Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Ublituximab (relapsing multiple sclerosis)

of 1 August 2024

At its session on 1 August 2024, 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 by the publication of the resolution of D 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 Ublituximab as follows:

Ublituximab

Resolution of: 1 August 2024
Entry into force on: 1 August 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 31 May 2023):

Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

Therapeutic indication of the resolution (resolution of 1 August 2024):

See therapeutic indication according to marketing authorisation.

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

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

Appropriate comparator therapy for ublituximab:

- Dimethyl fumarate or diroximel fumarate or glatiramer acetate or interferon beta-1a or interferon beta-1b or teriflunomide

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

Indication of a minor additional benefit

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

Appropriate comparator therapy for ublituximab:

- A patient-individual therapy taking into account the disease activity and prognosis factors,[1] selecting the following active ingredients:

  Fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod

1 e.g. age, symptomatology at onset, regression of relapses, lesion burden and localisation of lesions, presence of intrathecal immunoglobulin synthesis

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

An additional benefit is not proven.

Study results according to endpoints:[2]

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

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 the physical component summary score of the MSQoL-54.
Side effects	↔	Overall, no relevant differences for the benefit assessment. In detail, advantages and disadvantages of some specific adverse events.
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		

ULTIMATE I and II studies:

- Ublituximab **vs** teriflunomide
- Double-blind RCTs, treatment duration 96 weeks each

2 Data from the dossier assessment of the IQWiG (A24-13) and from the addendum (A24-68), unless otherwise indicated.

Mortality

Endpoint	Ublituximab		Teriflunomide		Ublituximab vs teriflunomide
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality[a]					
ULTIMATE I	99	1 (1.0)	91	0 (0.0)	–[b]
ULTIMATE II	75	0 (0.0)	94	0 (0.0)	–[b]
Total					–[b]

Morbidity

Endpoint	Ublituximab			Teriflunomide			Ublituximab vs teriflunomide
	N	N_E	Annual relapse rate [95% CI]	N	N_E	Annual relapse rate [95% CI]	Rate ratio [95% CI]; p value
Confirmed disease relapses (EDSS-based) - annual relapse rate							
ULTIMATE I	97	13	n.d.[c]	90	19	n.d.[c]	0.62 [0.13; 1.11]; 0.231
ULTIMATE II	75	5	0.04 [0.01; 0.15]	93	24	0.14 [0.05; 0.41]	0.27 [-0.01; 0.55]; 0.014
Total[d]							0.42 [0.15; 0.68]; 0.007
Subgroup analyses by sex							
ULTIMATE I							
Men	42	4	0.05 [n.d.]	35	11	0.18 [n.d.]	0.29 [0.07; 0.98]; 0.024
Women	55	9	0.10 [n.d.]	55	8	0.08 [n.d.]	1.17 [0.4; 3.5]; 0.741
ULTIMATE II							
Men	32	0	0.00 [n.d.]	36	12	0.19 [n.d.]	n.d.; < 0.001
Women	43	5	0.06 [n.d.]	57	12	0.12 [n.d.]	0.54 [0.15; 1.64]; 0.238
Total							Interaction: 0.033
Men	74	4	0.03 [n.d.]	71	23	0.19 [n.d.]	0.16 [0.04; 0.47]; < 0.001
Women	98	14	0.07 [0.02; 0.20]	112	20	0.09 [0.03; 0.25]	0.74 [0.19; 1.29]; 0.425

Endpoint	Ublituximab			Teriflunomide			Ublituximab vs teriflunomide
	N	Median time to event in months [95% CI] Patients with event n (%)		N	Median time to event in months [95% CI] Patients with event n (%)		HR [95% CI]; p value
Confirmed disability progression (EDSS-based)[e]							
ULTIMATE I	97	n.r. 1 (1.0)		90	n.r. 2 (2.2)		0.46 [0.04; 5.10]; 0.518
ULTIMATE II	75	n.r. 3 (4.0)		93	n.r. 6 (6.5)		0.59 [0.15; 2.38]; 0.457
Total[d]							0.52 [0.16; 1.72]; 0.276
Endpoint	**Ublituximab**			**Teriflunomide**			**Ublituximab vs teriflunomide**
	N[f]	Values at the start of the study MV (SD)	Change at week 96 MV [95%-CI]	N[f]	Values at the start of the study MV (SD)	Change at week 96 MV [95%-CI]	MD [95% CI]; p value
Severity of disability (MSFC)							
z-score[g]							
ULTIMATE I	97	0.03 (1.94)	0.64 [0.39; 0.89]	90	0.09 (1.74)	0.39 [0.14; 0.64]	0.25 [-0.01; 0.52]; 0.062
ULTIMATE II	75	-0.18 (2.58)	0.66 [0.36; 0.97]	93	0.01 (1.85)	0.54 [0.27; 0.82]	0.12 [-0.19; 0.43]; 0.455
Total[d]							0.19 [-0.02; 0.40]; 0.080
Walking ability (T25-FW [seconds][h])							
ULTIMATE I	97	6.86 (5.81)	0.13 [-0.19; 0.45]	90	6.33 (3.47)	0.16 [-0.16; 0.48]	-0.03 [-0.40; 0.34]
ULTIMATE II	75	7.12 (5.56)	-0.18 [-0.76; 0.40]	93	6.69 (4.05)	-0.22 [-0.75; 0.32]	0.04 [-0.67; 0.74]
Total[d]							0.01 [-0.38; 0.40]
Coordination (9-HPT [seconds][h])							
ULTIMATE I	97	0.04 (0.01)	0.002 [0.001; 0.004]	90	0.04 (0.01)	0.001 [-0.001; 0.002]	0.001 [-0.000; 0.003]

