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 Ravulizumab

of 6 February 2020

At its session on 6 February 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 ravulizumab as follows:

Ravulizumab

Resolution of: 6 February 2020
Entry into force on: 6 February 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 2 July 2019):

Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):
– in patients with haemolysis with clinical symptom(s) indicative of high disease activity
– in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1).

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

a) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with a high disease activity characterised by clinical symptoms of haemolysis

Appropriate comparator therapy:

Eculizumab

Extent and probability of the additional benefit of ravulizumab compared with eculizumab:

An additional benefit is not proven.

b) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months

Appropriate comparator therapy:

Eculizumab

Extent and probability of the additional benefit of ravulizumab compared with eculizumab:

An additional benefit is not proven.

Study results according to endpoints: [1]

a) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with a high disease activity characterised by clinical symptoms of haemolysis

Study 301: Ravulizumab **vs** eculizumab

Study design: randomised, open, two-armed

[1] Data from the dossier evaluation of the IQWiG (A19-59) unless otherwise indicated.

Mortality

Endpoint	Ravulizumab		Eculizumab		Ravulizumab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value [a]
Overall survival					
	125	0 (0)	121	0 (0)[b]	-

Morbidity

Endpoint	Ravulizumab		Eculizumab		Ravulizumab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value [a]
MAVE[c]					
	125	2 (1.6)[d]	121	1 (0.8)[e]	1.94 [0.18; 21.07]; 0.682
Fatigue (FACIT Fatigue improvement[f])					
	125	77 (61.6)	121	71 (58.7)	1.05 [0.86; 1.29]; 0.711
Transfusion avoidance[g]					
	125	92 (73.6)	121	80 (66.1)	1.11 [0.94; 1.31]; 0.246

Health-related quality of life

Endpoint	Ravulizumab			Eculizumab			Ravulizumab vs eculizumab
	N[h]	Values at start of study MV (SD)	Change at week 26 MV[i] (SE)	N[h]	Values at start of study MV (SD)	Change at week 26 MV[i] (SE)	MD [95% CI][i]; p value[j]
EORTC QLQ-C30 functional scales[k]							
Global health status	125	56.1 (20.3)	12.91 (1.6)	121	57.5 (20.3)	12.8 (1.7)	0.07 [−4.31; 4.45]; 0.975
Physical function	125	76.6 (17.1)	13.5 (1.2)	121	76.4 (17.6)	11.4 (1.2)	2.07 [−1.09; 5.23]; 0.199
Role function	125	72.0 (25.2)	17.5 (1.6)	121	73.0 (25.5)	16.3 (1.7)	1.25 [−3.08; 5.57]; 0.571
Emotional function	125	73.5 (23.5)	16.2 (1.4)	121	75.2 (20.4)	13.5 (1.4)	2.70 [−0.96; 6.36]; 0.148
Cognitive function	125	80.4 (22.2)	10.3 (1.4)	121	78.5 (24.0)	11.7 (1.5)	−1.39 [−5.22; 2.44]; 0.477
Social function	125	76.5	15.4 (1.7)	121	74.8	11.5 (1.7)	3.88 [−0.65; 8.41];

		(24.3)			(25.8)		0.093

Side effects

Endpoint	Ravulizumab		Eculizumab		Ravulizumab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value [a]
AEs *(additionally shown)*					
	125	110 (88.0)	121	105 (86.8)	-
SAEs					
	125	11 (8.8)	121	9 (7.4)	1.18 [0.51; 2.75]; 0.769
Discontinuation because of AEs					
	125	0 (0)	121	0 (0)	-
Meningococcal infections					
	125	0 (0)	121	0 (0)	-

