Gemeinsamer Bundesausschuss

Resolution

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:

Ponesimod (relapsing multiple sclerosis)

of 19 May 2022

At its session on 19 May 2022, 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 information on the benefit assessment of Ponesimod (relapsing multiple sclerosis) in the version of the resolution of 2 December 2021 (BAnz AT 29.12.2021 B4) shall be amended as follows:

1. Before number 1 "Additional benefit of the medicinal product in relation to the appropriate comparator therapy", the words "Therapeutic indication of the resolution (resolution of 2 December 2021):" shall be replaced by the words "Therapeutic indication of the resolution (resolution of 19 May 2022):".

2. Number 1 "Additional benefit of the medicinal product in relation to the appropriate comparator therapy" shall be amended as follows:

a) In the section before the heading "Study results by endpoints:", the letter b) shall be preceded by the following letters a1) and a2):

"a1) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy; EDSS score ≤ 3.5)

Appropriate comparator therapy:

- Interferon beta-1a or interferon beta-1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account the marketing authorisation

Extent and probability of the additional benefit of Ponesimod compared to teriflunomide:

Indication of a minor additional benefit

a2) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy; EDSS score > 3.5)

Appropriate comparator therapy:

- Interferon beta-1a or interferon beta-1b or glatiramer acetate or dimethyl fumarate or teriflunomide or ocrelizumab, taking into account the marketing authorisation

Extent and probability of the additional benefit of Ponesimod compared to teriflunomide:

An additional benefit is not proven."

b) In the section following the heading "Study results by endpoints:" the letter b) shall be preceded by the following letter a):

"a) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy

a1) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy; EDSS score ≤ 3.5)

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 the endpoint of confirmed disease relapses.
Health-related quality of life	↑	Advantage in deterioration in the SF-36v2 physical component score from the start of the study.
Side effects	↔	No relevant differences for the benefit assessment in the endpoints of SAEs and discontinuation due to AEs; in detail, disadvantage in the specific AE bradycardia, advantage in the specific AE alopecia.
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		

a2) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy; EDSS score > 3.5)

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	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment in the endpoints of SAEs and discontinuation due to AEs; in detail, disadvantage in the specific AE bradycardia, advantage in the specific AE alopecia.
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		

OPTIMUM study: Ponesimod vs teriflunomide, comparative study duration over 108 weeks

Mortality

Endpoint	Ponesimod		Teriflunomide		Ponesimod vs teriflunomide
	N	Adults with event n (%)	N	Adults with event n (%)	RR [95% CI]; p value[a]
Overall mortality[b]					
	565	0 (0)	566	2 (0.4)	0.20 [0.01; 4.16]; 0.212

Morbidity

Endpoint	Ponesimod			teriflunomide			Ponesimod vs teriflunomide
	N	n_E	Annual relapse rate [95% CI][c]	N	n_E	Annual relapse rate [95% CI][c]	Rate ratio [95% CI]; p value[c]
Confirmed disease relapses (EDSS-based)[d]							
Annual relapse rate							
	567	242	0.20 [0.17; 0.23]	566	344	0.29 [0.25; 0.33]	0.69 [0.57; 0.85]; < 0.001
EDSS score at the start of the study[e]							
≤ 3.5	472	157[f]	0.16 [0.13; 0.19]	474	268[f]	0.27 [0.23; 0.32]	0.59 [0.47; 0.74]; < 0.001
> 3.5	95	85[f]	0.47 [0.36; 0.60]	92	76[f]	0.41 [0.32; 0.54]	1.13 [0.78; 1.64]; 0.525
Total						Interaction:	0.009

Endpoint	Ponesimod		teriflunomide		Ponesimod vs teriflunomide
	N	Median time to event in months [95% CI] *Adults with event n (%)*	N	Median time to event in months [95% CI] *Adults with event n (%)*	HR [95% CI]; p value[g]
Confirmed disease relapses (EDSS-based)[d]					
Time until 1st confirmed relapse until the end of the study *(presented additionally)*	567	*n.a.* 166 (29.3)	566	*n.a.* 223 (39.4)	0.75 [0.61; 0.92]; 0.005
Confirmed disability progression (EDSS-based)[h]	567	*n.a.* 46 (8.1)	566	*n.a.* 56 (9.9)	0.84 [0.57; 1.24]; 0.373

