.2)	-14.8 (1.1)	95	26.9 (5.0)	-11.4 (1.1)	-3.47 [-6.52; -0.41]; 0.026
Total[d]	196	27.0 (6.3)	-14.5 (0.8)	192	27.0 (5.8)	-11.4 (0.8)	-3.12 [-5.21; -1.02]; 0.004 *SMD (Hedges'* g): -0.29 [-0.49; -0.09]
QLDS (at day 90)[e]							
SUI3001	84	27.3 (6.3)	-15.0 (1.2)	79	27.1 (6.5)	-14.3 (1.3)	-0.73 [-4.18; 2.73]; 0.679
SUI3002	78	26.7 (6.2)	-16.2 (1.2)	86	26.9 (5.0)	-15.0 (1.2)	-1.19 [-4.48; 2.09]; 0.475
Total[d]	162	27.0 (6.3)	-15.6 (0.9)	165	27.0 (5.8)	-14.6 (0.9)	-0.96 [-3.33; 1.41]; 0.425

a) Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
b) MV and SE (mean change to day 25 or week 90 per treatment arm) and MD, 95% CI and p-value (group comparison): MMRM; including baseline at start of study and stratification factors centre and antidepressant therapy at randomisation (antidepressant monotherapy/antidepressant therapy plus augmentation) as variables
c) Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention; scale range 0 to 20 points.
d) Pooled analysis based on IPD.
e) Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention; scale range 0 to 34 points

BHS: Beck Hopelessness Scale; EQ-5D: EuroQoL 5 Dimensions; IPD: individual patient data; CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; N: number of patients evaluated; RCT: randomised controlled trial; QLDS: Quality of Life in Depression Scale; SD: standard deviation; SE: standard error; SMD: standardised mean difference; VAS: visual analogue scale

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Health-related quality of life

There are no data.

Side effects

Endpoint; Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p-value[a]
Side effects (until day 90)					
Adverse events (AEs) presented additionally					
SUI3001	113	105 (92.9)	112	87 (77.7)	–
SUI3002	114	108 (94.7)	113	95 (84.1)	–
Total[b]	227	213 (93.8)	225	182 (80.9)	–
Serious adverse events (SAE)					
SUI3001	113	17 (15.0)	112	15 (13.4)	1.12 [0.59; 2.14] 0.723
SUI3002	114	13 (11.4)	113	17 (15.0)	0.76 [0.39; 1.49]; 0.420
Total[b]	227	30 (13.2)	225	32 (14.2)	0.93 [0.59; 1.48]; 0.756
Discontinuation due to AE					
SUI3001	113	5 (4.4)	112	5 (4.5)	0.99 [0.30; 3.33] 0.989
SUI3002	114	9 (7.9)	113	3 (2.7)	2.97 [0.83; 10.70]; 0.095
Total[b]	227	14 (6.2)	225	8 (3.6)	1.73 [0.74; 4.05]; 0.204
Nervous system disorders (SOC, AE)					
SUI3001	113	79 (69.9)	112	51 (45.5)	1.54 [1.21; 1.94]; < 0.001
SUI3002	114	87 (76.3)	113	57 (50.4)	1.51 [1.23; 1.87]; < 0.001
Total[b]	227	166 (73.1)	225	108 (48.0)	1.52 [1.30; 1.78]; < 0.001
Psychiatric disorders (SOC, AE)					
SUI3001	113	64 (56.6)	112	40 (35.7)	1.59 [1.18; 2.13]; 0.002
SUI3002	114	82 (71.9)	113	53 (46.9)	1.53 [1.22; 1.92]; < 0.001
Total[b]	227	146 (64.3)	225	93 (41.3)	1.56 [1.30; 1.87]; < 0.001
Gastrointestinal disorders (SOC, AE)					

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Endpoint; Study	Esketamine + antidepressant therapy		Placebo + antidepressant therapy		Esketamine + antidepressant therapy vs placebo + antidepressant therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p-value[a]
SUI3001	113	45 (39.8)	112	34 (30.4)	1.31 [0.91; 1.88]; 0.140
SUI3002	114	65 (57.0)	113	42 (37.2)	1.53 [1.15; 2.05]; 0.004
Total[b]	227	110 (48.5)	225	76 (33.8)	1.43 [1.14; 1.80]; 0.002
Eye disorders (SOC, AE)					
SUI3001	113	14 (12.4)	112	6 (5.4)	2.31 [0.92; 5.80]; 0.074
SUI3002	114	22 (19.3)	113	9 (8.0)	2.42 [1.17; 5.03]; 0.018
Total[b]	227	36 (15.9)	225	15 (6.7)	2.38 [1.34; 4.22]; 0.003

a. Cochran-Mantel-Haenszel method, unstratified.
b. Pooled analysis based on IPD.

IPD: individual patient data; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; n. c. = not calculated; RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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

Adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency

approx. 49,100 – 69,200 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: 25 May 2021):

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

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

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

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

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

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

The patient guideline has to be made available to patients.

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4. Treatment costs

Annual treatment costs:

Adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Esketamine[2]	Incalculable
Inpatient stay[3]	Incalculable
Appropriate comparator therapy:	
Inpatient stay[3]	Incalculable
Electroconvulsive therapy	€ 6,928.10

Costs for additionally required SHI services: not applicable

2 Hospital-specific NUB charges are agreed for billing in the inpatient area.
3 Includes crisis intervention/psychotherapy, acute medicinal therapy and initiation of adequate antidepressant medication or optimization of existing medication.

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II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 August 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 19 August 2021

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

Prof. Hecken

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