a) Calculation by the IQWiG; 95% CI (asymptotic); p value from unconditional exact test (CSZ method)
b) One patient died during the extension phase; the reason was a lung cancer diagnosed during the extension phase. The symptoms of lung cancer had already occurred during the randomised study phase.
c) Defined as the occurrence of one of the following events: Thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, peripheral artery disease (PAD), mesenteric/visceral venous thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic vein/portal vein thrombosis (Budd-Chiari syndrome), cerebral artery occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other
d) Both events were deep vein thromboses.
e) Mesenteric venous thrombosis
f) Patients with an improvement in the FACIT fatigue overall scale value of at least 3 points at week 26
g) Defined as the proportion of patients who did not require a transfusion in accordance with the guidelines specified in the protocol from the start of study until day 183 of the randomised study phase (week 26). A transfusion of red cell concentrate was administered when a patient showed Hb levels of ≤ 9 g/dl with clinical signs or symptoms of sufficient severity to warrant a transfusion or when the patient showed Hb levels of ≤ 7 g/dl regardless of clinical signs or symptoms. Patients who met these transfusion criteria were counted in the group of patients with transfusion needs, regardless of whether they actually received a transfusion.
h) Number of patients with values at the start of study; unclear how many patients were included in the evaluation to calculate the effect estimate
i) Changes, mean difference at the end of the randomised treatment phase (week 26), and 95% CI are based on MMRM model adjusted for treatment group, observed stratification characteristics for randomisation (transfusion history and screening LDH levels), respective values at start of study and study round, and interaction between study round and treatment group.
j) Calculation of the IQWiG, asymptotic p value assuming normal distribution
k) Higher values mean better health-related quality of life; a positive group difference (intervention – control) means an advantage for intervention.

Abbreviations used:
BTH: Breakthrough haemolysis; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: Haemoglobin; CI: Confidence interval; LDH: lactate dehydrogenase; MAVE: Major Adverse Vascular Event; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least

1) event; MMRM: mixed model with repeat measurements; MV: mean value; N: number of patients evaluated; PAD: peripheral artery disease; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; TIA: transitory ischaemic attack, AE: adverse event; ULN: upper limit of the norm; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	There is no relevant difference for the benefit assessment.
Morbidity	↔	There is no relevant difference for the benefit assessment.
Health-related quality of life	↔	There is no relevant difference for the benefit assessment.
Side effects	↔	There is no relevant difference for the benefit assessment.

Explanations:
↑, ↓: statistically significant and relevant effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant effect with low risk of bias
↔: no relevant difference
∅: no data available
n.r.: not rateable

b) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months

Study 302: Ravulizumab **vs** eculizumab

Study design: randomised, open, two-armed

Mortality

Endpoint	**Ravulizumab**		**Eculizumab**		**Ravulizumab vs Eculizumab**
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value [a]
Overall mortality					
	97	0 (0)	98	0 (0)	-

Morbidity

Endpoint	**Ravulizumab**		**Eculizumab**		**Ravulizumab vs Eculizumab**
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value [a]
MAVE[b]					
	97	0 (0)	96	0 (0)	-
Fatigue (FACIT Fatigue improvement[c])					
	97	36 (37.1)	98	33 (33.7)	1.10 [0.75; 1.61]; 0.682
Transfusion avoidance[d]					
	97	85 (87.6)	98	81 (82.7)	1.06 [0.94; 1.19]; 0.529

Health-related quality of life

Endpoint	Ravulizumab			Eculizumab			Ravulizumab vs eculizumab
	N[e]	Values at start of study MV (SD)	Change at week 26 MV[f] (SE)	N[e]	Values at start of study MV (SD)	Change at week 26 MV[f](SE)	MD [95% CI][f]; p value[g]
EORTC QLQ-C30 functional scales[h]							
Global health status	97	75.3 (17.2)	1.8 (1.7)	98	69.5 (16.5)	−2.7 (1.7)	4.52 [0.17; 8.87]; 0.042 Hedges' g: 0.29 [0.01; 0.57][g]
Physical function	97	88.3 (17.2)	4.0 (1.0)	98	87.6 (14.9)	1.8 (1.0)	2.24 [−0.10; 4.58]; 0.061
Role function	97	86.6 (21.3)	5.1 (1.9)	98	83.3 (19.0)	0.7 (1.9)	4.41 [−0.35; 9.17]; 0.069
Emotional function	97	87.2 (18.2)	3.8 (1.7)	98	78.9 (23.1)	4.2 (1.7)	−0.35 [−4.37; 3.66]; 0.864
Cognitive function	97	88.8 (19.8)	3.6 (1.5)	98	85.7 (21.8)	1.2 (1.6)	2.34 [−1.29; 5.98]; 0.207
Social function	97	85.2 (22.2)	8.3 (1.7)	98	80.6 (24.6)	8.7 (1.7)	−0.41 [−4.62; 3.79]; 0.848

