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 Talquetamab (multiple myeloma, at least 3 prior therapies)

of 7 March 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.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient talquetamab on 15 September 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company 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 1 VerfO on 14 September 2023.

Talquetamab for the treatment of multiple myeloma 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 benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 December 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-24) and the statements made in the written statement and

oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of talquetamab.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Talquetamab (Talvey) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

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

Justification:

In the dossier, the pharmaceutical company submitted data from the single-arm, open-label phase I/II MonumenTAL-1 study for the assessment of the additional benefit of talquetamab in the therapeutic indication of relapsed and refractory multiple myeloma (≥ 3 prior

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

therapies). This is an ongoing, multicentre study that has been conducted in 47 study sites in Europe, Israel, Korea and North America since 2017.

The aim of the MonumenTAL-1 study is to investigate the efficacy and safety of talquetamab as monotherapy in adults with relapsed or refractory multiple myeloma. All study participants had received ≥3 previous lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

The MonumenTAL-1 study is divided into 3 parts. Phase I is divided into part 1 (dose escalation) and part 2 (dose expansion of the recommended Phase 2 dose, RP2D). Phase II is referred to as part 3, in which a total of N = 339 study participants were divided into 3 indication-specific cohorts (A, B, C). Prior therapy with a T-cell redirection therapy (TCRDT, for example CAR-T cell therapy or bispecific antibodies) was excluded for study participants in cohort A and cohort C. The study participants in cohort B had to have received a TCRDT.

The cohorts also differed in terms of the dosage regimen:

- Cohort A: Talquetamab 0.4 mg/kg weekly, non-TCRDT pretreated, N = 143 patients
- Cohort B: Talquetamab 0.4 mg/kg weekly, TCRDT pretreated, N = 51 patients
- Cohort C: Talquetamab 0.8 mg/kg every 2 weeks, not pretreated with TCRDT, N = 145 patients

All 3 study cohorts were used for the present assessment of additional benefit, as they correspond to the therapeutic indication according to the product information of talquetamab. Cohorts A and C are shown aggregated as cohort "non-TCRDT pretreated" (N=288). For cohort B, the pharmaceutical company carried out a cut-off according to the approved therapeutic indication with regard to refractoriness to the last line of therapy. This population is used for the benefit assessment and labelled as "TCRDT pretreated" (N = 31). In the dossier, no data were available for the general information on the population for cohort B; these were subsequently submitted in the written statement procedure.

The primary endpoint of the MonumenTAL-1 study is the overall response rate (ORR) according to International Myeloma Working Group (IMWG) criteria, which is assessed by an independent review committee.

Furthermore, endpoints of the categories mortality, morbidity, health-related quality of life and adverse events were collected in the study.

For the study, four data cut-offs are available in total. The data cut-off from 17 January 2023 subsequently required by the EMA is used for the present benefit assessment.

Mortality

In the MonumenTAL-1 study, the endpoint of overall survival is defined as the time from the first dosage of talquetamab to death from any cause. At the time of the data cut-off relevant for the benefit assessment, 81 subjects (28.1%) in the non-TCRDT pretreated cohort had died. In the TCRDT pretreated cohort, 14 subjects (45.2%) died. The median survival time had not yet been reached in either cohort at the time of the data cut-off.

Due to the single-arm study design, a comparative assessment of the data on overall survival is not possible.

Morbidity

Progression-free survival (PFS)

PFS in the MonumenTAL-1 study is defined as the time between the date of first administration of talquetamab and the date of first documented disease progression according to IMWG criteria based on laboratory parameters as well as haematological and imaging procedures, or death from any cause, whichever occurs first.

The median PFS was 9.56 months in the non-TCRDT pretreated cohort and 5.03 months in the TCRDT pretreated cohort.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The “Mortality” endpoint component is already assessed via the “overall survival” secondary endpoint as an independent endpoint. The morbidity component "disease progression" was assessed according to IMWG criteria and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

Due to the single-arm study design, a comparative assessment of the results on PFS is not possible.

Overall response rate (ORR)

Overall response rate is the primary endpoint in the MonumenTAL-1 study and is defined as achieving a partial or better response as assessed by an independent review committee using the IMWG criteria. The overall response rate was 72.9% in the non-TCRDT pretreated cohort and 58.1% in the TCRDT pretreated cohort.

