Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient tebentafusp (Kimmtrak) was listed for the first time on 1 May 2022 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Kimmtrak for the treatment of uveal melanoma 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.

At its session on 20 October 2022, the G-BA decided on the benefit assessment of tebentafusp in the therapeutic indication "Monotherapy in the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 17 August 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 December 2023, due

to exceeding the € 30 million turnover limit within the period from April 2022 to March 2023. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO on 1 December 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of tebentafusp compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tebentafusp.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Tebentafusp (Kimmtrak) in accordance with the product information

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 16.05.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for tebentafusp as monotherapy:

Therapy according to doctor's instructions under consideration of

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

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to tebentafusp, the following active ingredients are approved for the present therapeutic indication: No active ingredients are explicitly approved for uveal melanoma. Ipilimumab, nivolumab, pembrolizumab, dabrafenib, encorafenib,

vemurafenib, binimetinib, cobimetinib, trametinib, dacarbazine, lomustine and talimogene laherparepvec are approved for metastatic melanoma.

The use of the active ingredients binimetinib, cobimetinib, dabrafenib, encorafenib, trametinib and vemurafenib is limited to patients with BRAF V600 mutations according to the marketing authorisation. Some of the marketing authorisations are tied to specific concomitant active ingredients.

on 2. It is assumed that resection with curative intent is not indicated. Furthermore, it is assumed that local or targeted treatment of liver metastases, in particular transarterial chemoembolisation (TACE) or transarterial radioembolisation (TARE; or selective internal radiotherapy (SIRT)), can be carried out in both study arms if this is indicated for the patients. Therefore, a non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication.

on 3. Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V are available for the active ingredients binimetinib, cobimetinib, dabrafenib, encorafenib, ipilimumab, nivolumab, pembrolizumab, talimogene laherparepvec, trametinib and vemurafenib as well as tebentafusp:

- Binimetinib: Resolution of 22 March 2019
- Cobimetinib: Resolution of 2 June 2016
- Dabrafenib: Resolutions of 16 June 2016, 17 March 2016
- Encorafenib: Resolution of 22 March 2019
- Ipilimumab: Resolutions of 2 August 2018, 7 April 2016, 20 December 2018, 2 August 2018
- Nivolumab: Resolutions of 15 December 2016, 20 December 2018
- Pembrolizumab: Resolution of 4 February 2016
- Talimogene laherparepvec: Resolution of 19 January 2023, 15 December 2016
- Tebentafusp: Resolution of 20 October 2022
- Trametinib: Resolution of 17 March 2016
- Vemurafenib: Resolution of 6 March 2014

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

The active ingredient tebentafusp to be assessed here is the only active ingredient that is explicitly approved for this indication.

When determining the appropriate comparator therapy, the actual medical treatment situation as it would be without the medicinal product to be assessed must be taken into account (in accordance with Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV)). A comparison with the active

ingredient itself under assessment, specifically a comparison of identical therapies, is ruled out regarding the question of the benefit assessment.

Accordingly, the evidence for determining the appropriate comparator therapy in the indication of metastatic uveal melanoma is limited. The present international guidelines recommend that patients with metastatic disease should be treated in specialised study sites, if possible as part of a clinical study. The guidelines and the written statement of the scientific-medical societies on the question of comparator therapy state that immune checkpoint inhibitors can be considered as treatment options. In this regard, the active ingredients ipilimumab, nivolumab and pembrolizumab are mentioned. The guidelines and the scientific-medical societies also state that chemotherapies have only (very) limited efficacy. However, this can be offered to patients if no suitable clinical study is available or no other therapy options are considered. Dacarbazine and lomustine are approved for this purpose.

With regard to MEK inhibitors, guidelines state that targeted therapies should only be used in the context of a clinical study. BRAF inhibitors are not listed in this body of evidence.

With regard to the determination of the appropriate comparator therapy for the present resolution, it is therefore not possible to specify a uniform therapy standard. For the treatment of HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma, a therapy according to doctor's instructions is therefore determined as appropriate comparator therapy. In this regard, the immune checkpoint inhibitors nivolumab and pembrolizumab (PD-1 inhibitors) and ipilimumab (CTLA-4 inhibitor), which are approved for metastatic melanoma, as well as lomustine and dacarbazine, which belong to the alkylating agents, are determined as treatment options as part of therapy according to doctor's instructions.

The investigators should have a choice of several treatment options.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of tebentafusp is assessed as follows:

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

Hint for a considerable additional benefit

Justification:

For demonstration of the additional benefit of tebentafusp for the treatment of inoperable or metastatic uveal melanoma, the pharmaceutical company presented the results of the IMCgp100-202 study.