ULTIMATE II	75	0.05 (0.01)	0.003 [0.001; 0.005]	93	0.05 (0.01)	0.000 [-0.001; 0.002]	0.003 [0.001; 0.004]
Total[d]							0.002 [0.001; 0.003]
Cognition (PASAT-3 [correct answers][g])							
ULTIMATE I	97	46.80 (9.65)	4.84 [2.84; 6.85]	90	45.93 (11.27)	3.67 [1.68; 5.66]	1.18 [-0.83; 3.19]
ULTIMATE II	75	46.68 (12.40)	4.68 [2.66; 6.71]	93	46.52 (12.01)	5.17 [3.30; 7.04]	-0.48 [-2.39; 1.43]
Total[d]							0.35 [-1.11; 1.81]

Endpoint	**Ublituximab**		**Teriflunomide**		**Ublituximab vs teriflunomide**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Fatigue (FIS – improvement/ deterioration at week 96)[i]					
Total score					
Improvement					
ULTIMATE I	97	17 (17.5)	90	9 (10.0)	1.75 [0.82; 3.73]; 0.144
ULTIMATE II	75	15 (20.0)	93	12 (12.9)	1.55 [0.77; 3.11]; 0.229
Total[d]					1.64 [0.99; 2.74]; 0.057
Deterioration					
ULTIMATE I	97	12 (12.4)	90	10 (11.1)	1.11 [0.51; 2.45]; 0.808
ULTIMATE II	75	6 (8.0)	93	9 (9.7)	0.83 [0.31; 2.22]; 0.734
Total[d]					0.99 [0.53; 1.83]; 0.970
Cognitive dimension					
Improvement					
ULTIMATE I	97	21 (21.6)	90	14 (15.6)	1.39 [0.75; 2.57]
ULTIMATE II	75	17 (22.7)	93	19 (20.4)	1.11 [0.62; 1.98]
Total[d]					1.24 [0.81; 1.89]
Deterioration					
ULTIMATE I	97	16 (16.5)	90	16 (17.8)	0.93 [0.49; 1.74]
ULTIMATE II	75	7 (9.3)	93	10 (10.8)	0.87 [0.35; 2.17]
Total					0.91 [0.54; 1.53]

Physical dimension					
Improvement					
ULTIMATE I	97	23 (23.7)	90	14 (15.6)	1.52 [0.84; 2.78]
ULTIMATE II	75	18 (24.0)	93	17 (18.3)	1.31 [0.73; 2.37]
Total[d]					1.42 [0.93; 2.16]
Deterioration					
ULTIMATE I	97	19 (19.6)	90	16 (17.8)	1.10 [0.60; 2.01]
ULTIMATE II	75	7 (9.3)	93	14 (15.1)	0.62 [0.26; 1.46]
Total[d]					0.89 [0.55; 1.46]
Social dimension					
Improvement					
ULTIMATE I	97	15 (15.5)	90	10 (11.1)	1.39 [0.66; 2.94]
ULTIMATE II	75	12 (16.0)	93	13 (14.0)	1.14 [0.56; 2.36]
Total[d]					1.26 [0.75; 2.12]
Deterioration					
ULTIMATE I	97	15 (15.5)	90	10 (11.1)	1.39 [0.66; 2.94]
ULTIMATE II	75	6 (8.0)	93	12 (12.9)	0.62 [0.24; 1.57]
Total[d]					1.00 [0.56; 1.77]