The overall response rate is presented additionally as a primary endpoint of the study.

Due to the single-arm study design, a comparative assessment of the data on overall response rate is not possible.

EQ-5D-VAS

General health status was collected in phase II of the MonumenTAL-1 study using the visual analogue scale of the European Quality of Life 5 Dimensions (EQ-5D-VAS).

The return rate of the EQ-5D-VAS was already less than 70% for cycle 1 day 1 in cohorts A, B and C, so that the analyses presented are considered unsuitable for the benefit assessment. In addition, no analyses could be identified for the TCRDT-pretreated cohort. Due to the low return rates, no data was subsequently submitted by the pharmaceutical company during the written statement procedure.

Regardless of this, a comparative assessment of the data on the EQ-5D VAS is not possible due to the single-arm study design.

Symptom scales of the EORTC-QLQ-C30

Symptomatology was collected in the MonumenTAL-1 study using the EORTC-QLQ-C30 symptom scales in N = 122 patients in cohort A and N = 109 patients in cohort C. Results are available on the change from baseline (MMRM analyses, mixed model repeated measures, continuous analysis). In the dossier, the pharmaceutical company only submitted MMRM analyses regarding the EORTC-QLQ-C30 for the separate cohorts (A, B, C). Aggregated data for the non-TCRDT pretreated cohort and data for the TCRDT pretreated cohort were not available in the dossier.

As part of the written statement procedure, the pharmaceutical company subsequently submitted evaluations of the MMRM analyses for the EORTC-QLQ-C30 for the aggregated cohort non-TCRDT pretreated (N = 231) and for the cohort TCRDT pretreated (N = 19), in each case for the last cycle with a return rate of > 70%. For the aggregated non-TCRDT pretreated cohort, the evaluations for cycle 3 day 1 are used here. For the TCRDT pretreated cohort, the pharmaceutical company submitted evaluations for cycle 1 day 1, which corresponds to the time of administration of the first full-dose of talquetamab, which occurs 2-4 days after completion of step-up dosage. The evaluations for cycle 1 day 1 can therefore only show a very short-term change as a result of the step-up dosage and are considered non-interpretable for the assessment of the symptomatology. Therefore, the evaluations for the TCRDT pretreated cohort are not used.

Regardless of this, a comparative assessment of the data on the symptom scales of the EORTC QLQ-C30 is not possible due to the single-arm study design.

Cancer symptomatology (using PGIS)

The endpoint of cancer symptomatology was collected in the MonumenTAL-1 study using the patient-reported instrument PGIS on a five-point scale reflecting the severity of symptoms. In the dossier, the pharmaceutical company submitted only descriptive data for N = 231 patients

of the non-TCRDT pretreated cohort at baseline and at cycle 3 day 1. For cohort TCRDT pretreated, no data were available in the dossier for the cut-off relevant for the benefit assessment.

As part of the written statement procedure, the pharmaceutical company subsequently submitted evaluations of the MMRM analyses of the PGIS for the aggregated data of the non-TCRDT pretreated cohort (N = 231) and for the TCRDT pretreated cohort (N = 19), in each case for the last cycle with a return rate of > 70%. For the aggregated non-TCRDT pretreated cohort, the evaluations for cycle 3 day 1 are used here. For the TCRDT pretreated cohort, the pharmaceutical company submitted evaluations for cycle 1 day 1. Please refer to the comments on the symptom scales of the EORTC-QLQ-C30. The evaluations of the PGIS for cycle 1 day 1 for the TCRDT pretreated cohort are not used.

Regardless of this, a comparative assessment of the data on cancer symptomatology is not possible due to the single-arm study design.

Quality of life

Quality of life was collected in the MonumenTAL-1 study using the EORTC-QLQ-C30 functional scales in N = 122 patients in cohort A and N = 109 patients in cohort C. Results are available on the change from baseline (MMRM analyses). In the dossier, the pharmaceutical company only submitted MMRM analyses of the EORTC QLQ-C30 for the separate cohorts (A, B, C). Aggregated data for the non-TCRDT pretreated cohort and data for the TCRDT pretreated cohort were not available in the dossier.