The pivotal IMCgp100-202 study is an ongoing, randomised, multicentre, controlled, unblinded phase II study comparing tebentafusp with a therapy according to doctor's instructions (dacarbazine, ipilimumab and pembrolizumab).

The study has been conducted in 58 study sites and 14 countries (North America, Europe, Australia, Ukraine and Russia) since October 2017.

The total of 378 enrolled HLA-A*02:01-positive patients with untreated advanced or metastatic uveal melanoma were stratified by LDH status and randomised in a 2:1 ratio to the two study arms. During the treatment phase, they received either weekly tebentafusp or a therapy according to doctor's instructions (dacarbazine, ipilimumab or pembrolizumab) every three weeks.

Besides the primary study endpoint of overall survival, data on morbidity (symptomatology (EORTC QLQ-C30) and health status (EQ-5D-5L VAS)), quality of life (EORTC QLQ-C30) and side effects were collected.

In the dossier, the pharmaceutical company presents the results of the pre-specified primary data cut-off from 13 October 2020 and, in addition, for overall survival, a data cut-off from 3 July 2023, in which the patients were followed up for at least 36 months. The pre-specified data cut-off from 13 October 2020 is used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the IMCgp100-202 study as the time between randomisation and death, regardless of the underlying cause of death.

For overall survival, there was a statistically significant difference to the advantage of tebentafusp over dacarbazine, ipilimumab and pembrolizumab.

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

In the subgroup analyses for the endpoint of overall survival, there is an interaction between treatment and the stratification characteristic LDH (≤ ULN vs > ULN; p = 0.04). For the LDH ≤ ULN subgroup, there is a statistically significant difference to the advantage of tebentafusp. There is no statistically significant difference for the LDH > ULN subgroup. This result of the subgroup analysis for the characteristic LDH is considered relevant, but does not lead to correspondingly differentiated statements in the quantification of the additional benefit in the present assessment in the overall assessment.

Morbidity

Symptomatology (EORTC QLQ-C30)

Disease symptomatology was surveyed in the IMCgp100-202 study using the cancer-specific questionnaire EORTC QLQ-C30.

In the study, the return rates in the comparator arm were already below 70% at baseline. In addition, the difference in return rates between the treatment arms was over 15%. The results presented are therefore unsuitable for the benefit assessment and will not be used.

Health status (EQ-5D, visual analogue scale)

The health status was surveyed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

The results of the questionnaire were not used because the return rates were already low at baseline and differed greatly between the groups.

Quality of life

Health-related quality of life (EORTC QLQ-C30)

Health-related quality of life was surveyed in the IMCgp100-202 study using the functional scales and the global scale of general health status of the EORTC QLQ-C30 questionnaire.

The results on health-related quality of life of the EORTC QLQ-C30 are not used for the benefit assessment, as the return rates in the comparator arm were already below 70% at baseline and the difference in the return rates between the treatment arms was above 15%.

Side effects

Endpoints in the category of side effects were followed up to 90 days after the end of treatment.

Total adverse events (AE) (presented additionally)

In the IMCgp100-202 study, an adverse event occurred in all patients in the comparator arm and in 95% of the patients in the intervention arm.

Serious adverse events (SAEs) and discontinuation due to AEs

There was no statistically significant difference between the study arms for the endpoints of SAEs and discontinuation due to AEs.

Severe AEs (CTCAE grade ≥ 3)

There was a statistically significant disadvantage of tebentafusp with regard to severe adverse events with CTCAE grade 3 or 4.

Specific AEs

In detail, tebentafusp showed a statistically significant advantage over dacarbazine, ipilimumab and pembrolizumab with regard to the specific AE respiratory, thoracic and mediastinal disorders (SOC, SAEs).

In contrast, tebentafusp showed a statistically significant disadvantage compared to dacarbazine, ipilimumab and pembrolizumab with regard to the specific AEs of skin reactions, severe skin reactions, gastrointestinal disorders, eye disorders, headache, paraesthesia, general disorders and administration site conditions and vascular disorders.

In the side effects category, a disadvantage of tebentafusp over dacarbazine, ipilimumab and pembrolizumab can therefore be identified in the overall assessment.

Overall assessment

For the benefit assessment of tebentafusp for the treatment of HLA (human leukocyte antigen)-A*02:01-positive adults with unresectable or metastatic uveal melanoma, results from the IMCgp100-202 study on mortality, morbidity (symptomatology and health status), health-related quality of life and side effects are available.

The results for the endpoint of overall survival show that treatment with tebentafusp, compared to dacarbazine, ipilimumab, and pembrolizumab, achieves an prolongation of overall survival, which is considered a significant improvement.

