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 (reassessment of an orphan drug > EUR 30 million turnover limit: uveal melanoma, HLA-A*02:01-positive)

of 16 May 2024

At its session on 16 May 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 is amended as follows:

1. The information on tebentafusp in the version of the resolution of 20 October 2022 (BAnz AT 18.11.2022 B2) is repealed.
2. Annex XII shall be amended in alphabetical order to include the active ingredient tebentafusp as follows:

Tebentafusp

Resolution of: 16 May 2024
Entry into force on: 16 May 2024
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 16 May 2024):

See therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

Therapy according to doctor's instructions under consideration of

- Dacarbazine,
- Ipilimumab,
- Lomustine,
- Nivolumab,
- Pembrolizumab

Extent and probability of the additional benefit of tebentafusp compared to dacarbazine, ipilimumab and pembrolizumab:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

1 Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-128) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↓↓	Disadvantage in the endpoint of severe AEs (CTCAE ≥ 3) and in detail disadvantages in specific AEs.

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

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 according to doctor's instructions		Intervention vs control
	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 (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
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]; < 0.001 AD = 5.7 months
Subgroups according to lactate dehydrogenase (LDH)[c]					
LDH ≤ ULN	162	28.6 [22.2; n.d.] *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	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

Morbidity

Symptomatology (EORTC QLQ-C30)	
	No suitable data
General health status (EQ-5D VAS)	
	No suitable data

Health-related quality of life

EORTC QLQ-C30	
	No suitable data

Side effects

Endpoint	**Tebentafusp**		**Therapy according to doctor's instructions**		Intervention vs control
	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 (%)*	Hazard ratio [95% CI] p value[a]
Total adverse events (presented additionally)[d]					
	245	n.d. *245 (100)*	111	n.d. *105 (94.6)*	–
Serious adverse events (SAE)[d]					
	245	n.d. *68 (27.8)*	111	n.d. *24 (21.6)*	1.35 [0.84; 2.15]; 0.21
Severe adverse events (CTCAE grade 3 or 4)[d]					
	245	n.d. *132 (53.9)*	111	n.d. *38 (34.2)*	2.01 [1.40; 2.88]; < 0.01
Therapy discontinuation due to adverse events					
	245	n.d. *8 (3.3)*	111	n.d. *7 (6.3)*	0.45 [0.16; 1.24]; 0.12
Specific adverse events					
Cytokine release syndrome	No suitable data				
Skin reactions[e]	245	n.d. *229 (93.5)*	111	n.d. *51 (45.9)*	6.26 [4.56; 8.6]; < 0.01
Severe skin reactions[e]	245	n.d. *49 (20.0)*	111	n.d. *0 (0)*	n.d.[f]
Immune-mediated AEs	Endpoint not operationalised				
Gastrointestinal disorders (SOC, AEs)	245	n.d. *194 (79.2)*	111	n.d. *66 (59.5)*	1.68 [1.27; 2.23]; < 0.01

Eye disorders (SOC, AEs)	245	n.d. *79 (32.2)*	111	n.d. *15 (13.5)*	2.54 [1.46; 4.41]; < 0.01
Headache (PT, AEs)	245	n.d. *75 (30.6)*	111	n.d. *11 (9.9)*	3.22 [1.71; 6.06]; < 0.01
Paraesthesia (PT, AEs)	245	n.d. *27 (11.0)*	111	n.d. *1 (0.9)*	12.3 [1.67; 90.53]; 0.01
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	245	n.d. *4 (1.6)*	111	n.d. *6 (5.4)*	0.27 [0.08; 0.96]; 0.04
General disorders and administration site conditions (SOC, severe AEs)	245	n.d. *21 (8.6)*	111	n.d. *2 (1.8)*	4.76 [1.12; 20.31]; 0.04
Vascular disorders (SOC, severe AEs)	245	n.d. *28 (11.4)*	111	n.d. *3 (2.7)*	3.97 [1.2; 13.08]; 0.02

a Overall survival: Cox proportional hazards model, p value from log-rank test, each stratified by LDH status; endpoints in the side effects category: Cox proportional hazards model, no information on stratification and calculation of the p value
b Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
c ULN = 250 U/L; data (data cut-off 13.10.2020) from the dossier assessment of the G-BA (from 01.08.2022) for procedure D-768 tebentafusp
d Without progression events collected via SOC "Benign, malignant and unspecified neoplasms (including cysts and polyps)"
e Operationalised via the SOC "Skin and subcutaneous tissue disorders"
f The pharmaceutical company does not provide any information on HR (including 95% CI) and p value. In the present data constellation, a statistically significant difference to the disadvantage of tebentafusp must be assumed with an event rate of 20% (n = 49) in the intervention arm vs 0% (n = 0) in the comparator arm and with clearly separating Kaplan-Meier curves at an early stage in the course of the study.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; LDH = lactate dehydrogenase; n.d.= no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; ULN = upper limit of normal; vs = versus

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

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

approx. 100 - 130 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: 29 February 2024):

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 and venereology, 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:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tebentafusp	€ 605,881.61 - € 619,990.00
Appropriate comparator therapy:	
Dacarbazine	€ 4,694.71 - € 12,497.72
Ipilimumab	€ 65,157.24
Lomustine	€ 1,291.70
Nivolumab	€ 75,915.32 - € 76,207.30

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

Costs for additionally required SHI services: not applicable

Other SHI benefits:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Tebentafusp	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	52.1	€ 4,100
Appropriate comparator therapy					
Dacarbazine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87.0	€ 8700
Dacarbazine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Ipilimumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	4.0	€ 400
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	13.0 – 26.1	€ 1,300 – € 2,600

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:

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

– 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 16 May 2024.

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

Berlin, 16 May 2024

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

Prof. Hecken