As part of the written statement procedure, the pharmaceutical company subsequently submitted evaluations of the MMRM analyses of the EORTC QLQ-C30 for the aggregated data of the non-TCRDT pretreated cohort (N = 231) and for the TCRDT pretreated cohort (N = 19), in each case for the last cycle with a return rate of > 70%. For the aggregated non-TCRDT pretreated cohort, the evaluations for cycle 3 day 1 are used here. Please refer to the comments on the symptom scales of the EORTC-QLQ-C30. The evaluations of the functional scales of the EORTC-QLQ-C30 for cycle 1 day 1 for the TCRDT pretreated cohort are not used.

Regardless of this, a comparative assessment of the data on the functional scales of the EORTC QLQ-C30 is not possible due to the single-arm study design.

Side effects

In the MonumenTAL-1 study, at least one adverse event (AE) occurred in all patients in the non-TCRDT pretreated and TCRDT pretreated cohorts. The overall rate of AEs is only presented additionally.

Severe AEs occurred in 77.8% of the non-TCRDT pretreated cohort and 96.8% of the TCRDT pretreated cohort. Blood and lymphatic system disorders were observed most frequently.

Serious AEs occurred in 50.7% of the non-TCRDT pretreated cohort and 61.3% of the TCRDT pretreated cohort. Infections and infestations were observed most frequently.

An AE leading to discontinuation of study medication occurred in 6.6% of the non-TCRDT pretreated cohort and in 6.5% of the TCRDT pretreated cohort.

A comparative assessment of side effects is not possible due to the single-arm study design.

Overall assessment

Data from the label-enabling, single-arm, multicentre phase I/II MonumenTAL-1 study are available for the benefit assessment.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for the MonumenTAL-1 study. However, these data do not allow for a comparative assessment due to the single-arm study design.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on data from the single-arm phase I/II MonumenTAL-1 study.

Due to the single-arm design of this study, a comparative assessment is not possible. The reliability of data is therefore assessed as a hint.

The overall assessment gives a hint for the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Talvey with the active ingredient talquetamab.

Talquetamab received a conditional marketing authorisation as an orphan drug for the treatment of 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.

Data from the label-enabling, single-arm, multicentre phase I/II MonumenTAL-1 study are available for the benefit assessment.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for the MonumenTAL-1 study. However, these data do not allow for a comparative assessment due to the single-arm study design.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

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 resolution is based on the information from the dossier of the pharmaceutical company. These are based on the information in the G-BA's resolution on the benefit assessment of ciltacabtagene autoleucel (resolution of 17 August 2023) and idecabtagene vicleucel (resolution of 16 June 2022) in the same therapeutic indication and are in line with the patient numbers on which the procedure for teclistamab was based (resolution of 15 February 2024). Since the target population is the same, the pharmaceutical company's approach is considered plausible.

The uncertainties identified in connection with the benefit assessments for the active ingredients mentioned continue to exist. Nevertheless, the information provided is the best possible estimate based on the data currently available.

This results in about 1,210 to 1,310 subjects in the SHI target population.

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 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.

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: 1 February 2024).

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

The (daily) doses recommended in the product information were used as the calculation basis.

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 for the maximum treatment duration, if specified in the product information.

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.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Weekly dosage regimen				
Talquetamab step-up phase day 1 (0.01 mg/kg)	Single dose	1	1	1
Talquetamab step-up phase day 3 (0.06 mg/kg)	Single dose	1	1	1
Talquetamab step-up phase day 5 (0.4 mg/kg)	Single dose	1	1	1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Talquetamab treatment phase (0.4 mg/kg)	1 x every 7 days	51.4	1	51.4
Biweekly (every 2 weeks) dosage regimen				
Talquetamab step-up phase day 1 (0.01 mg/kg)	Single dose	1	1	1
Talquetamab step-up phase day 3 (0.06 mg/kg)	Single dose	1	1	1
Talquetamab step-up phase day 5 (0.4 mg/kg)	Single dose	1	1	1
Talquetamab step-up phase day 7 (0.8 mg/kg)	Single dose	1	1	1
Talquetamab treatment phase (0.8 mg/kg)	1 x every 14 days	25.6	1	25.6

Consumption:

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: 77.7 kg).[2]

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

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					
Weekly dosage regimen					
Talquetamab step-up phase day 1	0.01 mg/kg	0.8 mg	1 x 3 mg	1	1 x 3 mg
Talquetamab step-up phase day 3	0.06 mg/kg	4.7 mg	2 x 3 mg	1	2 x 3 mg
Talquetamab step-up phase day 5	0.4 mg/kg	31.1 mg	1 x 40 mg	1	1 x 40 mg
Talquetamab treatment phase	0.4 mg/kg	31.1 mg	1 x 40 mg	51.4	51.4 x 40 mg
Biweekly (every 2 weeks) dosage regimen					
Talquetamab step-up phase day 1	0.01 mg/kg	0.8 mg	1 x 3 mg	1	1 x 3 mg
Talquetamab step-up phase day 3	0.06 mg/kg	4.7 mg	2 x 3 mg	1	2 x 3 mg
Talquetamab step-up phase day 5	0.4 mg/kg	31.1 mg	1 x 40 mg	1	1 x 40 mg
Talquetamab step-up phase day 7	0.8 mg/kg	62.2 mg	2 x 40 mg	1	2 x 40 mg
Talquetamab treatment phase	0.8 mg/kg	62.2 mg	2 x 40 mg	25.6	51.2 x 40 mg

Costs:

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:

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	Packaging size	Costs (pharmacy discount price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Talquetamab 3 mg	1	€ 558.37	€ 2.00	€ 30.29	€ 526.08
Talquetamab 40 mg	1	€ 7,128.99	€ 2.00	€ 403.85	€ 6,723.14

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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.

For talquetamab, a premedication consisting of a corticosteroid, an antihistamine and an antipyretic is administered during the step-up phase prior to each administration of talquetamab in accordance with the product information. The number of treatment days during the step-up phase depends on the dosage regimen of talquetamab in the treatment phase (weekly 0.4 mg/kg or every 2 weeks 0.8 mg/kg).

According to the product information for talquetamab, prophylactic antibiotics should be given in accordance with local guidelines. The product information for talquetamab does not provide any specific information on this, which is why the necessary costs are non-quantifiable.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing

price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: 77.7 kg).[3]

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	Treatment days/ year	Costs/ patient / year
Medicinal product to be assessed							
Premedication prior to each dose of talquetamab during the step-up phase; for talquetamab in the weekly dosage regimen							
Paracetamol (500 – 1 000 mg, p.o.)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	3	€ 2.68 – € 3.01
Dexamethasone (16 mg, IV)	10 AMP at 8 mg	€ 20.38	€ 2.00	€ 0.72	€ 17.66	3	€ 17.66
Dimetindene (1 mg/ 10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.29	€ 16.43	3	€ 32.86
Premedication prior to each dose of talquetamab during the step-up phase; for talquetamab in the biweekly (every 2 weeks) dosage regimen							
Paracetamol (500 – 1 000 mg, p.o.)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	4	€ 2.68 – € 3.01
Dexamethasone (16 mg, IV)	10 AMP at 8 mg	€ 20.38	€ 2.00	€ 0.72	€ 17.66	4	€ 17.66
Dimetindene (1 mg/ 10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.29	€ 16.43	4	€ 32.86

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

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	Treatment days/ year	Costs/ patient / year
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

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Other SHI services:

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 drugs 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 are not added to the pharmacy sales price but rather follow the rules for calculating in the 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 special agreement on contractual unit costs of retail pharmacist services (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:

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.

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

On 14 September 2023, the pharmaceutical company submitted a dossier for the benefit assessment of talquetamab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 December 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 5 January 2024.

The oral hearing was held on 22 January 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 09 February 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 27 February 2024, and the proposed resolution was approved.

At its session on 7 March 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 December 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	17 January 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	22 January 2024	Conduct of the oral hearing
Working group Section 35a	31 January 2024 14 February 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	27 February 2024	Concluding discussion of the draft resolution
Plenum	7 March 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 March 2024

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

Prof. Hecken