In the endpoint category of morbidity and health-related quality of life (assessed using the EORTC QLQ-C30 and EQ-5D VAS), there are no assessable data for the benefit assessment due to low return rates and significant differences in the return rates between the treatment arms. Statements on morbidity and quality of life are given a high priority, especially in the palliative treatment setting presented here.

For the side effects, a statistically significant disadvantage of tebentafusp was identified with regard to the endpoint of severe AEs (CTCAE ≥ 3). In detail, adverse effects predominate among the specific side effects. Tebentafusp is therefore at an overall disadvantage in the side effects category.

In the overall analysis, the positive effect in overall survival is offset by negative effects in the endpoint category of side effects. Taking into account the extent of the positive effect on overall survival in an advanced palliative treatment setting, the G-BA came to the conclusion that the disadvantage in terms of side effects in the overall assessment does not justify a downgrading in the extent of the additional benefit.

As a result, a considerable additional benefit of tebentafusp for the treatment of HLA (human leukocyte antigen)-A*02:01-positive adults with unresectable or metastatic uveal melanoma compared to dacarbazine, ipilimumab and pembrolizumab was identified.

Reliability of data (probability of additional benefit)

The ongoing, randomised, multicentre, controlled phase II IMCgp100-202 study forms the basis of the present benefit assessment.

Overall, the risk of bias at the study level is rated as low.

The risk of bias for the endpoint of overall survival and side effects is classified as low.

No assessable data are available for the endpoint categories of morbidity and health-related quality of life. These endpoint categories are given a high priority, especially in the palliative treatment setting presented here.

In summary, the G-BA derives a hint for the identified additional benefit with regard to the significance.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient tebentafusp due to the exceeding of the € 30 million turnover limit.

Tebentafusp is approved for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adults with unresectable or metastatic uveal melanoma.

For the assessment, the pharmaceutical company submits the results of the still ongoing, randomised, multicentre phase II IMCgp100-202 study comparing tebentafusp to a therapy according to doctor's instructions (dacarbazine, ipilimumab or pembrolizumab).

For overall survival, there is a statistically significant difference. The magnitude of the effect is assessed as a significant improvement.

The presented results of the endpoint categories of morbidity and quality of life are not used for the benefit assessment as the return rates of the measurement instruments EORTC QLQ-C30 and EQ-5D VAS were already low at baseline and differed greatly between the groups.

For the side effects, a statistically significant disadvantage of tebentafusp was identified with regard to the endpoint of severe AEs (CTCAE ≥ 3). In detail, adverse effects predominate among the specific side effects as well.

In the overall analysis, the positive effect in overall survival is offset by negative effects in the endpoint category of side effects. Taking into account the extent of the positive effect on overall survival in an advanced palliative treatment setting, the G-BA came to the conclusion that the disadvantage in terms of side effects in the overall assessment does not justify a downgrading in the extent of the additional benefit.

For HLA-A*02:01-positive adults with unresectable or metastatic uveal melanoma, the G-BA identified a considerable additional benefit of tebentafusp compared to therapy according to doctor's instructions (dacarbazine, ipilimumab and pembrolizumab).

The significance is rated as hint.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are subject to methodological uncertainties. Uncertainties arise due to the fact that the pharmaceutical company only considers patients with metastatic uveal melanoma who have been diagnosed for the first time, whereas patients who have already been diagnosed and whose tumour has subsequently metastasised are not included in the calculation. Further uncertainties exist in the calculation of the percentage of metastatic patients due to the incomprehensible range from the sources and with regard to the estimated percentage of inoperable patients due to a lack of sufficient evidence to determine the percentage.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

The costs for the first year of treatment are shown for the cost representation in the resolution.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

According to the product information, it is recommended that the first three treatments with tebentafusp be administered in an inpatient setting. In subsequent treatment cycles, tebentafusp may be administered during an inpatient stay or in an appropriate outpatient care centre where full resuscitation equipment is immediately available to treat cytokine release syndrome.

For the cost calculation, the case scenarios a) purely inpatient administration and b) inpatient administration in the first three treatments and subsequent outpatient treatment are considered.