Health-related quality of life

Endpoint	**Ublituximab**		**Teriflunomide**		**Ublituximab vs teriflunomide**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
MSQoL-54 – improvement/ deterioration at week 96[j]					
Summary score Physical Health Composite Score (PHCS)					
Improvement					
ULTIMATE I	97	24 (24.7)	90	12 (13.3)	1.86 [0.99; 3.49]; 0.049
ULTIMATE II	75	11 (14.7)	93	10 (10.8)	1.36 [0.61; 3.04]; 0.592
Total[d]					1.65 [1.01; 2.70]; 0.047
Deterioration					
ULTIMATE I	97	5 (5.2)	90	7 (7.8)	0.66 [0.22; 2.01]; 0.532

ULTIMATE II	75	1 (1.3)	93	10 (10.8)	0.12 [0.02; 0.95]; 0.014
Total[d]					0.37 [0.14; 0.93]; 0.035
Summary score Mental Health Composite Score (MHCS)					
Improvement					
ULTIMATE I	97	20 (20.6)	90	15 (16.7)	1.24 [0.68; 2.27]; 0.532
ULTIMATE II	75	19 (25.3)	93	17 (18.3)	1.39 [0.78; 2.47]; 0.354
Total[d]					1.31 [0.86; 1.99]; 0.205
Deterioration					
ULTIMATE I	97	7 (7.2)	90	7 (7.8)	0.93 [0.34; 2.54]; 0.911
ULTIMATE II	75	5 (6.7)	93	16 (17.2)	0.39 [0.15; 1.01]; 0.046
Total[d]					0.57 [0.29; 1.12]; 0.104

Side effects

Endpoint	**Ublituximab**		**Teriflunomide**		**Ublituximab vs teriflunomide**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Total adverse events (AE) (presented additionally)					
ULTIMATE I	99	81 (81.8)	91	76 (83.5)	–
ULTIMATE II	75	63 (84.0)	94	85 (90.4)	–
Serious adverse events (SAE)					
ULTIMATE I	99	5 (5.1)	91	7 (7.7)	0.66 [0.22; 2.00]; 0.531
ULTIMATE II	75	10 (13.3)	94	5 (5.3)	2.51 [0.90; 7.02]; 0.071
Total[d]					1.36 [0.66; 2.77]; 0.404
Subgroup analyses by sex					
ULTIMATE I					
Men	43	1 (2.3)	35	5 (14.3)	0.16 [0.02; 1.33]; 0.048
Women	56	4 (7.1)	56	2 (3.6)	2.00 [0.38; 10.48]; 0.531

ULTIMATE II					
Men	32	1 (3.1)	37	1 (2.7)	1.16 [0.08; 17.75]; 0.993
Women	43	9 (20.9)	57	4 (7.0)	2.98 [0.98; 9.04]; 0.043·
Total					Interaction: 0.018
Men	75	2 (2.7)	72	6 (8.3)	0.31 [0.07; 1.40]; 0.126[d]
Women	99	13 (13.1)	113	6 (5.3)	2.62 [1.05; 6.56]; 0.040[d]
Severe adverse events (CTCAE grade ≥ 3)					
ULTIMATE I	99	17 (17.2)	91	13 (14.3)	1.20 [0.62; 2.33]; 0.623
ULTIMATE II	75	12 (16.0)	94	4 (4.3)	3.76 [1.26; 11.18]; 0.010
Total					1.73 [0.9996; 3.01]; 0.0502
Therapy discontinuation due to adverse events					
ULTIMATE I	99	6 (6.1)	91	0 (0)	11.96 [0.68; 209.36]; 0.018
ULTIMATE II	75	1 (1.3)	94	0 (0)	3.75 [0.15; 90.75]; 0.343
Total					8.18 [0.99; 67.83]; 0.051
Specific adverse events					
Infusion-related reactions (AEs)[k]					
ULTIMATE I	99	44 (44.4)	91	10 (11.0)	4.04 [2.17; 7.55]; < 0.001
ULTIMATE II	75	30 (40.0)	94	11 (11.7)	3.42 [1.84; 6.36]; < 0.001
Total					3.74 [2.41; 5.82]; < 0.001
Infections and infestations (SOC, SAEs)					
ULTIMATE I	99	4 (4.0)	91	2 (2.2)	1.84 [0.34; 9.80]; 0.533
ULTIMATE II	75	2 (2.7)	94	3 (3.2)	0.84 [0.14; 4.87]; 0.910
Total					1.28 [0.39; 4.20]; 0.688
Lymphopenia (PT, severe AEs)					
ULTIMATE I	99	6 (6.1)	91	0 (0)	11.96 [0.68; 209.36]; 0.018

