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 Sutimlimab (cold agglutinin disease)

of 15 June 2023

At its session on 15 June 2023, 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 Sutimlimab as follows:

Sutimlimab

Resolution of: 15 June 2023
Entry into force on: 15 June 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 15 November 2022):

Enjaymo is indicated for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD).

Therapeutic indication of the resolution (resolution of 15 June 2023):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Sutimlimab is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adults with cold agglutinin disease associated with haemolytic anaemia</u>

Extent of the additional benefit and significance of the evidence of sutimlimab:

Hint for a minor additional benefit.

Study results according to endpoints:[1]

Adults with cold agglutinin disease associated with haemolytic anaemia

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 fatigue.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant difference for the benefit assessment.
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		

CADENZA study

- randomised, multicentre, controlled phase III study
- Part A: 26-week comparison of sutimlimab vs placebo
- Population: Patients with primary CAD without blood transfusion in recent medical history

Mortality

Endpoint	Sutimlimab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Deaths					
	22	0 (0)	20	0 (0)	

[1] Data from the dossier assessment of the G-BA (published on 3. April 2023), and from the amendment to the dossier assessment, unless otherwise indicated.

Morbidity

Endpoint	Sutimlimab				Placebo				Intervention vs control
	Baseline		Change from baseline		Baseline		Change from baseline		Mean value difference [95% CI] p value Hedges' g [95% CI]
	N	MV (SD)	N	LS mean (SE)	N	MV (SD)	N	LS mean (SE)	
Health status (EQ-5D-5L VAS)[b,c]									
	22	61.18 (19.48)	18	13.29 (3.77)	20	65.95 (18.79)	18	2.54 (3.77)	10.75 [-0.09; 21.60] 0.052
Fatigue (FACIT Fatigue)[d,e,f]									
	22	31.67 (12.80)	19	10.89 (1.82)	20	32.99 (10.95)	20	0.76 (1.81)	10.13 [4.97; 15.29] < 0.001 1.18 [0.52; 1.84]

Endpoint	Sutimlimab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Thromboembolic events					
	22	1 (4.5)	20	0 (0)	

Health-related quality of life

Endpoint	Sutimlimab				Placebo				Intervention vs control
	Baseline		Change from baseline		Baseline		Change from baseline		Mean value difference [95% CI] p value
	N	MV (SD)	N	LS mean (SE)	N	MV (SD)	N	LS mean (SE)	
SF-12[c,g]									
PCS	21	43.4 (6.0)	18	5.5 (1.4)	20	39.0 (7.7)	18	1.6 (1.4)	3.97 [-0.25; 8.20] 0.064
MCS	21	43.9 (10.4)	18	5.65 (2.3)	20	49.8 (10)	18	-0.48 (2.3)	6.13 [-0.40; 12.67] 0.065

Side effects

Endpoint	Sutimlimab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[h] Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	22	21 (95.5)	20	20 (100)	
Serious adverse events (SAE)					
	22	3 (13.6)	20	1 (5.0)	n.d. n.d. 0.499
Severe adverse events (CTCAE grade ≥ 3)					
	22	5 (22.7)	20	3 (15.0)	n.d. n.d. 0.632
Therapy discontinuation due to adverse events					
	22	3 (13.6)	20	0 (0)	n.d. n.d. 0.175
Adverse events of special interest					
Within 24 hours after an infusion[i]	22	11 (50.0)	20	7 (35.0)	n.d. n.d. 0.358
Cardiac disorders	22	1 (4.5)	20	1 (5.0)	n.d. n.d. 1.0
Gastrointestinal disorders	22	0 (0)	20	1 (5.0)	n.d. n.d. n.d.
General disorders and administration site conditions	22	3 (13.6)	20	2 (10.0)	n.d. n.d. 0.897
Infections and infestations	22	3 (13.6)	20	1 (5.0)	n.d. n.d. 0.499
Injury, poisoning and procedural complications	22	3 (13.6)	20	0 (0)	n.d. n.d. 0.175

Endpoint	Sutimlimab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[h] Absolute difference (AD)[a]
Metabolism and nutrition disorders	22	1 (4.5)	20	1 (5.0)	n.d. n.d. 1.0
Musculoskeletal and connective tissue disorders	22	1 (4.5)	20	0 (0)	n.d. n.d. n.d.
Skin and subcutaneous tissue disorders	22	1 (4.5)	20	1 (5.0)	n.d. n.d. 1.0
Vascular disorders	22	1 (4.5)	20	0 (0)	n.d. n.d. n.d.
Infections (grade ≥ 3)	22	2 (9.1)	20	1 (5.0)	n.d. n.d. 0.875
Serious infections	22	1 (4.5)	20	1 (5.0)	n.d. n.d. 1.0
Breakthrough haemolysis	22	2 (9.1)	20	3 (15.0)	n.d. n.d. n.d.
Hypersensitivity and anaphylactic reactions	22	5 (21.7)	20	3 (15.0)	n.d. n.d. 0.897
ADA	22	2 (9.1)	20	n.d.	n.d. n.d. n.d.

