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)
Talquetamab (multiple myeloma, at least 3 prior therapies)

of 7 March 2024

At its session on 7 March 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 Talquetamab as follows:

Talquetamab

Resolution of: 7 March 2024
Entry into force on: 7 March 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 August 2023):

Talvey is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Therapeutic indication of the resolution (resolution of 7 March 2024):

See therapeutic indication according to marketing authorisation.

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

Talquetamab is approved as a medicinal product for the treatment of rare diseases in accordance with 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 relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy</u>

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adults with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The 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 ∅: No data available. n.a.: not assessable		

MonumentTAL-1 study: single-arm, open-label phase I/II study, results of the data cut-off from 17 January 2023

Cohort A: Non-TCRDT[2] pretreated, talquetamab 0.4 mg/kg weekly

Cohort B: TCRDT pretreated, talquetamab 0.4 mg/kg weekly

Cohort C: Non-TCRDT pretreated, talquetamab 0.8 mg/kg every 2 weeks

[1] Data from the dossier assessment of the G-BA (published on 15. Dezember 2023), and from the amendment to the dossier assessment from 09.02.2024, unless otherwise indicated.

[2] TCRDT, T cell redirection therapy, e.g. CAR-T cell therapy or bispecific antibodies

Mortality

Endpoint	Talquetamab			
	Non-TCRDT pretreated		TCRDT pretreated	
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)
Overall survival				
	288	n.r. [25.56; n.r.] 81 (28.1)	31	n.r. [8.15; n.r.] 14 (45.2)

Morbidity

	Talquetamab			
	Non-TCRDT pretreated		TCRDT pretreated	
	N	LS mean[b] [95% CI] p value	N	LS mean[b] [95% CI] p value
Symptom scales of the EORTC QLQ-C30 [c, d] - change from baseline for cycle 3 day 1				
Appetite loss	231	28.6 [23.9; 33.4] < 0.0001	19	--- [a]
Constipation	231	1.8 [-1.6; 5.2] 0.29	19	--- [a]
Diarrhoea	231	-2.4 [-5.8; 1.0] 0.16	19	--- [a]
Insomnia	231	1.3 [-2.8; 5.5] 0.53	19	--- [a]
Fatigue	231	1.8 [-1.3; 4.9] 0.26	19	--- [a]
Nausea / vomiting	231	1.4 [-0.3; 3.0] 0.10	19	--- [a]
Pain	231	-7.3 [-10.7; -3.9] < 0.0001	19	--- [a]
Dyspnoea	231	-5.8 [-9.0; -2.5] 0.0005	19	--- [a]
Disease symptomatology (PGIS) [d, e] – change from baseline				
Cycle 3 day 1	231	-0.6 [-0.7; -0.4] < 0.0001	---	--- [a]
	N	Patients with event n (%)	N	Patients with event n (%)
Overall response according to IRC (presented additionally) [f]				

Overall response rate	288	210 (72.9)	31	18 (58.1)
sCR	288	77 (26.7)	31	8 (25.8)
CR	288	104 (36.1)	31	10 (32.3)
VGPR	288	173 (60.1)	31	16 (51.6)
PR	288	37 (12.8)	31	2 (6.5)
	N	Median time in months [95% CI] Patients with event n (%)	N	Median time in months [95% CI] Patients with event n (%)
Progression-free survival [g]				
	288	9.56 [7.46; 12.09] 162 (56.3)	31	5.03 [2.86; 13.01] 21 (67.7)

Health-related quality of life

EORTC QLQ-C30 [d, h]	**Talquetamab**			
	Non-TCRDT pretreated		**TCRDT pretreated**	
	N	LS mean[b] [95% CI] p value	N	LS mean[b] [95% CI] p value
Functional scales of the EORTC QLQ-C30 – change from baseline for cycle 3 day 1				
Global health status / Global quality of life	231	0.6 [-2.1; 3.4] 0.66	19	--- [a]
Physical functioning	231	-1.5 [-4.0; 1.1] 0.26	19	--- [a]
Role functioning	231	-4.3 [-8.2; -0.5] 0.03	19	--- [a]
Cognitive functioning	231	0.7 [-1.78; 3.25] 0.57	19	--- [a]
Emotional functioning	231	3.9 [1.4; 6.4] 0.002	19	--- [a]
Social functioning	231	-3.0 [-6.6; 0.7] 0.11	19	---[a]