ULTIMATE II	75	5 (6.7)	94	0 (0)	13.75 [0.77; 244.78]; 0.011
Total					12.78 [1.68; 97.37]; 0.014
Alopecia (PT, AEs)					
ULTIMATE I	99	1 (1.0)	91	10 (11.0)	0.09 [0.01; 0.70]; 0.003
ULTIMATE II	75	4 (5.3)	94	17 (18.1)	0.29 [0.10; 0.84]; 0.013
Total					0.21 [0.09; 0.53]; < 0.001

a. The results on overall mortality are based on the data on fatal AEs.
b. An effect estimate (including confidence interval and p value) was not carried out due to the low number of events.
c. Information provided by the pharmaceutical company: As the regression models did not converge, effect estimators could not be reported.
d. Calculated from meta-analysis
e. Defined as an increase in EDSS score by ≥ 1 point from baseline in patients with an EDSS score from 0 up to and including 5.5 at the start of the study or by ≥ 0.5 points from baseline in patients with an EDSS score > 5.5 points at the start of the study; confirmed over a period of 24 weeks
f. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at the start of the study can be based on other patient numbers.
g. Higher (increasing) values mean better symptomatology; positive effects (intervention minus control) mean an advantage of ublituximab.
h. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage of ublituximab.
i. An increase/ decrease by ≥ 15% of the range of values compared to the start of the study is considered a clinically relevant deterioration/ improvement (range of values for the cognitive dimension and for the physical dimension 0 to 40, for the social dimension 0 to 80 and for the total score 0 to 160).
j. An increase/ decrease by ≥ 15 points compared to the start of the study is considered a clinically relevant improvement/ deterioration (range of values 0 to 100).
k. Includes: flu-like illness (PT, AEs), fever (PT, AEs)

Abbreviations used:
CTCAE: Common Terminology Criteria for Adverse Events; 9-HPT: 9-Hole Peg Test; EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; HR: hazard ratio; n. d.: no data available; CI: confidence interval; MHCS: Mental Health Composite Score; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life 54; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; n.r. = not reached; n_E: number of events (multiple events per patient possible); PASAT-3: Paced Auditory Serial Addition Test-3; PHCS: Physical Health Composite Score; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SOC: system organ class; SAE: serious adverse event; T25-FW: Timed 25-Foot Walk; AE: adverse event

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

Summary of results for relevant clinical endpoints

No data available.

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

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

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

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

Approx. 39,500 - 177,300[3] patients

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

Approx. 30,800 to 97,600[3] 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 Briumvi (active ingredient: ublituximab) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 15 July 2024):

https://www.ema.europa.eu/en/documents/product-information/briumvi-epar-product-information_en.pdf

3 An upper limit of a maximum of 223,000 is assumed for the total number of patients in the therapeutic indication.

Treatment should be initiated and monitored by specialists in neurology or neurology and psychiatry with experience in the treatment of multiple sclerosis.

For adults with relapsing forms of multiple sclerosis who have not yet received any disease-modifying therapy and do not demonstrate severe disease progression, there is an effect modification for the sex characteristic: The advantage of ublituximab in the endpoint of confirmed disease relapses is only confirmed in the subgroup of men, whereas in the subgroup of women, there is a disadvantage in the endpoint of serious adverse events.

4. Treatment costs

Annual treatment costs:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ublituximab Additionally required SHI services: Total:	€ 25,471.53 € 21.54 € 25,493.07
Appropriate comparator therapy:	
Dimethyl fumarate	€ 10,364.06
Diroximel fumarate	€ 11,240.26
Glatiramer acetate	€ 11,292.86
Interferon beta-1a	€ 24,464.34
Interferon beta-1b	€ 18,484.34
Teriflunomide	€ 7,117.76

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2024

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ublituximab Additionally required SHI services: Total:	€ 25,471.53 € 21.54 € 25,493.07
Appropriate comparator therapy:	
Fingolimod	€ 1,578.96
Natalizumab	€ 24,518.26
Ocrelizumab Additionally required SHI services: Total:	€ 25,238.16 € 21.54 € 25,259.70
Ofatumumab Additionally required SHI services: Total:	€ 14,734.52 € 11.40 € 14,745.92
Ozanimod	€ 19,211.37
Ponesimod	€ 15,309.62

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2024

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient / year	Costs/ patient / year
Medicinal product to be assessed					
Ublituximab	Surcharge for production of a parenteral solution with monoclonal antibodies	€ 100	1	2.2	€ 220
Appropriate comparator therapy for patient group b)					
Natalizumab	Surcharge for production of a parenteral solution with monoclonal antibodies	€ 100	1	13	€ 1,300

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:

a) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and do not demonstrate severe disease progression

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

b) Adults with relapsing forms of multiple sclerosis (RMS) who have not yet received disease-modifying therapy and show indications of severe disease progression, as well as adults who show active disease progression despite treatment with disease-modifying therapy

- 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 August 2024.

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

Berlin, 1 August 2024

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

Prof. Hecken