Endpoint	Ponesimod			teriflunomide			Ponesimod vs teriflunomide
	N[i]	Values at the start of the study MV (SD)	Change at week 108 MV (SE)[j]	N[i]	Values at the start of the study MV (SD)	Change at week 108 MV (SE)[j]	MD [95% CI]; p value[j]
Severity grade of the disability							
MSFC z score[k]	471	0.00 (0.72)	0.03 (0.02)	470	0.00 (0.73)	-0.04 (0.02)	0.07 [0.02; 0.12]; 0.006 Hedges' g: 0.18 [0.05; 0.31]
Cognition (PASAT-3 [correct answers])[k]	472	48.14 (10.57)	1.51 (0.27)	472	48.16 (10.83)	0.90 (0.27)	0.61 [-0.13; 1.35]
Coordination (9-HPT [seconds])[l]	474	23.59 (13.11)	-0.15 (0.14)	473	22.90 (6.60)	0.79 (0.14)	-0.94 [-1.34; -0.55]
Walking ability (T25-WT [seconds])[l]	473	5.86 (2.85)	0.35 (0.11)	471	5.87 (2.95)	0.25 (0.11)	0.10 [-0.21; 0.40]
Fatigue							
PGI-S[l,m]	520[n]	3.20 (2.38)	0.33 (0.09)	519[n]	3.25 (2.32)	0.49 (0.09)	-0.15 [-0.35; 0.05]; 0.131

Health-related quality of life

Endpoint	Ponesimod		teriflunomide		Ponesimod vs teriflunomide
	N	Adults with event n (%)	N	Adults with event n (%)	RR [95% CI]; p value[a]
SF-36v2, physical component score (PCS)[o,p]					
Improvement[q]	567	58 (10.2)	566	66 (11.7)	0.88 [0.63; 1.22]; 0.533
Deterioration[r]	567	65 (11.5)	566	103 (18.2)	0.63 [0.47; 0.84]; 0.001
EDSS score at the start of the study[e]					
≤ 3.5	472	48 (102)	474	89 (18.8)	0.54 [0.39; 0.75]; < 0.001
> 3.5	95	17 (17.9)	92	14 (15.2)	1.18 [0.62; 2.25] 0.682
Total				Interaction:	0.021
SF-36v2, mental component score (MCS)[o,p]					
Improvement[q]	567	116 (20.5)	566	122 (21.6)	0.95 [0.76; 1.19]; 0.683
Deterioration[r]	567	132 (23.3)	566	133 (23.5)	0.99 [0.80; 1.22]; 0.957

Side effects

Endpoint	Ponesimod		teriflunomide		Ponesimod vs teriflunomide
	N	Adults with event n (%)	N	Adults with event n (%)	RR [95% CI]; p value[a]
AEs *(presented additionally)*	565	502 (88.8)	566	499 (88.2)	-
SAEs	565	49 (8.7)	566	46 (8.1)	1.07 [0.73; 1.57]; 0.821
Discontinuation due to AEs	565	49 (8.7)	566	34 (6.0)	1.44 [0.95; 2.20]; 0.097
Bradycardia (PT, AEs)	565	4 (0.7)	566	0 (0.0)	-[s,t]; 0.046

Infections and infestations (SOC, SAEs)	565	7 (1.2)	566	4 (0.7)	1.75 [0.52; 5.96][s]; 0.530
Alopecia (PT, AEs)	565	18 (3.2)	566	72 (12.7)	0.25 [0.15; 0.41]; < 0.001

[a] IQWiG calculation, unconditional exact test (CSZ method).
[b] The results on overall mortality are based on the information on lethal AEs.
[c] Annual relapse rate and CI (per treatment arm) and rate ratio with CI and p value (group comparison): Negative binomial model, adjusted for EDSS at the start of the study (≤ 3.5; > 3.5), treatment with disease-modifying therapy within 2 years before randomisation (yes; no), number of relapses 1 year before randomisation (≤ 1; ≥ 2); logarithmised observation period as offset variable.
[d] Defined as an increase by ≥ 0.5 points (unless EDSS was previously at 0, then ≥ 1.0 points required) or an increase by ≥ 1.0 points in at least 2 functional systems, or an increase by ≥ 2.0 points in at least 1 functional system (excluding bladder/ intestine and cerebral nervous system), after previously clinically stable assessment and provided the increase is consistent with the patient's symptoms.
[e] EDSS scores at the start of the study as recorded in the eCRF.
[f] Discrepancy between data in Module 4 A and study documents; in Module 4 A 45 vs 84 relapses are given for the subgroup EDSS ≤ 3.5, 28 vs 22 relapses for the subgroup EDSS > 3.5.
[g] HR, CI and p value: Cox proportional hazards model, presumptively stratified by EDSS at the start of the study (≤ 3.5; > 3.5), treatment with disease-modifying therapy within 2 years before randomisation (yes; no) and number of relapses 1 year before randomisation (≤ 1; ≥ 2). According to the statistical analysis plan (SAP), the latter stratification variable was not part of the model for the endpoint of confirmed disability progression. The pharmaceutical company does not provide a justification for the procedure deviating from the SAP. However, this is not expected to have a relevant impact on the result.
[h] Defined as an increase by at least 1.5 points on the EDSS in adults with an EDSS score of 0.0 at the start of the study; an increase of at least 1.0 point in adults with an EDSS score of 1.0 to 5.0 at the start of the study; or an increase of at least 0.5 points in adults with an EDSS score ≥ 5.5 at the start of the study; confirmed over a 24-week period.
[i] Number of adults for whom results were available based on information in the study documents at week 108. It is unclear whether earlier measurement points were also included in the calculation of the effect estimate. Values at the start of the study may be based on other patient numbers.
[j] MV and SE (change per treatment arm) as well as MD, 95% CI and p value (group comparison): MMRM with treatment, visit, treatment × visit and baseline × visit as fixed effects; as well as baseline, EDSS at the start of the study (≤ 3.5; > 3.5), treatment with disease-modifying therapy within 2 years before randomisation (yes; no) and number of relapses 1 year before randomisation (≤ 1; ≥ 2) as covariates; the pharmaceutical company states in Module 4 A that the number of relapses in the year before randomisation (≤ 1, ≥ 2) was included as a covariate in the calculation; according to the statistical analysis plan (SAP), this was not part of the model for the endpoint of severity grade of disability. The pharmaceutical company does not provide a justification for the procedure deviating from the SAP. However, this is not expected to have a relevant impact on the result.
[k] Higher (increasing) values mean better symptomatology; positive effects (intervention minus control) mean an advantage of ponesimod.
[l] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage of ponesimod.
[m] Mean change over the entire course of study.
[n] Number of adults with value at the start of the study and at least one follow-up value.
[o] No data are available on the subscales of the SF-36v2.
[p] Approximately 10% missing values at the start of the study; these are presumably counted as adults without an event; precise information on this, also on the handling of missing values in the course of the study, is not available in the pharmaceutical company's dossier.
[q] Clinically relevant improvement is defined as an increase by ≥ 10.80 points (MCS) or by ≥ 10.05 points (PCS) compared to baseline (scale range 2 to 74 points for MCS and 4 to 71 points for PCS; determined using the 1998 norm sample).
[r] Clinically relevant deterioration is defined as a decrease by ≥ 10.80 points (MCS) or by ≥ 10.05 points (PCS) compared to baseline (scale range 2 to 74 points for MCS and 4 to 71 points for PCS; determined using the 1998 norm sample).
[s] IQWiG calculation of RR and CI (asymptotic); in the case of 0 events in one study arm, the correction factor 0.5 was used in the calculation in both study arms.

[t] Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods; no presentation of effect estimate and CI, as not informative.

9-HPT: 9-Hole Peg Test; EDSS: Expanded Disability Status Scale; HR: Hazard Ratio; ITT: Intention-To-Treat; CI: Confidence Interval; MCS: Mental Component Summary; MD: Mean difference; MMRM: Mixed Model with Repeated Measures; MSFC: Multiple Sclerosis Functional Composite; MV: Mean Value; n: number of patients with (at least 1) event; N: number of patients evaluated; n_E: Number of events; n.a. = not achieved; PASAT-3: Paced Auditory Serial Addition Test-3; PCS: Physical Component Summary; PGI-S: Patient Global Impression of Severity; PT: Preferred Term; RCT: Randomised Controlled Trial; RR: Relative Risk; SAP: Statistical Analysis Plan; SD: Standard Deviation; SE: Standard Error; SF 36v2: Short Form-36 Health Survey Version 2; SOC: System Organ Class; SAE: Serious Adverse Event; T25-FW: Timed 25-Foot Walk; AE: Adverse Event

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3. In number 2 "Number of patients or demarcation of patient groups eligible for treatment", the letter b) shall be preceded by the following letter a):

"a) <u>Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy</u>

approx. 186,000 – 200,000 patients".

4. In number 3 "Requirements for a quality-assured application", the words "(last access: 10 August 2021)" shall be replaced by the words "(last access: 21 February 2022)".

5. In number 4 "Treatment costs", after the heading "Annual treatment costs:", letter b) shall be preceded by the following letter a):

"a) Adults with relapsing multiple sclerosis (RMS), who have not previously received disease-modifying therapy or whose disease is not highly active but have been pretreated with disease-modifying therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ponesimod	€ 22,998.39
Appropriate comparator therapy:	
Interferon beta-1a	€ 20,326.95
Interferon beta-1b	€ 16,875.25
Glatiramer acetate	€ 11,293.73
Dimethyl fumarate	€ 11,267.59
teriflunomide	€ 13,118.23
Ocrelizumab	€ 25,238.54
Additionally required SHI services:	€ 143.80
Total:	€ 25,382.34

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2022)

Other SHI services:

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

“.

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 19 May 2022.

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

Berlin, 19 May 2022

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

Prof. Hecken