Side effects

Endpoint	Talquetamab			
	Non-TCRDT pretreated		TCRDT pretreated	
	N	Patients with event n (%)	N	Patients with event n (%)
AE (presented additionally)	288	288 (100)	31	31 (100)
AE CTCAE grade ≥ 3	288	224 (77.8)	31	30 (96.8)
SAE	288	146 (50.7)	31	19 (61.3)
AEs which led to the discontinuation of the study medication	288	19 (6.6)	31	2 (6.5)
Severe AEs with incidence ≥ 10% at SOC level				
Blood and lymphatic system disorders	288	172 (59.7)	31	25 (80.6)
Metabolism and nutrition disorders	288	58 (20.1)	31	---
Infections and infestations	288	54 (18.8)	31	8 (25.8)
Investigations	288	42 (14.6)	31	5 (16.1)
Serious AEs with incidence ≥ 10% at SOC level				
Infections and infestations	288	50 (17.4)	31	5 (16.1)
Immune system disorders [i]	288	39 (13.5)	31	4 (12.9)
AEs of special interest with incidence > 10%				
Cytokine release syndrome				
SAE	288	39 (13.5)	31	4 (12.9)

a. The return rate is > 70% only for cycle 1, day 1. This corresponds to the time of administration of the first full dose of talquetamab, which occurs 2-4 days after completion of step-up dosage. These evaluations are considered non-interpretable. For cycle 3, day 1, the return rate is below 70%.
b. LS means based on MMRM model
c. Values from 0 to 100; higher values correspond to more severe disease symptomatology.
d. The PRO data was collected from phase II (study part 3) onwards.
e. Scale 0 and 4. Higher values are associated with higher symptom severity.
f. Primary endpoint of the MonumenTAL-1 study
g. Information from the dossier of the pharmaceutical company
h. Values from 0 to 100; higher values correspond to better functioning or health/ quality of life.
i. Events affecting PT cytokine release syndrome

Abbreviations used:
CR: complete response; CTCAE = Common Terminology Criteria for Adverse Events; IRC: Independent Review Committee; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; MV = mean value;

N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not considered; n.r. = not reached; PFS, progression-free survival; PR: partial response; PT = preferred term; sCR: stringent complete response; SD = standard deviation; TCRDT = T-cell redirection therapy; AE = adverse event; VGPR: very good partial response

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

Adults with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

approx. 1,210 – 1,310 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 Talvey (active ingredient: talquetamab) at the following publicly accessible link (last access: 5 January 2024):

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

Treatment with talquetamab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with multiple myeloma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient card. Training material for all healthcare professionals who are expected to prescribe or use talquetamab includes instructions on the identification, treatment and monitoring of neurological toxicities, including ICANS (immune effector cell-associated neurotoxicity syndrome).

The patient card is intended to explain the risks of cytokine release syndrome and neurological toxicities (including ICANS) and when patients should seek urgent medical treatment in the event of signs and symptoms. In addition, the patient card reminds patients that they should remain in the vicinity of a medical facility where they received talquetamab for 48 hours after all doses of the step-up phase have been administered.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will assess new information on this medicinal product at least annually and update the product information as necessary.

4. Treatment costs

The annual treatment costs shown refer to the first year of treatment.

Annual treatment costs:

Adults with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Talquetamab[3]	€ 353,870.78 – € 365,972.43
Additionally required SHI services	€ 53.20 – € 53.53

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2024)

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:

Adults with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

– No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 7 March 2024.

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

[3] Includes the costs of the step-up phase and the treatment phase

Berlin, 7 March 2024

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

Prof. Hecken