Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Siponimod (Secondary Progressive Multiple Sclerosis)

of 20 August 2020

At its session on 20 August 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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. Annex XII shall be amended in alphabetical order to include the active ingredient siponimod as follows:

Siponimod

Resolution of: 20 August 2020
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 13 January 2020):

Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity (see section 5.1).

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

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with relapses~~flares~~.

Appropriate comparator therapy:

- Interferon-beta 1a or interferon-beta 1b or ocrelizumab

Extent and probability of the additional benefit of siponimod compared with the appropriate comparator therapy:

An additional benefit is not proven.

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without relapses~~flares~~.

Appropriate comparator therapy:

- Best supportive care

Extent and probability of the additional benefit of siponimod compared with best supportive care:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with relapses~~flares~~.

No suitable data were submitted.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data submitted.
Morbidity	∅	No data submitted.
Health-related quality of life	∅	No data submitted.
Side effects	∅	No data submitted.

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

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without relapses~~flares~~.

EXPAND study: RCT; comparison of siponimod + BSC vs placebo + BSC

Mortality

Endpoint	Siponimod + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	HR [95% CI]; p value[a]
Overall mortality	127	no data available 1 (0.8)	61	no data available 1 (1.6)	no data available

[1] Data from the dossier assessment of the IQWiG (A20-10) and the addendum (A20-51) unless otherwise indicated.

Morbidity

Endpoint	**Siponimod + BSC**			**Placebo + BSC**			**Intervention vs control**
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*		N	Median time to event in weeks [95% CI] *Patients with event n (%)*		HR [95% CI]; p value[a]
Confirmed disability progression (EDSS based)	127	n.a. 24 (18.9)		61	n.a. 16 (26.2)		0.57 [0.28; 1.16]; 0.121
Fatigue	Endpoint not surveyed						
	N	n/exposure	Annual relapse rate [95% CI][b]	N	n/exposure	Annual relapse rate [95% CI][b]	Rate ratio [95% CI]; p value[b]
Confirmed ~~flare-ups~~disease relapses (EDSS based)							
Annual ~~flare~~ relapse rate	127	14 / no data available	0.06 [0.03; 0.10]	61	15 / no data available	0.14 [0.08; 0.26]	0.41 [0.18; 0.92]; 0.031
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*		N	Median time to event in weeks [95% CI] *Patients with event n (%)*		HR [95% CI]; p value[c]
Time to first confirmed ~~flare~~ relapse *(presented additionally)*	127	n.a. 13 (10.2[d])		61	n.a. 12 (19.7[d])		0.38 [0.16; 0.89]; 0.026

Endpoint	Siponimod + BSC			Placebo + BSC			Intervention vs control
	N[e]	Values at start of study MV (SD)	Change at Month 12 MV (SE)[f]	N[e]	Values at start of study MV (SD)	Change at Month 12 MV (SE)[f]	MD [95% CI]; p value[f]
Severity of disability							
MSFC-z score[g]	113	−0.10 (0.65)	0.04 (0.04)	53	−0.11 (0.60)	0.02 (0.06)	0.02 [−0.11; 0.15]; 0.743
T25-FW[h]	121	16.45 (15.80)	6.14 (1.76)	60	14.44 (12.19)	7.90 (2.61)	−1.76 [−8.05; 4.54]; 0.579
9-HPT[h]	124	39.67 (22.21)	−1.03 (1.16)	60	34.81 (17.19)	0.00 (1.70)	−1.03 [−5.13; 3.07]; 0.620
PASAT-3[g]	115	37.80 (14.41)	3.13 (0.87)	56	34.57 (13.48)	3.44 (1.29)	−0.31 [−3.39; 2.77]; 0.842
Cognitive function							
SDMT[g]	118	36.5 (13.9)	−0.3 (0.9)	57	37.1 (12.1)	−3.0 (1.2)	2.73 [0.17; 5.29]; 0.037 Hedges' g: 0.34 [0.02; 0.65][d]
BVMT-R[g]							
Total recall[i]	113	20.3 (8.9)	−0.7 (0.7)	56	18.2 (7.9)	−0.2 (1.0)	−0.52 [−2.55; 1.52]; 0.616
Delayed recall[i]	113	7.9 (3.3)	−0.5 (0.3)	56	7.2 (3.3)	0.4 (0.4)	−0.85 [−1.75; 0.05]; 0.064
Vision (LCVA)[g]	110	0.39 (0.26)	0.00 (0.03)	55	0.39 (0.26)	−0.01 (0.03)	0.02 [−0.06; 0.09]; 0.632
Walking ability (MSWS-12)[h]	118	70.06 (24.52)	4.46 (2.32)	57	68.25 (23.57)	4.72 (3.08)	−0.26 [−6.89; 6.36]; 0.938
Physical function (MSIS-29)[h]	117	52.15 (21.74)	1.53 (2.28)	56	53.61 (23.26)	0.41 (3.00)	1.12 [−5.22; 7.46]; 0.727
Mental function (MSIS-29)[h]	117	34.73 (21.90)	3.33 (2.39)	55	41.68 (24.26)	1.35 (3.21)	1.98 [−4.77; 8.73]; 0.563
Health status (EQ-5D VAS)[g]	117	58.8 (19.0)	−2.2 (1.7)	58	56.5 (20.2)	−0.2 (2.5)	−2.02 [−7.93; 3.89]; 0.501

