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
Tebentafusp (uveal melanoma, HLA-A*02:01-positive)

of 20 October 2022

At its session on 20 October 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 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 Tebentafusp as follows:

Tebentafusp

Resolution of: 20 October 2022
Entry into force on: 20 October 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 1 April 2022):

Kimmtrak is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Therapeutic indication of the resolution (resolution of 20 October 2022):

See therapeutic indication according to marketing authorisation.

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

Tebentafusp 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>Human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma</u>

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

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

IMCgp100-202 study: Tebentafusp **vs** therapy at the doctor's discretion (dacarbazine, ipilimumab or pembrolizumab)

Study design: open-label, randomised, multicentre, controlled phase II study, data cut-off from 13 October 2020

Mortality

Endpoint	Tebentafusp		Therapy at the doctor's discretion		Intervention vs control
	N[g]	Median survival time in months [95% CI][c] *Patients with event n (%)*	N[g]	Median survival time in months [95% CI][c] *Patients with event n (%)*	Hazard ratio [95% CI][b] p value[b] Absolute difference (AD)[a]
Overall survival					
	252	21.7 [18.6; 28.6] *87 (34.5)*	126	16.0 [9.7; 18.4] *63 (50.0)*	0.51 [0.37; 0.71] < 0.0001 AD = + 5.7 months
Subgroups according to lactate dehydrogenase (LDH)					
LDH ≤ ULN[d]	162	28.6 [22.2; -[e]] *28 (17.3)*	80	18.4 [16.0; 21.4] *29 (36.3)*	0.35 [0.21; 0.60] < 0.001 AD = + 10.2 months
LDH > ULN[d]	90	9.1 [7.0; 11.1] *59 (65.6)*	46	6.7 [3.6; 8.3] *34 (73.9)*	0.70 [0.46; 1.09] 0.105

[1] Data from the dossier assessment of the G-BA (published on 1. August 2022), unless otherwise indicated.

Morbidity

General health status (EQ-5D-5L VAS)
There are no assessable data.
Disease symptomatology (EORTC QLQ-C30)
There are no assessable data.

Health-related quality of life

There are no assessable data.

Side effects

Endpoint	**Tebentafusp**		**Therapy at the doctor's discretion**		Intervention vs control
	N[h]	Median time to event in weeks [95% CI] *Patients with event n (%)*	N[h]	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value
Adverse events in total					
	245	0.1 [n.a.; n.a.] *245 (100)*	111	1.7 [1.1; 3.0] *105 (94.6)*	-
Serious adverse events (SAE)					
	245	n.a. *69 (28.2)*	111	n.a. *26 (23.4)*	1.31 [0.83; 2.06] n.d.
Severe adverse events (CTCAE grade 3 or 4)					
	245	*133 (54.3)*	111	*40 (36.0)*	-[f]
Therapy discontinuation due to adverse events					
	245	*8 (3.3)*	111	*7 (6.3)*	-[f]
Adverse events of special interest (AESI)					
Liver function test elevations					
AESI regardless of severity grade					
	245	*99 (40.4)*	111	*32 (28.8)*	n.d.
Severe AESI (grade ≥ 3)					
	245	*29 (11.8)*	111	*7 (6.3)*	n.d.
Serious AESI					
	245	*8 (3.3)*	111	*3 (2.7)*	n.d.

Endpoint	Tebentafusp		Therapy at the doctor's discretion		Intervention vs control
	N[h]	Median time to event in weeks [95% CI] *Patients with event n (%)*	N[h]	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value
Cytokine release syndrome					
AESI regardless of severity grade					
	245	*217 (88.6)*	111	*3 (2.7)*	n.d.
Severe AESI (grade ≥ 3)					
	245	*2 (0.8)*	111	*0 (0)*	n.d.
Skin rash					
AESI regardless of severity grade					
	245	*203 (82.9)*	111	*31 (27.9)*	n.d.
Severe AESI (grade ≥ 3)					
	245	*45 (18.4)*	111	*0 (0)*	n.d.
Serious AESI					
	245	*12 (4.9)*	111	*0 (0)*	n.d.

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] HR calculated with a Cox regression model
[C] Kaplan-Meier method
[d] ULN = 250 U/L
[e] The pharmaceutical company indicates this value as missing.
[f] Due to the lack of consideration of the different treatment and thus, also durations of observation, the effect estimators are not used in the benefit assessment.
[g] ITT population comprises all study participants allocated to the respective treatment at randomisation, regardless of whether the study participants actually received the allocated treatment.
[h] Safety population: defined as all randomised study participants who received at least one full or incomplete dose of tebentafusp or therapy according to doctor's instructions. Allocation is based on the first treatment dose administered.
Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS = visual analogue scale of the EuroQol-5 dimension; HR = hazard ratio; n.d. = no data available; CI = confidence interval; LDH = lactate dehydrogenase; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; ULN = upper limit of normal; vs = versus

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

approx. 110 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 Kimmtrak (active ingredient: tebentafusp) at the following publicly accessible link (last access: 17 August 2022):

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

Treatment with tebentafusp should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with uveal melanoma as well as specialists in dermatology, specialists in ophthalmology and other specialists participating in the Oncology Agreement.

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. This aims to promote the prompt diagnosis and treatment of cytokine release syndrome (CRS), thereby reducing its severity.

Patients treated with Kimmtrak must have an HLA-A*02:01 genotype detected by a validated genotyping assay.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tebentafusp	€ 802,758.44 – € 822,354.74

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

Costs for additionally required SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Cost/ patient/ year
Tebentafusp	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.1	€ 4,220.10

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 October 2022.

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

Berlin, 20 October 2022

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

Prof. Hecken