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tebentafusp	Once on day 1[2]	1	1.0	1.0
	Once on day 8	1	1.0	1.0
	Continuously from day 15, 1 x every 7 days	50.1	1.0	50.1
Appropriate comparator therapy				
Dacarbazine	Continuously, Day 1 to 5 of a 21-day cycle	17.4	5.0	87.0
	Continuously, Day 1 of a 21-day cycle	17.4	1.0	17.4
Ipilimumab	4 x 21-day cycles	4.0	1.0	4.0
Lomustine	Continuously[4], 42-day cycle	6.0	1.0	6.0[4]
Nivolumab	Continuously, 14-day cycle	26.1	1.0	26.1
	Continuously, 28-day cycle	13.0	1.0	13.0

2 KIMMTRAK must only be administered under the direction and supervision of a physician experienced in the application of anticancer drugs and capable of treating cytokine release syndrome in a setting where full resuscitation equipment is immediately available. It is recommended that at least the first three KIMMTRAK infusions be given in an inpatient setting.

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[3].

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Medicinal product to be assessed					
Tebentafusp	Day 1: 20 µg Day 8: 30 µg From day 15: 68 µg	Day 1: 20 µg Day 8: 30 µg From day 15: 68 µg	Day 1: 1 x 0.1 mg Day 8: 1 x 0.1 mg From day 15: 1 x 0.1 mg	52.1	52.1 x 0.1 mg
Appropriate comparator therapy					
Dacarbazine	200 mg/m² = 382 mg – 250 mg/m² = 477.5 mg	382 mg – 477.5 mg	2 x 200 mg – 1 x 500 mg	87.0	174 x 200 mg – 87.0 x 500 mg
	850 mg/m² = 1,623.5 mg	1,623.5 mg	1 x 1,000 mg + 1 x 500 mg + 1 x 200 mg	17.4	17.4 x 1,000 mg + 17.4 x 500 mg + 17.4 x 200 mg
Ipilimumab	3 mg/kg = 233.1 mg	233.1 mg	1 x 200 mg + 1 x 50 mg	4.0	4.0 x 200 mg + 4.0 x 50 mg
Lomustine[4]	70 mg/m² = 133.7 mg – 100 mg/m² = 191 mg	133.7 mg – 191 mg	4 x 40 mg	6.0	24.0 x 40 mg
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
	480 mg	480 mg	4 x 120 mg	13.0	52.0 x 120 mg

3 Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

4 The cumulative total dose should not reach 1,000 mg lomustine/m² body surface area as there is a risk of pulmonary fibrosis.

Costs:

In the inpatient setting:

Tebentafusp fulfils the criteria of the NUB agreement for 2023 according to the list of information pursuant to Section 6, paragraph 2 KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services), which is why a hospital-specific fee is negotiated between the contracting parties at local level with the respective hospital for the inpatient costs incurred for the medicinal product. These costs cannot be specifically quantified. The actual costs incurred may therefore vary from hospital to hospital. As an approximation, the manufacturer's sales price plus 19% value added tax is used to calculate the inpatient costs for the medicinal product.

Designation of the therapy	Packaging size	Cost (manufacturer sales price)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Tebentafusp	1 CIS	€ 10,000.00	€ 1,900	€ 11,900
Abbreviations: CIS = concentrate for the preparation of an infusion solution				

In the outpatient setting:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tebentafusp 0.1 mg	1 CIS	€ 12,314.66	€ 2.00	€ 700.00	€ 11,612.66
Appropriate comparator therapy					
Dacarbazine 200 mg	10 PII	€ 348.37	€ 2.00	€ 42.66	€ 303.71
Dacarbazine 500 mg	1 PIF	€ 95.58	€ 2.00	€ 10.67	€ 82.91
Dacarbazine 1,000 mg	1 PIF	€ 179.86	€ 2.00	€ 21.33	€ 156.53
Ipilimumab 50 mg	1 CIS	€ 13,783.97	€ 2.00	€ 783.91	€ 12,998.06
Ipilimumab 200 mg	1 CIS	€ 3,489.23	€ 2.00	€ 195.98	€ 3,291.25
Lomustine 40 mg	20 HC	€ 748.40	€ 2.00	€ 100.55	€ 645.85
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 85.05	€ 1,459.91
Abbreviations:					

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; PIF = powder for the preparation of an infusion solution; PII = powder for the preparation of a solution for injection or infusion					

LAUER-TAXE® last revised: 15 April 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

Premedication

To minimise the risk of hypotension associated with cytokine release syndrome (CRS), the patient may have to be administered intravenous fluids before starting the tebentafusp infusion. In the inpatient treatment setting, the costs for premedication are included in the per case flat rate. The additional costs for premedication incurred in the outpatient treatment setting cannot be precisely quantified due to the largely lacking dosage data for premedication.

Other SHI benefits:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more

detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 October 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 December 2023, the pharmaceutical company submitted a dossier for the benefit assessment of tebentafusp to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 4 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient tebentafusp.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 October 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	3 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 April 2024	Conduct of the oral hearing
Working group Section 35a	17.04.2024; 30 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

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

Prof. Hecken