Side effects

Endpoint	Ravulizumab		Eculizumab		Ravulizumab vs Eculizumab
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI] p value [a]
AEs *(additionally shown)*					
	97	85 (87.6)	98	86 (87.8)	-
SAEs					
	97	4 (4.1)	98	8 (8.2)	0.51 [0.16; 1.62]; 0.253
Discontinuation because of AEs					
	97	0 (0)	98	0 (0)	-
Meningococcal infections					
	97	0 (0)	98	0 (0)	-

a) Own calculation 95% CI (asymptotic); p value from unconditional exact test (CSZ method)
b) Defined as the occurrence of one of the following events: Thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, peripheral artery disease (PAD), mesenteric/visceral venous thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic vein/portal vein thrombosis (Budd-Chiari syndrome), cerebral artery occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other
c) Patients with an improvement in the FACIT fatigue overall scale of at least 3 points at week 26
d) Defined as the proportion of patients who did not require a transfusion in accordance with the guidelines specified in the protocol from the start of study until day 183 of the randomised study phase (week 26). A transfusion of red cell concentrate was administered when a patient showed Hb levels of ≤ 9 g/dl with clinical signs or symptoms of sufficient severity to warrant a transfusion or when the patient showed Hb

levels of ≤ 7 g/dl regardless of clinical signs or symptoms. Patients who met these transfusion criteria were counted in the group of patients with transfusion needs, regardless of whether they actually received a transfusion.

e) Number of patients with values at the start of study; unclear how many patients were included in the evaluation to calculate the effect estimate

f) Changes, mean difference at the end of the randomised treatment phase (week 26), and 95% CI are based on MMRM model adjusted for treatment group, observed stratification characteristics for randomisation (transfusion history), respective values at start of study and study round, and interaction between study round and treatment group.

g) Calculation of the IQWiG assuming asymptotic normal distribution

h) Higher values mean better health-related quality of life; a positive group difference (intervention – control) means an advantage for intervention.

Abbreviations used:
BTH: Breakthrough haemolysis; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: Haemoglobin; CI: Confidence interval; LDH: lactate dehydrogenase; MAVE: Major Adverse Vascular Event; MedDRA: Medical Dictionary for Regulatory Activities; MD: Mean difference; MMRM: mixed model with repeated measurements; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PAD: peripheral artery disease; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; TIA: transitory ischaemic attack, AE: adverse event; ULN: upper limit of the norm; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	There is no relevant difference for the benefit assessment.
Morbidity	↔	There is no relevant difference for the benefit assessment.
Health-related quality of life	↔	There is no relevant difference for the benefit assessment.
Side effects	↔	There is no relevant difference for the benefit assessment.

Explanations:
↑, ↓: statistically significant and relevant effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant effect with low risk of bias
↔: no relevant difference
∅: no data available
n.r.: not rateable

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

a) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with a high disease activity characterised by clinical symptoms of haemolysis
approx. 210–560 patients

b) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months

approx. 50−140 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 Ultomiris® (active ingredient: ravulizumab) at the following publicly accessible link (last access: 20 November 2019):
https://www.ema.europa.eu/documents/product-information/ultomiris-epar-product-information_de.pdf

Treatment with ravulizumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with haematological disorders.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training materials to all doctors and patients expected to use ravulizumab.

In addition to the product information, the training material for doctors contains a guide for the prescribing doctor. In addition to the package insert, the training material for patients contains a guide for patients as well as a patient card.

4. Treatment costs

Annual treatment costs:

a) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with a high disease activity characterised by clinical symptoms of haemolysis

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ravulizumab	€ 354,324.30
Appropriate comparator therapy:	
Eculizumab	€ 365,689.50–498,667.50

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

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Ravulizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426
Eculizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	22–30	€ 1562 – 2130

b) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ravulizumab	€ 354,324.30
Appropriate comparator therapy:	
Eculizumab	€ 365,689.50–498,667.50

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

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Ravulizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6	€ 426

Eculizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	22–30	€ 1562 – 2130

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 6 February 2020.

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

Berlin, 6 February 2020

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

Prof. Hecken