<u>CARDINAL study - presented additionally</u>

- Single-arm phase III study
- Part A of the study with 26-week treatment phase, part B with 2-year follow-up treatment phase
- Population: Patients with CAD who have received at least one blood transfusion within the last 6 months

Mortality

Endpoint	Sutimlimab	
	N	Patients with event n (%)
Deaths		
	24	3 (12.5)

Morbidity

Endpoint	Sutimlimab	
	N	*MV (SD)*
Health status (EQ-5D-5L VAS)[b]		
Baseline	23	61.96 (14.67)
Change from baseline at week 26	16	16.75 (16.90)
Change from baseline at week 123	19	8.84 (18.8)
Fatigue (FACIT Fatigue)[d,f]		
Baseline, MV (SD)	22	32.50 (10.63)
Change from baseline to TAT, LS mean (SE)	21	9.41 (1.85)
Change from baseline at week 123, MV (SD)	19	6.79 (11.28)

Endpoint	Sutimlimab	
	N	Patients with event n (%)
Thromboembolic events		
	24	2 (8.3)

Health-related quality of life

Endpoint	Sutimlimab	
	N	*MV (SD)*
SF-12[g]		
PCS: Baseline	22	38.7 (8.7)
PCS: Change from baseline at week 26	16	5.4 (7.6)
PCS: Change from baseline at week 87	18	6.4 (9)
MCS: Baseline	22	49.8 (8.2)
MCS: Change from baseline at week 26	16	4.4 (10)
MCS: Change from baseline at week 87	18	1.6 (10.4)

Side effects

Endpoint	Sutimlimab	
	N	Patients with event n (%)
Total adverse events (presented additionally)		
Part A	24	22 (91.7)
Part B	22	22 (100)
Serious adverse events (SAE)		
Part A	24	7 (29.2)
Part B	22	12 (54.5)
Severe adverse events (CTCAE grade ≥ 3)		
Part A	24	7 (29.2)
Part B	22	15 (68.2)
Therapy discontinuation due to adverse events		
Part A	24	1 (4.2)
Part B	22	3 (13.6)

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Scale 0–100. A higher score represents better health status.
[c] ANCOVA with change from week 26 to baseline as dependent variable, treatment arm as independent variable and baseline value as covariate.
[d] MMRM: Change from baseline was the dependent variable, baseline and visit the independent variables.
[e] Change from baseline to TAT, defined as the mean of visits in weeks 23, 25 and 26. If a value is missing from one of these dates, it is calculated as the average of the available values, unless there is no value from all 3 dates.
[f] Scale 0–52. A higher score means fewer conditions.
[g] Scale 0–100. A higher score represents a higher quality of life.
[h] Calculated post hoc with Boschloo's exact test for small sample sizes.
[i] TEAEs that occurred within 24 hours of infusion were defined as AEs of special interest. The listing is made according to MedDRA system organ class.

Abbreviations used:
AD = absolute difference; ADA = anti-drug antibody ANCOVA = analysis of covariance; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D-5L VAS = Visual Analogue Scale of the European Quality of Life 5-Dimension 5-Level; FACIT Fatigue = Functional Assessment of Chronic Illness Therapy - Fatigue Scale; n.d. = no data; CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; MV = mean; N = number of patients evaluated; n = number of patients with (at least one) event; RR = relative risk; SD = standard deviation; SE = standard error; SF-12 = Short-Form 12 Health Survey; TAT = Treatment Assessment Timepoint; vs = versus

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

Adults with cold agglutinin disease associated with haemolytic anaemia

approx. 370 – 1,510 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 Enjaymo (active ingredient: sutimlimab) at the following publicly accessible link (last access: 2 May 2023):

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

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

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. In particular, the training material contains information and warnings on the risk of serious infections and meningococcal infections.

Patients shall be vaccinated according to the current recommendations for patients with persistent complement deficiency diseases, including vaccines against meningococci and streptococci. Patients should receive booster vaccinations according to local recommendations.

4. Treatment costs

Annual treatment costs:

Adults with cold agglutinin disease associated with haemolytic anaemia

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Sutimlimab	€ 234,589.85

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

Costs for additionally required SHI services: not applicable

5. 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 sutimlimab

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with sutimlimab for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD) on the basis of the marketing authorisation granted under Medicinal Products Act:

Adults with cold agglutinin disease associated with haemolytic anaemia

- No active ingredient 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 15 June 2023.

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

Berlin, 15 June 2023

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

Prof. Hecken