Health-related quality of life

Health-related quality of life	Endpoint not surveyed

Side effects

Endpoint	Siponimod + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	HR [95% CI]; p value
AE *(presented additionally)*	No usable data				
SAE					
Discontinuation because of AE					
Infections					
Bradycardia					

[a] Cox proportional hazards model adjusted for country and EDSS at the start of study.
[b] Adjusted annual relapse rate and CI (per treatment arm) as well as rate ratio with CI and p value (group comparison): Negative binomial model, adjusted for EDSS at the start of study; time a patient was in the study (logarithmic time in years) as offset
[C] Cox proportional hazards model adjusted for country, EDSS and number of T1 lesions at the start of study.
[d] Calculation of the IQWiG.
[e] Patient numbers taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study can be based on other patient figures.
[f] MMRM with the terms for treatment, rounds, and value at the start of study as well as the interaction term for treatment and rounds; for the endpoints cognitive function, vision, and walking ability as well as physical and mental function with additional term for country.
[g] A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for siponimod.
[h] A negative change from start of study to end of study means an improvement; a negative effect estimate means an advantage for siponimod.
[i] Total recall: Summarised result of three consecutive learning tests in which patients were shown the same sheet of paper with a geometric shape for 10 seconds. Patients had to trace the shape as accurately as possible and describe where it was located on the paper. Delayed recall: After 25 minutes, there was a recall.

Abbreviations used:
BSC: best supportive care; BVMT-R: Brief Visuospatial Memory Test-Revised; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; 9 HPT: 9-Hole Peg Test; HR = hazard ratio; CI = confidence interval; LCVA: Low Contrast Visual Acuity; MD: mean difference; MMRM: mixed model with repeated measurements; MSFC: Multiple Sclerosis Functional Composite; MSIS 29: Multiple Sclerosis Impact Scale 29; MSWS 12: Multiple Sclerosis Walking Scale 12; MV: mean; N = number of patients evaluated; n = number of patients with (at least one) event (related to the time-to-event analysis) or number of relapses~~flares~~ (related to the annual ~~flare~~ relapse rate); n.a. = not achieved; PASAT: Paced Auditory Serial Addition Test; RCT: randomised controlled trial; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SE: standard error; SAE: serious adverse event; T25-FW: Timed 25-Foot Walk; AE: adverse event; VAS: visual analogue scale; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment.
Morbidity	↔	No difference relevant for the benefit assessment.
Health-related quality of life	∅	No data submitted.
Side effects	n.a.	The present data are not assessable.
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		

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

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with relapses~~flares~~.

approx. 7,900 to 17,300 patients

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without relapses~~flares~~.

approx. 5,300 to 11,600 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 Mayzent® (active ingredient: siponimod) at the following publicly accessible link (last access: 4 June 2020):
https://www.ema.europa.eu/documents/product-information/mayzent-epar-product-information_de.pdf

Treatment with siponimod should only be initiated and monitored by specialists in neurology who are experienced in the treatment of multiple sclerosis.

Before starting treatment with siponimod, patients must undergo CYP2C9 genotyping to determine their CYP2C9 metabolism status. Siponimod should not be used in patients with a CYP2C9*3*3 genotype. In these patients, the use of siponimod leads to significantly increased plasma levels of the active ingredient. In patients with a CYP2C9*2*3 or -*1*3 genotype, the recommended maintenance dose is 1 mg once daily. In all patients with a different CYP2C9 genotype, the recommended maintenance dose of siponimod is 2 mg.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide all doctors who intend to prescribe Mayzent® with an updated training package for doctors. This must include a summary of the characteristics of the medicinal product, a check list for doctors, a guide for patients/caregiver, and a pregnancy reminder card for women of childbearing age.

4. Treatment costs

Annual treatment costs:

a) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, with relapses~~flares~~.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Siponimod	€ 27,327.51 – 28,066.94
Additionally required SHI services:	€ 82.00
Total:	€ 27,409.51 – 28,148.94
Appropriate comparator therapy:	
Interferon beta-1a	€ 21,844.91
Interferon beta-1b	€ 15,825.59
Ocrelizumab Additionally required SHI services: Total:	€ 24,601.74 € 142.34 € 24,744.08

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2020

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Ocrelizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	2	€ 142

b) Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease, defined by clinical findings or imaging of the inflammatory activity, without relapses~~flares~~.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Siponimod	€ 27,327.51 – 28,066.94
Additionally required SHI services:	€ 82.00
Total:	€ 27,409.51 – 28,148.94
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 August 2020.

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

Berlin, 20 August 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken