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 Ciltacabtagene autoleucel (new therapeutic indication/ reassessment of an orphan drug after exceeding the 30 million euro limit: multiple myeloma, after at least 1 prior therapy, refractory to lenalidomide)

of 15 May 2025

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 all reimbursable medicinal products with new active ingredients. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. 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

Ciltacabtagene autoleucel indicated for the treatment of relapsing/ refractory multiple myeloma 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. Ciltacabtagene autoleucel concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act. Ciltacabtagene autoleucel (Carvykti) was listed for the first time on 15 February 2023 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

At their session on 17 August 2023, the G-BA decided on the benefit assessment of ciltacabtagene autoleucel in the therapeutic indication "CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy" in accordance with Section 35a SGB V. The resolution was limited to 1 July 2026 in order to carry out a new benefit assessment after expiry of the deadline, taking into account significant results from the CARTITUDE-4 study on all patient-relevant endpoints.

On 19 April 2024, ciltacabtagene autoleucel received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7). Ciltacabtagene autoleucel (Carvykti) has since been approved for the treatment of adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

With the marketing authorisation of the new therapeutic indication granted on 1 June 2024, the pharmaceutical company submitted the dossier to the G-BA for benefit assessment of an orphan drug in accordance with Section 35a, paragraph 1, sentence 11 SGB V on time. In addition to information on the new therapeutic indication, the dossier also contained information on the therapeutic indication, which was subject to benefit assessment and the limitation.

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 Chapter 5 Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the G-BA, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 13 June 2024, the pharmaceutical company informed the G-BA that the medicinal product Carvykti had exceeded the turnover limit of 30 million euros in the first quarter of 2024.

By letter dated 21 June 2024, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 December 2024, due to exceeding the € 30 million limit. Based on the information provided by the pharmaceutical company in the letter dated 13 June 2024, the G-BA assumes that the € 30 million limit was exceeded within the period from April 2023 up to and including March 2024 at the latest.

By resolution of 18 July 2024, the orphan drug procedure, which was started with the granting of the marketing authorisation of the new therapeutic indication in accordance with Section 35a, paragraph 1, sentence 11 SGB V, was temporarily suspended.

Due to exceeding the € 30 million limit, the pharmaceutical company has submitted the dossier on the following therapeutic indication to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO in due time on 27 November 2024:

"Carvykti is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide".

The present procedure due to the exceeding of the 30 million euro limit thus relates to the entire approved therapeutic indication of Carvykti, which is why the initial resolution of 17 August 2023 is repealed by the present resolution on the benefit assessment of ciltacabtagene autoleucel, thus also invalidating the limitation of the period of validity of the initial resolution.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 March 2025 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 ciltacabtagene autoleucel 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 ciltacabtagene autoleucel.

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 Ciltacabtagene autoleucel (Carvykti) in accordance with the product information

Carvykti is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

Therapeutic indication of the resolution (resolution of 15.05.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

a) Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

Appropriate comparator therapy for ciltacabtagene autoleucel:

An individualised therapy with selection of

- daratumumab in combination with bortezomib and dexamethasone,
- daratumumab in combination with carfilzomib and dexamethasone,
- daratumumab in combination with pomalidomide and dexamethasone (DPd),
- isatuximab in combination with carfilzomib and dexamethasone,
- isatuximab in combination with pomalidomide and dexamethasone (only for subjects with at least two prior therapies),
- elotuzumab in combination with pomalidomide and dexamethasone (only for subjects with at least two prior therapies),
- pomalidomide in combination with bortezomib and dexamethasone (PVd, only for subjects who are refractory to an anti-CD38 antibody),
- pomalidomide in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies),
- carfilzomib in combination with dexamethasone,
- panobinostat in combination with bortezomib and dexamethasone (only for subjects who have received at least four prior therapies),
- bortezomib in combination with pegylated liposomal doxorubicin (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies),
- bortezomib in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies),
- daratumumab monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies),
- cyclophosphamide as monotherapy or in combination with dexamethasone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies),

- melphalan as monotherapy or in combination with prednisolone or prednisone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies),
- high-dose therapy with autologous stem cell transplant (only for subjects who have undergone prior therapy and are eligible for an autologous stem cell transplant; after achieving remission)

  and

- high-dose therapy with allogeneic stem cell transplant[2] (only for subjects who have undergone prior therapy and are eligible for an allogeneic stem cell transplant; after achieving remission).

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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

[2] The regulations of the G-BA apply in accordance with Section 136b, paragraph 1, sentence 1, number 2 SGB V for hospitals approved in accordance with Section 108 SGB V (minimum quantity regulations, MQR).

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. The following active ingredients are approved in the therapeutic indication of relapsed/ refractory multiple myeloma:

bortezomib, carfilzomib, carmustine, ciltacabtagene autoleucel, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, elranatamab, idecabtagene vicleucel, isatuximab, ixazomib, lenalidomide, melphalan, melphalan flufenamide, panobinostat, pomalidomide, prednisolone, prednisone, selinexor, teclistamab, talquetamab and vincristine

The marketing authorisations are in part linked to (specific) concomitant active ingredients and to the type of the prior therapy.

On 2. In the therapeutic indication of relapsed/ refractory multiple myeloma, autologous and allogeneic stem cell transplants are generally considered as non-medicinal treatment options.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Elranatamab – resolution of 4 July 2024
- Talquetamab – resolution of 7 March 2024
- Teclistamab – resolution of 15 February 2024
- Ciltacabtagene autoleucel – resolution of 17 August 2023
- Selinexor – resolution of 16 March 2023
- Melphalan flufenamide – resolution of 16 March 2023
- Idecabtagene vicleucel - resolution of 16 June 2022 and 19 September 2024, amended by the resolution of 19 December 2024
- Carfilzomib – resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolutions of 15 February 2018, 3 February 2022 and 15 September 2022
- Elotuzumab – resolutions of 1 December 2016 and 16 December 2021
- Isatuximab – resolutions of 4 November 2021
- Ixazomib – resolution of 21 April 2022
- Panobinostat – resolution of 17 March 2016

- Pomalidomide – resolutions of 17 March 2016 and 5 December 2019

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

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. A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available.

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

National and international guidelines as well as the scientific-medical societies generally refer to an individualised therapy which is influenced by various factors. According to the S3 guideline, the active ingredients and combinations of active ingredients used in prior therapies as well as the type and duration of the response to the respective prior therapies play a key role in the choice of therapy. Particularly among heavily pretreated patients with at least four prior therapies, the general condition is also relevant for the selection of the most suitable patient-individual therapy option.

The treatment decision on individualised therapy is therefore made taking into account the patient's general condition, the active ingredients and combinations of active ingredients used in prior therapies, the type and duration of the response to the respective prior therapies and the suitability for a stem cell transplant.

One criterion for individualised therapy is the duration of the response to the prior therapy. If the disease progresses under the respective prior therapy or if the duration of response after completion of the respective prior therapy is less than 12 months, it will not be considered again in the further course of treatment in accordance with the generally recognised state of medical knowledge. Accordingly, this therapy using the specific active ingredients or combinations of active ingredients in the further course of treatment may again be a suitable treatment option for relapsed patients in whom a response in the form of a complete remission (CR), a very good partial response (VGPR) and a partial response (PR) of more than 12 months after the end of therapy was achieved with a specific previous therapy.

The therapy recommendations of the S3 guideline differentiate between the treatment setting of the first to third recurrence and from the fourth recurrence onwards. This is due to the heterogeneous patient population in the advanced lines of therapy, for whom the substances used in the earlier lines of therapy are increasingly no longer an option and who therefore have a poorer prognosis.

On patients with one to three prior therapies

With regard to the relapsed/ refractory disease situation after one to three prior therapies, the S3 guideline initially states that a triplet therapy with two new substances (monoclonal antibody, immunomodulatory agent, proteasome inhibitor) and a steroid should be used for patients. Furthermore, with reference to the respective approved therapeutic indications of the active ingredients, the guideline on the therapy of the 1st to 3rd relapse states that regarding each combination therapy all product classes can be generally used and combined in individual order. This is also done against the background that the therapeutic benefit of triplet therapies over doublet therapies is offset by increased therapy toxicity, meaning that they are unsuitable for all patients.

On approved triplet therapies in the individualised therapy

According to the explanations in the S3 guideline, all approved triplet therapies with two new substances and a steroid can be considered. Accordingly, the triplet therapies elotuzumab in combination with pomalidomide and dexamethasone, daratumumab in combination with bortezomib and dexamethasone, daratumumab in combination with carfilzomib and dexamethasone, daratumumab in combination with pomalidomide and dexamethasone, isatuximab in combination with carfilzomib and dexamethasone, isatuximab in combination with pomalidomide and dexamethasone, pomalidomide in combination with bortezomib and dexamethasone as well as panobinostat in combination with bortezomib and dexamethasone were included in the individualised therapy of the appropriate comparator therapy.

The therapy option "pomalidomide in combination with bortezomib and dexamethasone (PVd) (only for subjects who are refractory to an anti-CD38 antibody and lenalidomide)" is restricted to patients with a specific refractoriness to the active ingredients or combinations of active ingredients used in the previous treatments.

The suitability of patients for the use of PVd as part of individualised therapy must be demonstrated based on the type and duration of response to the respective prior therapies in accordance with the specified limitations.

Panobinostat in combination with bortezomib and dexamethasone is approved for the treatment of adults with relapsed and refractory multiple myeloma who have received at least two prior therapies. The restriction to adults who have received at least four prior therapies is due to the following reasons:

By resolution of 17 March 2016, a non-quantifiable additional benefit of panobinostat in combination with bortezomib and dexamethasone was identified in the orphan benefit assessment procedure. This is based on the results of the approval study PANORAMA-1, which show no difference in overall survival compared to bortezomib and dexamethasone, but an increase in relevant side effects. The statements made by the clinical experts at the oral hearing on panobinostat showed accordingly that these intensified side effects are to be considered significant and can only be partially influenced by therapy.[3]

With regard to the significance of panobinostat in combination with bortezomib and dexamethasone, meta-analyses available from the systematic evidence search indicate a higher significance of the other triplet therapies in patients in earlier lines of therapy.[4]

Doublet therapy in individualised therapy

[3] Benefit assessment procedure of the G-BA for the active ingredient panobinostat, resolution of 17 March 2016

[4] Noori et al. Safety and efficacy of elotuzumab combination therapy for patients with multiple myeloma: a systematic review and meta-analysis. Expert Rev Anticancer Ther 2023;23(3):327-338.

In addition to the triplet therapies, the dual combination of carfilzomib and dexamethasone is also determined as an appropriate comparator therapy as part of the individualised therapy. By G-BA resolution of 15 February 2018, a hint for a considerable additional benefit of this combination therapy compared to bortezomib in combination with dexamethasone was identified in the benefit assessment for adults after at least one prior therapy.

Stem cell transplant

Ciltacabtagene autoleucel is a therapeutic approach of a CAR-T cell therapy, so it can be assumed that patients may also be eligible for a stem cell transplant after prior therapy at the time of treatment with ciltacabtagene autoleucel. For patients who have undergone at least two prior therapies, high-dose therapy with stem cell transplant is only an option for a very small percentage of patients. Therefore, when determining the appropriate comparator therapy, it is assumed that high-dose therapy with stem cell transplant is generally not an option for patients who have received at least two previous lines of therapy at the time of treatment with ciltacabtagene autoleucel.

Stem cell transplant remains a relevant treatment option for patients who have undergone prior therapy. Autologous stem cell transplant should be offered to all patients who are eligible for transplantation but have not undergone transplantation as part of first-line therapy. In addition, an autologous re-transplantation can be performed if the progression-free survival after the first transplantation generally lasted at least 18 months.

Allogeneic stem cell transplant is a treatment option for patients with primary refractoriness and early relapse after autologous stem cell transplant.

The available guidelines do not contain any specific recommendations on the regular use of maintenance treatment after autologous stem cell transplant beyond first-line therapy. In addition, lenalidomide is only approved as maintenance treatment for adults with newly diagnosed disease following autologous stem cell transplant and this patient population is refractory to lenalidomide. Therefore, maintenance treatment following autologous stem cell transplantation is not considered part of the appropriate comparator therapy.

On patients with at least four prior therapies

According to the S3 guideline, all therapy options suitable for the treatment of patients who have undergone three prior therapies can be considered for patients who have undergone at least four prior therapies.

For patients who have undergone at least four prior therapies, it is assumed for the determination of the appropriate comparator therapy that this patient group will generally continue to receive antineoplastic treatment in the present therapeutic indication. Best supportive care is therefore not considered an appropriate comparator therapy.

On approved triplet therapies in the individualised therapy

In accordance with the S3 guideline, patients with at least four prior therapies should also first be assessed to determine whether triplet therapy is appropriate and possible based on the status of the prior therapies. This means that patients who have undergone at least four prior therapies are also eligible for all approved triplet therapies that have already been named among the approved triplet therapies for patients who have undergone one to three prior therapies as part of individualised therapy (see above).

Other approved therapy options in individualised therapy

In addition, the S3 guideline for patients who have undergone at least four prior therapies also refers to doublet therapies, classic cytostatic agents, bispecific antibodies and CAR-T cell therapies.

In addition to the triplet therapies, the dual combination of carfilzomib and dexamethasone is also determined as an appropriate comparator therapy as part of the individualised therapy.

For at least double-refractory patients who are ineligible for triplet therapy, the dual combinations of pomalidomide in combination with dexamethasone, bortezomib in combination with pegylated liposomal doxorubicin and bortezomib in combination with dexamethasone can also be considered.

For at least triple refractory subjects who are ineligible for triplet or doublet therapy, daratumumab, cyclophosphamide and melphalan, each as monotherapy, as well as cyclophosphamide in combination with dexamethasone and melphalan in combination with prednisone or prednisolone, are also suitable comparators as part of individualised therapy.

Ineligibility for triplet or doublet therapy should be justified on the basis of the patients' refractoriness and comorbidity and taking into account the toxicity of the respective therapy.

On the approved active ingredients that were not determined as appropriate comparator therapy in the context of individualised therapy:

Among the approved active ingredients that have not been determined as appropriate comparator therapy as part of individualised therapy in the present determination of the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, guideline recommendations and the reality of care:

The CAR-T cell therapies idecabtagene vicleucel is approved for the treatment of patients who have undergone at least two prior therapies.

By resolution of the G-BA on the benefit assessment according to Section 35a SGB V, it was determined that an additional benefit of idecabtagene vicleucel is not proven.

The active ingredient selinexor is approved for the treatment setting after at least one prior therapy in combination with bortezomib and dexamethasone. For this combination therapy,

it was determined by resolution of 16 March 2023 that an additional benefit compared to the appropriate comparator therapy is not proven.

Melphalan flufenamide is a therapy option for the treatment of subjects with at least three prior therapies. For melphalan flufenamide, the G-BA determined by resolution of 16 March 2023 that an additional benefit is not proven, as no suitable data were available to enable an assessment of the additional benefit.

Teclistamab is a therapy option for the treatment of subjects with at least three prior therapies. By resolution of 15 February 2024, it was determined that an additional benefit of teclistamab is not proven, as no data were available to enable the assessment of an additional benefit.

Talquetamab is a therapy option for the treatment of subjects who have undergone at least three prior therapies. As part of a benefit assessment for medicinal products for the treatment of a rare disease, the G-BA resolution of 7 March 2024 identified a hint for a non-quantifiable additional benefit of talquetamab since the scientific data did not allow quantification.

The active ingredient elranatamab is approved for the treatment setting after at least three prior therapies. For this monotherapy, it was determined by resolution of 4 July 2024 that an additional benefit compared to the appropriate comparator therapy is not proven.

In the benefit assessment of the resolution of 16 March 2023, it was identified that an additional benefit of the combination of active ingredients selinexor in combination with dexamethasone compared to the appropriate comparator therapy is not proven.

Monotherapy with bortezomib is no longer recommended as a therapeutic alternative in relevant guidelines due to its proven inferiority in terms of overall survival and is therefore not considered an appropriate comparator therapy.

The use of older chemotherapeutic agents, such as doxorubicin monotherapy, is of secondary importance according to the S3 guideline and is therefore not considered to be appropriate comparator therapy.

Overall, for adults with relapsed and refractory multiple myeloma who have received at least one prior therapy, , have demonstrated disease progression on the last therapy, were refractory to lenalidomide and have received pretreatment with an immunomodulator and a proteasome inhibitor, an individualised therapy is determined as the appropriate comparator therapy by selecting the above-mentioned active ingredients and combinations of active ingredients and taking into account the general condition, the active ingredients and combinations of active ingredients used in the prior therapies and the type and duration of the response to the respective therapies.

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

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 ciltacabtagene autoleucel is assessed as follows:

a) Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

a1) Adults with relapsed and refractory multiple myeloma, who have received one to three prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

Hint for a considerable additional benefit

a2) Adults with relapsed and refractory multiple myeloma, who have received at least four prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

An additional benefit is not proven.

Justification:

The pharmaceutical company presented the results of the pivotal phase III CARTITUDE-4 study for the benefit assessment of ciltacabtagene autoleucel for the treatment of adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

The ongoing CARTITUDE-4 study is an open-label, randomised controlled trial comparing ciltacabtagene autoleucel versus PVd or DPd in patients with multiple myeloma who have received one to three prior therapies, including an immunomodulatory agent and a proteasome inhibitor, and are refractory to lenalidomide. In addition, the patients had disease progression during or within six months of the last therapy. Patients with more than three prior therapies were not enrolled.

In the intervention arm of the CARTITUDE-4 study, all patients received at least one cycle of bridge therapy (PVd or DPd, depending on previous myeloma therapy) after leukapheresis, followed by conditioning therapy for lymphocyte depletion and ciltacabtagene autoleucel infusion.

The primary endpoint of the CARTITUDE-4 study is progression-free survival (PFS). Other endpoints include overall survival, complete response as well as stringent complete response, overall response, MRD negativity as well as adverse events and quality of life.

The CARTITUDE-4 study has been conducted since June 2020 at a total of 81 study sites in Europe, Asia, USA and Australia. The planned end of the study is after the occurrence of approximately 250 deaths within the total population.

A total of 419 subjects were enrolled in the study (ITT population) and randomised in a 1:1 ratio to either treatment with ciltacabtagene autoleucel (N = 208) or a comparator therapy

with a choice of DPd or PVd (DPd n = 183 or PVd n = 28; total N = 211). Stratification was done according to treatment choice (DPd vs PVd), International Staging System (ISS) stage (I vs II vs III) and number of previous myeloma therapies (1 vs 2 or 3). Evaluations of the fourth, pre-specified data cut-off from 1 May 2024 were presented, which represents the final pre-specified analysis for PFS and the pre-specified second interim analysis for overall survival after 250 PFS events. The mean age was 60 years in both study arms.

In the written statement procedure, the pharmaceutical company submitted sensitivity analyses on the endpoint category of side effects and on patient-reported outcomes (PROs) in the endpoint categories of morbidity and health-related quality of life.

In addition, the pharmaceutical company presented an indirect comparison of the CARTITUDE-1 and LocoMMotion studies in the written statement procedure, in which the patient population was tailored to at least four prior therapies and lenalidomide refractoriness, among other things. At the oral hearing, the pharmaceutical company stated that these evaluations should be regarded as supplementary sensitivity analyses, but that the CARTITUDE-4 study should be used for the benefit assessment for the entire therapeutic indication. For this reason, the indirect comparison of the CARTITUDE-1 and LocoMMotion studies is not considered in the present benefit assessment.

Implementation of the appropriate comparator therapy:

The two therapy options (PVd and DPd) offered for the comparator arm of the study are included in the individualised therapy determined as the appropriate comparator therapy and represent relevant therapy options in this therapeutic indication. In the written statement procedure, the clinical experts also emphasised that the two options enable an individualised treatment decision to be made, depending on the risk or presence of the main comorbidity (polyneuropathy). The rationale for the use of DPd and PVd in the study was the high percentage of lenalidomide-refractory patients in their approval studies, analogous to the condition of lenalidomide refractoriness in the therapeutic indication of ciltacabtagene autoleucel.

It is assumed that the majority of patients enrolled in the CARTITUDE-4 study received adequate individualised therapy in line with the appropriate comparator therapy. However, uncertainties remain because statements on the additional benefit of ciltacabtagene autoleucel based on the results of the CARTITUDE-4 study can only be made for patients in this therapeutic indication for whom treatment with DPd or PVd represents the optimum individualised therapy.

However, this uncertainty is not considered to be so high that the reliability of data of the available results from the study should be regarded as limited. Therefore, there are no implications for the present benefit assessment.

On bridge therapy:

According to the product information, bridge therapy should be considered before administering ciltacabtagene autoleucel according to the physician's estimate. In the CARTITUDE-4 study, all patients underwent bridge therapy. At the oral hearing, the clinical experts stated that bridge therapy prior to administration of ciltacabtagene autoleucel should be regarded as a standard procedure that all patients receive. Therefore, no uncertainties are derived from this for the present benefit assessment.

Limitation of the data basis:

Since patients with one to three prior therapies were enrolled in the CARTITUDE-4 study, no data are available for the assessment of the additional benefit of ciltacabtagene autoleucel compared with the appropriate comparator therapy for patients who have already received at least four prior therapies. For this reason, the assessment is carried out separately for two patient groups, according to the number of prior therapies.

Extent and probability of the additional benefit

a1) Adults with relapsed and refractory multiple myeloma, who have received one to three prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

Mortality

Overall survival was operationalised in the CARTITUDE-4 study as the time between randomisation and the date of death from any cause.

The corresponding Kaplan-Meier curves show an intersecting course. In the first 12 months, the intervention arm shows an initially stronger drop in the Kaplan-Meier curve than the control arm. After about 12 months, the Kaplan-Meier curves intersect, with the curve of the intervention arm lying above that of the control arm in the further course of the observation period.

According to the European regulatory authority's European Public Assessment Report (EPAR) of 22 February 2024, the patients in the intervention arm died in the early phase of the study (up to study month 3) prior to ciltacabtagene autoleucel infusion. No subgroup with a higher risk of early death could be identified. The clinical experts emphasised the relevance and diligent monitoring of patients during bridge therapy in the written statement procedure.

Overall, there was a statistically significant difference in favour of ciltacabtagene autoleucel compared to DPd or PVd. Overall, the statistically significant advantage is considered to be a clear prolongation of survival time.

Morbidity

Progression-free survival (PFS)

Progression-free survival is the primary endpoint of the CARTITUDE-4 study and is operationalised as the time between randomisation and the date of first documented disease progression according to International Myeloma Working Group (IMWG) criteria, or death from any cause, whichever occurs earlier.

There was a statistically significant difference in favour of ciltacabtagene autoleucel compared to DPd or PVd.

The PFS endpoint is a composite endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is 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. The overall statement on the additional benefit in the present assessment remains unaffected.

EORTC QLQ-C30 - symptom scales

In the CARTITUDE-4 study, disease symptomatology is assessed using the cancer-specific EORTC-QLQ-C30 questionnaire. In the dossier, the pharmaceutical company presented responder analyses for the time to first or confirmed deterioration and improvement by ≥ MCID (Minimal Clinically Important Difference) 10 points, as well as continuous evaluations using a mixed model for repeated measures (MMRM) for the change from baseline.

Due to the expected progressive course of the disease in multiple myeloma, an analysis of the deterioration of symptomatology is primarily relevant for the present benefit assessment.

No fair comparison of the therapeutic concepts in the treatment arms is possible in the evaluations of the PROs. This is explained below:

The first assessment of the PROs in the intervention arm was conducted within 72 h before leukapheresis (3 to 6 days after randomisation). Subsequently, PROs were assessed in the intervention arm on day 1 of the first cycle of bridge therapy (no later than 7 days after randomisation), as well as on day 1 of chemotherapy for lymphocyte depletion and on day 28 after ciltacabtagene autoleucel infusion.

With this assessment structure, no PROs were assessed in the intervention arm during bridge therapy (median for 2.6 months), and in the period between chemotherapy for lymphocyte depletion and 28 days after CAR T-cell infusion (there was no assessment on the day of CAR T-cell infusion, a total of approx. 5 weeks without assessment). However, these therapy phases are inherent parts of the therapeutic concept in the intervention arm, in which patients are exposed to high levels of burden. Due to this assessment scheme, the results of the CARTITUDE-4 study on the patient-reported outcomes cannot be meaningfully interpreted.

In the control arm, PROs were assessed continuously and more frequently from the start of treatment than in the intervention arm, meaning that potential effects on the patients could have been assessed earlier or more clearly, whereas in the intervention arm an event could only occur later due to the less frequent assessments. This means that there are assessments in the comparator arm that have no counterpart in the intervention arm. Due to the different assessment density in the intervention and control arms during the initial phase of the CARTITUDE-4 study, no fair comparison between the study arms can be made on the basis of the responder analyses presented in the dossier, taking into account all assessments in both study arms.

In contrast, the MMRM analyses presented in the dossier take into account only survey time points in the two study arms that can be assigned to each other over time, but the percentage of patients included in these evaluations differs significantly between the study arms. In addition to the shortcomings already described above, the continuous evaluations are therefore not suitable for the benefit assessment due to highly differentiated return rates.

In the written statement procedure, the pharmaceutical company submitted sensitivity analyses in which individual assessments in both study arms were excluded from the responder analyses, resulting in a comparable assessment density. In addition, the pharmaceutical company submitted MMRM analyses as sensitivity analyses in the written statement procedure, in which all survey time points of the study are included.

However, the sensitivity analyses (responder analyses) presented do not overcome the limitation that PROs were not assessed during relevant phases of the intervention therapeutic concept. Relevant therapy phases are now not included in either study arm.

Assuming an adequate assessment structure, MMRM analyses in certain data situations appear to be a suitable methodological approach for different therapeutic concepts such as single therapy with CAR-T cells compared to continuous therapy in cycles. The subsequently submitted MMRM analyses are not suitable for the benefit assessment due to the lack of an adequate assessment structure in the present case.

Overall, the responder analyses submitted by the pharmaceutical company (time to first/ first confirmed improvement/ deterioration) and the continuous analyses from the statement of the pharmaceutical company are not suitable for the benefit assessment.

In summary, the results on disease symptomatology (EORTC-QLQ-C30) cannot be interpreted meaningfully for the reasons mentioned and therefore cannot be used for the benefit assessment.

Cancer symptomatology (PGIS)

The endpoint of cancer symptomatology was collected in the CARTITUDE-4 study using the patient-reported instrument PGIS on a five-point scale reflecting the severity of symptoms. In the dossier, the pharmaceutical company submitted responder analyses for the time to first or confirmed deterioration and improvement ≥ threshold value of 1 point.

Please refer to the comments on the symptom scales of the EORTC QLQ-C30 with regard to the limitations of the survey time points. In the written statement procedure, corresponding sensitivity analyses for the PGIS were subsequently submitted by the pharmaceutical company.

Due to the limitations of the survey time points for the PROs explained in the section "EORTC QLQ-C30 - Symptom scales", the evaluations of the PGIS are not used for the benefit assessment.

Health status (EQ-5D VAS)

In the CARTITUDE-4 study, health status is assessed using the visual analogue scale (VAS) of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D) and presented in the dossier as responder analyses for the time to first or confirmed deterioration and improvement, as well as continuous evaluations using MMRM for the change from baseline.

Please refer to the comments on the symptom scales of the EORTC QLQ-C30 with regard to the limitations of the survey time points. In the written statement procedure, corresponding sensitivity analyses for the health status were subsequently submitted by the pharmaceutical company.

Due to the limitations of the survey time points for the PROs explained in the section "EORTC QLQ-C30 - Symptom scales", the evaluations of the health status (EQ-5D VAS) are not used for the benefit assessment.

Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) - Total symptom score

The Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) developed by the pharmaceutical company is used in the CARTITUDE-4 study to collect symptoms of multiple myeloma. In the dossier, the pharmaceutical company presented evaluations of the total symptom score, which summarises the results of the items on symptomatology. In the dossier, the pharmaceutical company presented the results for the time to first or confirmed deterioration and improvement by ≥ threshold value of 15 points, as well as continuous evaluations using MMRM on the change from baseline.

It could not be deduced from the information presented that the MySIm-Q can be used as a valid instrument for collecting symptoms and impairments in patients with multiple myeloma. Irrespective of this, there are limitations with regard to the survey time points in the study (see comments on the symptom scales of the EORTC QLQ-C30).

In the written statement procedure, the pharmaceutical company submitted data on the validity of the questionnaire, confirming that the MySIm-Q is a valid survey instrument. In addition, sensitivity analyses that addressed the limitations of the survey time points (see comments on the symptom scales of the EORTC QLQ-C30) were submitted.

Due to the limitations of the survey time points for the PROs explained in the section "EORTC QLQ-C30 - Symptom scales", the evaluations of the MySIm-Q total symptom score are not used for the benefit assessment.

Quality of life

EORTC QLQ-C30 - Functional scales

In the CARTITUDE-4 study, health-related quality of life is assessed using the functional scales of the cancer-specific EORTC-QLQ-C30 questionnaire. In the dossier, the pharmaceutical company presented responder analyses for the time to first or confirmed deterioration or improvement by ≥10 points MCID, as well as continuous evaluations using MMRM for the change from baseline.

Due to the expected progressive course of the disease in multiple myeloma, an analysis of the deterioration of health-related quality of life is primarily relevant for the present benefit assessment.

Please refer to the comments on the symptom scales of the EORTC QLQ-C30 with regard to the limitations of the survey time points. In the written statement procedure, corresponding sensitivity analyses for the EORTC QLQ-C30 functional scales were subsequently submitted by the pharmaceutical company.

Due to the limitations of the survey time points for the PROs explained in the section "EORTC QLQ-C30 - Symptom scales", the evaluations of the EORTC QLQ-C30 functional scales are not used for the benefit assessment.

Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) - Total impact score

In the CARTITUDE-4 study, the MySIm-Q questionnaire developed by the pharmaceutical company was used to collect impairments caused by symptomatology.

In the dossier, the pharmaceutical company presented evaluations of the total impact score, which summarises the results of the items on impairment. In the dossier, the pharmaceutical company presented the results for the time to first or confirmed deterioration and

improvement by ≥ threshold value of 15 points, as well as continuous evaluations using MMRM on the change from baseline.

Please refer to the comments on the EORTC QLQ-C30 symptom scales with regard to the limitations of the survey time points and to the comments on the MySIm-Q total symptom score with regard to validity.

In the written statement procedure, the pharmaceutical company submitted data on the validity of the questionnaire, as well as sensitivity analyses that addressed the limitations of the survey time points (see comments on the EORTC QLQ-C30 symptom scales).

Due to the limitations of the survey time points for the PROs explained in the section "EORTC QLQ-C30 - Symptom scales", the evaluations of the MySIm-Q total symptom score are not used for the benefit assessment.

Side effects

Cross-endpoint note

In the CARTITUDE-4 study, adverse events (AEs), the serious AEs based on them (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), serious adverse events (SAEs) and AEs of special interest are collected for patients in full at different lengths of time between the two treatment arms. In IQWiG's benefit assessment, there were uncertainties as to the time period over which all events were fully collected and which time periods were considered in the evaluations presented. In both treatment arms, the evaluations also included AEs, SAEs and severe AEs that were collected after the end of the complete survey if the principal investigator suspected a causal relationship with the study medication.

Due to this limitation, only the endpoints "discontinuation due to AEs" and severe AEs (CTCAE grade ≥ 3) were used for IQWiG's benefit assessment.

In addition, treatment with ciltacabtagene autoleucel was considered a subsequent therapy in the dossier if patients experienced disease progression on bridge therapy. This approach was considered inappropriate. Rather, it is assumed that in the intervention arm, treatment with ciltacabtagene autoleucel will also be given in the event of disease progression under the bridge therapy as part of the current line of therapy and therefore does not represent a subsequent therapy.

In the written statement procedure, the pharmaceutical company submitted information and sensitivity analyses that largely clarified the uncertainties addressed in IQWiG's benefit assessment. Specifically, information was provided on the time up to which all events in the side effects category were fully observed. In addition, two sensitivity analyses in which different survey time periods are taken into account were subsequently submitted. Sensitivity analysis 1 includes the AEs per endpoint up to the maximum duration of observation in which all events were collected for the individual patients. For sensitivity analysis 2, in addition to the maximum observation periods with complete collection of all events, the start of a subsequent therapy is taken into account, depending on which occurs first.

The evaluations of sensitivity analysis 1 are used for the benefit assessment.

In both sensitivity analyses, treatment with ciltacabtagene autoleucel is also evaluated as part of the current line of therapy and not as subsequent therapy if disease progression on bridge therapy occurred in the intervention arm. This approach is rated as appropriate.

Adverse events (AEs)

One AE occurred in all study participants. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and discontinuation due to AEs

No statistically significant differences between the treatment arms were found for SAEs, severe AEs and therapy discontinuation due to AEs in the CARTITUDE-4 study.

PRO-CTCAE

In the dossier, the pharmaceutical company presented evaluations of patient-reported collection of side effects using the PRO-CTCAE. Please refer to the comments on the symptom scales of the EORTC QLQ-C30 with regard to the limitations of the survey time points.

In addition, it is unclear whether the pre-specified selection of AEs frequently anticipated in multiple myeloma ensures collection of all important potential AEs of the active ingredients used in the intervention and control arms.

According to information provided by the pharmaceutical company, the selection of the pre-specified items was not systematic, which is why these evaluations are only presented additionally in the dossier.

Due to the limitations of the survey time points for the PROs explained in the section "EORTC QLQ-C30 - Symptom scales" and the non-systematic selection of the pre-specified items, the evaluations of the PRO-CTCAE were not used for the benefit assessment.

Specific AEs

In the dossier, the pharmaceutical company presented evaluations for the AEs of special interest cytokine release syndrome, neurotoxicity and secondary malignancies. In accordance with the above-mentioned "Cross-endpoint note", there were uncertainties regarding the period of the complete survey. These overarching uncertainties were largely clarified by the pharmaceutical company's statement.

Nevertheless, the AEs of special interest mentioned above are still not suitable for the benefit assessment, as it remains unclear to what extent they are systematically collected on the basis of a pre-specified list.

In addition, the evaluation of AEs of special interest cytokine release syndrome and neurotoxicity was only planned from the time of infusion and exclusively for the intervention arm. In addition, the underlying symptoms (e.g. rigors) were not documented separately for the cytokine release syndrome. In contrast, infusion-related reactions (especially under DPd) were not specifically collected as a specific AE, but the underlying symptoms were collected via the individual PTs, e.g. in PT rigors. Due to the difference in data collection between the intervention and comparator arms, it is not possible to make any statements regarding the endpoints cytokine release syndrome and infusion-related reactions. The data for cytokine release syndrome and infusion-related reactions are not suitable for the present benefit assessment.

In addition to the lack of clarity regarding the systematic collection, the results of the secondary malignancies are not suitable for the present benefit assessment, as the duration of observation to date is insufficient.

Neurotoxicity was used as severe neurological toxicity (SAEs of the SOC Nervous system disorders) in the present benefit assessment on the basis of the evaluations subsequently submitted by the pharmaceutical company in the written statement procedure. From the evaluations subsequently submitted by the pharmaceutical company in the written statement procedure, severe infections are used as AEs of SOC Infections and infestations as specific AEs in the present benefit assessment.

The specific AEs listed below were systematically collected, therefore the sensitivity analysis 1 subsequently submitted in the written statement procedure was used in the present benefit assessment.

There was no statistically significant difference between the study arms for the specific AE of severe infections (SAE, SOC Infections and infestations).

There was a significant difference in favour of ciltacabtagene autoleucel for the specific AE of insomnia (PT, AEs).

There were significant differences to the disadvantage of ciltacabtagene autoleucel in each of the following specific AEs: severe neurological toxicity (SAE, SOC Nervous system disorders), headache (PT, AEs), thrombocytopenia (PT, severe AEs, CTCAE grade 3 or 4), anaemia (PT, severe AEs, CTCAE grade 3 or 4), lymphopenia (PT, severe AEs, CTCAE grade 3 or 4), leucopenia (PT, severe AEs, CTCAE grade 3 or 4), metabolism and nutrition disorders (SOC, severe AEs, CTCAE grade 3 or 4), hypogammaglobulinaemia (PT, severe AEs, CTCAE grade 3 or 4).

Effect modifications:

For the specific AE of anaemia (severe AEs), there was an effect modification by the sex characteristic: There was a statistically significant difference to the disadvantage of ciltacabtagene autoleucel for both women and men. However, the extent of the effect differs, and the effect is more pronounced in women.

There was an effect modification by age for the specific AE of metabolism and nutrition disorders (SOC, severe AEs, CTCAE grade 3 or 4). From an age ≥65 years, there was a statistically significant difference to the disadvantage of ciltacabtagene autoleucel. At an age <65 years, there was no significant difference between the study arms.

Conclusion on side effects

In the overall assessment, there were no statistically significant differences between the treatment arms in the endpoint category of side effects for SAEs, severe AEs, and discontinuations due to AEs. In detail, the specific AEs predominantly show disadvantages of ciltacabtagene autoleucel.

Since these disadvantages are not reflected in the overall rates of AEs, SAEs and severe AEs, these differences do not lead to a change in the assessment of additional benefit. Therefore, neither an advantage nor a disadvantage is derived for the endpoint category of side effects overall.

<u>Overall assessment</u>

For the assessment of the additional benefit of ciltacabtagene autoleucel for the treatment of adults with relapsed and refractory multiple myeloma who have previously received one to three therapies, including an immunomodulator and a proteasome inhibitor, who demonstrated disease progression on the last therapy and are refractory to lenalidomide, results are available for the endpoint categories of mortality, morbidity, quality of life and side effects from the CARTITUDE-4 study for comparing ciltacabtagene autoleucel versus DPd or PVd.

For overall survival, there was a statistically significant difference to the advantage of the ciltacabtagene autoleucel, the overall extent of which is assessed as a clear prolongation of survival.

With regard to morbidity, health-related quality of life and side effects, no suitable data are available based on the patient-reported outcomes (EORTC QLQ-C30, PGIS, EQ-5D VAS, MySIm-Q and PRO-CTCAE), as the PROs were not collected in relevant phases of the CAR-T cell therapeutic concept.

There were no significant differences between the treatment arms in terms of side effects for SAEs, severe AEs and discontinuation due to AEs respectively. In detail, the specific AEs predominantly show disadvantages of ciltacabtagene autoleucel.

Overall, neither an advantage nor a disadvantage is derived for the endpoint category of side effects.

In summary, a considerable additional benefit of ciltacabtagene autoleucel over individualised therapy of DPd or PVd is identified for adults with relapsed and refractory multiple myeloma who have received one to three prior therapies (pretreatment includes an immunomodulator and a proteasome inhibitor), have demonstrated disease progression on the last therapy and are refractory to lenalidomide.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III CARTITUDE-4 study.

At the study level, the risk of bias is considered low.

The risk of bias at the endpoint level is estimated to be low for the endpoint of overall survival and high for the endpoints in the category of side effects.

An uncertainty for overall survival results from crossing Kaplan-Meier curves.

The Kaplan-Meier curves for overall survival cross after about 12 months, after which the advantage for patients treated with ciltacabtagene autoleucel becomes apparent.

Further limitations result from the fact that no statements on symptomatology and health-related quality of life can be made for the present assessment, as no suitable data are available from the endpoints assessed in this regard.

Only patients with a correspondingly good general condition are eligible for treatment with the CAR-T cell therapy ciltacabtagene autoleucel and for the comparator therapies of DPd and PVd. It is unclear to what extent the inclusion criteria of the CARTITUDE-4 study are transferable to the German healthcare context, or whether all patients in the therapeutic indication of ciltacabtagene autoleucel are actually eligible for this therapy.

In summary, the G-BA deduces a hint for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

a2) Adults with relapsed and refractory multiple myeloma, who have received at least four prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

An additional benefit is not proven.

Justification:

The CARTITUDE-4 study is unsuitable for deriving the additional benefit, as only subjects who have received one to three prior therapies were enrolled in this study. Thus, an additional benefit for adults who have received at least four prior therapies is not proven.

2.1.4 Summary of the assessment

The present assessment is the assessment of a new therapeutic indication for the active ingredient ciltacabtagene autoleucel. Carvykti was approved as an orphan drug. Because of exceeding the EUR 30 million turnover limit for ciltacabtagene autoleucel in accordance with Section 35a, para. 1, sentence 12 SGB V, a regular assessment of the new therapeutic indication is carried out. Carvykti is indicated in adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; the pretreatment includes an immunomodulator and a proteasome inhibitor. It also involves the reassessment of the initially approved therapeutic indication before the expiry of the deadline.

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of several therapy options, including daratumumab in combination with pomalidomide and dexamethasone (DPd) as well as pomalidomide in combination with bortezomib and dexamethasone (PVd, only for subjects who are refractory to an anti-CD38 antibody), taking into account the subject's general condition, the active ingredients and combinations of active ingredients used in the prior therapies, as well as the type and duration of the response to the respective prior therapies and the suitability for stem cell transplant.

The results of the open-label, randomised, controlled phase III CARTITUDE-4 study, in which ciltacabtagene autoleucel was compared with DPd or PVd, are available for the benefit assessment.

Since the CARTITUDE-4 study only included patients who have received one to three prior therapies, no data are available for this sub-population of patients who have received at least four prior therapies in the therapeutic indication. For this reason, the assessment is carried out separately for two patient groups, according to the number of prior therapies.

a1) Adults with relapsed and refractory multiple myeloma, who have received one to three prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

a2) Adults with relapsed and refractory multiple myeloma, who have received at least four prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

On patient group a1)

For overall survival, there was a statistically significant difference to the advantage of the ciltacabtagene autoleucel, the overall extent of which is assessed as a clear prolongation of survival.

With regard to morbidity, health-related quality of life and side effects, no suitable data are available based on the patient-reported outcomes (EORTC QLQ-C30, PGIS, EQ-5D VAS, MySIm-Q and PRO-CTCAE), as the PROs were not collected in relevant phases of the CAR-T cell therapeutic concept.

There were no significant differences between the treatment arms in terms of side effects for SAEs, severe AEs and discontinuation due to AEs respectively. In detail, the specific AEs predominantly show disadvantages of ciltacabtagene autoleucel.

Overall, neither an advantage nor a disadvantage is derived for the endpoint category of side effects.

There are relevant uncertainties in the reliability of data, particularly with regard to transferability to the German healthcare context, which is why the reliability of data is categorised overall as a hint.

In summary, there is a hint for a considerable additional benefit of ciltacabtagene autoleucel in patient group a1) compared to an individualised therapy of DPd or PVd.

On patient group a2)

Only patients who have received one to three prior therapies were enrolled in the CARTITUDE-4 study. Overall, no data are available for patients who have received at least four prior therapies, which is why an additional benefit for patient group a2) is not proven.

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 contain a range for the number of patients who have received at least one prior therapy. There are no differentiated data on patient numbers depending on the number of prior therapies (one to three vs at least four). In the procedure for elranatamab (G-BA's resolution of 4 July 2024), a number of approximately 1,100 to 1,180 patients was identified for "adults with relapsed and refractory multiple myeloma who have received at least four prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and who have demonstrated disease progression on the last therapy".

This number is estimated as a rough approximation in the present procedure for patient group a2). Accordingly, the difference between a2) and the number of patients in the total population results for patient group a1).

The number of patients in the SHI target population is subject to uncertainty. This is especially due to the transfer of percentage values from incidence reports to prevalence data. Due to the transfer of the percentage value of patients with at least four prior therapies (approx.

1,100 to 1,180 patients) from the procedure for elranatamab, the following uncertainties also arise:

When calculating the percentage values of subjects with multiple myeloma and at least three prior therapies including an immunomodulatory agent, proteasome inhibitor and anti-CD38 antibody, only subjects who were receiving causal therapy at the time of observation are considered. On the basis of the submitted calculation, it cannot be checked whether a complete and correct collection of all active ingredients approved for the therapeutic indication was carried out. The calculated percentage value does not take into account all subjects with a prior therapy who received a fourth line of therapy in the same year.

The transfer of the percentage values from the MagnetisMM-3 study (elranatamab) to the total population is subject to the uncertainty that there are further inclusion and exclusion criteria for the study population compared to the healthcare context, which can make transferability more difficult.

In addition, the transfer of the percentage value of elranatamab results in further uncertainty due to the deviation of the populations: The number of approximately 1,100 to 1,180 patients refers to a population that was pretreated with an anti-CD38 antibody. This limitation is not stated in the therapeutic indication of ciltacabtagene autoleucel. Instead, it is limited to patients who are refractory to lenalidomide, whereas the limitation on refractoriness to exactly this active ingredient is not mentioned in the therapeutic indication of elranatamab.

Due to the uncertainties described above, the following percentage values are assumed for the best possible estimate of the target population:

- predicted prevalence of patients with plasmacytoma and malignant plasma cell neoplasms (ICD-10 C90.-) for 2024: 23,254 – 37,924
- Percentage value of subjects with multiple myeloma (ICD-10 C90.0) by excluding cases with ICD-10 C90.1, C90.2 and C90.3: 96.4%
- Percentage of subjects with multiple myeloma requiring treatment: 85 – 92%
- Percentage of patients who have received at least one prior therapy, including an immunomodulator and a proteasome inhibitor as well as refractoriness to lenalidomide in any prior line of therapy and refractoriness to the last prior line of therapy (total population): 13%
- Percentage of SHI-insured subjects: 88%
- Number of SHI-insured subjects in the total population: 2,360 – 3,550
- Number of patients in patient group a2) (adults with relapsed and refractory multiple myeloma, who have received at least four prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor): approx. 1,100 – 1,180
- Number of patients in patient group a1) (adults with relapsed and refractory multiple myeloma who have received one to three prior therapies, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor), corresponds to the difference between the number in the total population and patient group a2): approx. 1,180 to 2,460 patients

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 Carvykti (active ingredient: ciltacabtagene autoleucel) at the following publicly accessible link (last access: 8 April 2025):

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer ciltacabtagene autoleucel includes instructions for identifying, preventing, treating, and monitoring cytokine release syndrome and neurological side effects as well as on the risk of secondary malignancy with T cell origin. It also includes instructions on storage and transport as well as the cell thawing process, availability of one dose of tocilizumab at the point of treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

The patient training programme should explain the risks of cytokine release syndrome and serious neurologic side effects as well as the need to report symptoms immediately to the treating physician, and to carry the patient emergency card at all times.

Ciltacabtagene autoleucel must be used in a qualified treatment facility. The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the use of the medicinal product for novel therapies (Advanced Therapy Medicinal Product, ATMP) ciltacabtagene autoleucel in the therapeutic indication of multiple myeloma. Annex 1 "Use of CAR-T cells in B-cell neoplasms" of the ATMP Quality Assurance Guideline provides further details.

A Direct Healthcare Professional Communication ("Rote-Hand-Brief") which reports on the occurrence of secondary malignancies of T-cell origin, including chimeric antigen receptor (CAR)-positive malignancies, is available for the currently approved CD19- or BCMA-targeted CAR T-cell therapies. Patients who have been treated with CAR-T cell products should therefore be monitored throughout their lives for the occurrence of secondary malignancies.

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 2025).

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

Ciltacabtagene autoleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Ciltacabtagene autoleucel is administered as a single intravenous infusion according to the specifications in the product information.

Ciltacabtagene autoleucel concerns genetically modified, patient's own (autologous) T cells, which are usually obtained by leukapheresis. Since leukapheresis is part of the manufacture of the medicinal product according to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for the medicinal product to be assessed.

Inpatient treatments

Some treatment options of the appropriate comparator therapy are carried out on an inpatient basis. The inpatient costs are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG (Diagnosis Related Group) multiplied by the federal base rate value of 2025 (€ 4,394.22). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee according to Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (from 28 March 2024: € 250) and the treatment-specific nursing revenue valuation ratio.

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.

For bortezomib in combination with pegylated liposomal doxorubicin, a treatment duration of eight cycles is assumed, even if the actual treatment duration may differ from patient to patient.

When combining melphalan with prednisone or prednisolone, the treatment regimens and dosages follow the underlying product information for melphalan, prednisone or prednisolone.

For the cyclophosphamide + dexamethasone combination which was defined as the appropriate comparator therapy, no study that would allow cost representation could be identified. The costs can therefore not be quantified.

a) Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ciltacabtagene autoleucel				
Ciltacabtagene autoleucel	Single dose	1	1	1
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
An individualised therapy with selection of				
Bortezomib in combination with pegylated liposomal doxorubicin (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies)				
Bortezomib	Day 1, 4, 8, 11: 21-day cycle	8	4	32
Doxorubicin (pegylated, liposomal)	Day 4: 21-day cycle	8	1	8
Bortezomib in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies)				
Bortezomib	Day 1, 4, 8, 11: 21-day cycle	4 – 8	4	16 – 32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12: 21-day cycle	4 - 8	8	32 – 64
Carfilzomib in combination with dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16: 28-day cycle	13.0	6	78.0
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23: 28-day cycle	13.0	8	104.0
Cyclophosphamide monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)				
Cyclophosphamide	Continuously, 1 x daily or Continuously, 1 x every 21-28 days or Continuously, every 2-5 days	13.0 – 365.0	1	13.0 – 365.0
Cyclophosphamide in combination with dexamethasone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)				
No specification possible				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Daratumumab monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	23.0	1	23.0
Daratumumab in combination with pomalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	23.0	1	23.0
Pomalidomide	Day 1 – 21: 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22: 28-day cycle	13.0	Cycle 1 – 2: 0 Cycle 3 – 6: 2 From cycle 7 onwards: 3	29.0[5]
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1 - 9: 1 x every 7 days Week 10 - 24: 1 x every 21 days From week 25: 1 x every 28 days	21.0	1	21.0

[5] On the days of daratumumab administration, 20 mg of the dexamethasone dose is used as premedication and 20 mg on the day after daratumumab administration

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bortezomib	Day 1, 4, 8 and 11: 21-day cycle	8	4	32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8	Cycle 1 - 3: 6 Cycle 4 - 8: 7	53[6]
Daratumumab in combination with carfilzomib and dexamethasone				
Daratumumab	Cycle 1–2: Day 1, 8, 15, 22 Cycle 3–6: Day 1, 15 From cycle 7 onwards: Day 1 28-day cycle	13.0	Cycle 1–2: 4 Cycle: 3-6: 2 From cycle 7 onwards: 1	23.0
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13.0	6	78.0
Dexamethasone	Day 1, 2, 8, 9, 15.16, 22: 28-day cycle	13.0	Cycle 1–2: 3 Cycle: 3-6: 5 From cycle 7 onwards: 6	68.0[7]
Elotuzumab in combination with pomalidomide and dexamethasone (only for subjects with at least 2 prior therapies)				
Elotuzumab	1st - 2nd cycle: Day 1, 8, 15, 22 From 3rd cycle: Day 1 28-day cycle	13.0	1st - 2nd cycle: 4 From 3rd cycle: 1	19.0
Pomalidomide	Day 1 – 21: 28-day cycle	13.0	21	273.0

[6] On the days of daratumumab administration, 20 mg of the dexamethasone dose is used as premedication.

[7] On the days of daratumumab administration, the treatment dose of dexamethasone is used as premedication.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone	Day 1, 8, 15, 22: 28-day cycle	13.0	4	52.0
Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with at least 2 prior therapies)				
Isatuximab	1st cycle: Day 1, 8, 15, 22 From 2nd cycle: Day 1, 15 28-day cycle	13.0	1st cycle: 4 From 2nd cycle: 2	28.0
Pomalidomide	Day 1 - 21: 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22: 28-day cycle	13.0	4	52
Isatuximab in combination with carfilzomib and dexamethasone				
Isatuximab	1st cycle: Day 1, 8, 15, 22 From 2nd cycle: Day 1, 15 28-day cycle	13.0	1st cycle: 4 From 2nd cycle: 2	28.0
Carfilzomib	Day 1, 2, 8, 9, 15, 16: 28-day cycle	13.0	6	78.0
Dexamethasone PO / IV	Day 1, 2, 8, 9, 15, 16, 22, 23: 28-day cycle	13.0	8	104.0[8]
Melphalan monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)				
Melphalan	Continuously, 1 x every 28 days	13.0	1	13.0
Melphalan in combination with prednisone or prednisolone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)				
Melphalan	Day 1 of a 28 – 42-day cycle	8.7 – 13.0	1	8.7 – 13.0

[8] On the days of isatuximab and/or carfilzomib administration, 20 mg of the dexamethasone dose is administered intravenously as premedication.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Prednisolone	Day 1 – 4 of a 28 – 42-day cycle	8.7 – 13.0	4	34.8 – 52.0
Melphalan	Day 1 of a 28 – 42-day cycle	8.7 – 13.0	1	8.7 – 13.0
Prednisone	Day 1 – 4 of a 28 – 42-day cycle	8.7 – 13.0	4	34.8 – 52.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Panobinostat in combination with bortezomib and dexamethasone (only for subjects who have received at least four prior therapies)				
Panobinostat	1st - 16th cycle: Day 1, 3, 5, 8, 10, 12 21-day cycle	8 – 16	6	48 – 96
Bortezomib	1st - 8th cycle: Day 1, 4, 8, 11 9th - 16th cycle: Day 1, 8 21-day cycle	8 – 16	1st – 8th cycle: 4 9th - 16th cycle: 2	32 – 48
Dexamethasone	1st - 8th cycle: Day 1, 2, 4, 5, 8, 9, 11, 12 9th - 16th cycle: Day 1, 2, 8, 9 21-day cycle	8 – 16	1st – 8th cycle: 8 9th - 16th cycle: 4	64 – 96
Pomalidomide in combination with bortezomib and dexamethasone (only for subjects who are refractory to an anti-CD38 antibody)				
Pomalidomide	Day 1 – 14: 21-day cycle	17.4	14	243.6
Bortezomib	1st - 8th cycle: Day 1, 4, 8, 11 From 9th cycle: Day 1, 8 21-day cycle	17.4	1st - 8th cycle: 4 From 9th cycle: 2	50.8
Dexamethasone	1st - 8th cycle: Day 1, 2, 4, 5, 8, 9, 11, 12 From 9th cycle: Day 1, 2, 8, 9 21-day cycle	17.4	1st - 8th cycle: 8 From 9th cycle: 4	101.6

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pomalidomide in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies)				
Pomalidomide	Day 1 – 21 of a 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 of a 28-day cycle	13.0	4	52.0
High-dose therapy with autologous stem cell transplant (only for subjects who have undergone 1 prior therapy and are eligible for an autologous stem cell transplant; after achieving remission)				
Bone marrow transplantation/ stem cell transfusion, autogenous, for plasmacytoma, without specific collection	once		19.0 (average length of stay)	19.0
Stem cell collection from autologous donors without chemotherapy, age > 15 years, without most severe CC, without sepsis, without complicating constellation	once		4.2 (average length of stay)	4.2
High-dose therapy with allogeneic stem cell transplant (only for subjects who have undergone 1 prior therapy and are eligible for an allogeneic stem cell transplant; after achieving remission)				
No specification possible				

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)[9].

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

As it is not always possible to achieve the exact calculated dose per day with the commercially available dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

[9] Federal health reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

a) Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

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					
Ciltacabtagene autoleucel					
Ciltacabtagene autoleucel	≤ 100 kg: 0.5 – 1 x 10^6 CAR-positive viable T cells per kg BW	0.5 – 1 x 10^6/kg	1 single infusion bag	1	1 single infusion bag
	> 100 kg: 0.5 – 1 x 10^8 CAR-positive viable T cells	0.5 – 1 x 10^8/kg			
Appropriate comparator therapy					
An individualised therapy with selection of					
Bortezomib in combination with pegylated liposomal doxorubicin (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies)					
Bortezomib	1.3 mg/m^2	2.5 mg	1 x 2.5 mg	32	32 x 2.5 mg
Doxorubicin (pegylated, liposomal)	30 mg/m^2	57.3 mg	1 x 20 mg + 1 x 50 mg	8	8 x 20 mg + 8 x 50 mg
Bortezomib in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies)					
Bortezomib	1.3 mg/m^2	2.5 mg	1 x 2.5 mg	16 – 32	16 – 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32 – 64	32 – 64 x 20 mg
Carfilzomib in combination with dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m^2 Thereafter 56 mg/m^2	1st cycle day 1, 2 38.2 mg Thereafter 107 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78.0	154 x 10 mg + 78 x 30 mg + 76 x 60 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Dexamethasone	20 mg	20 mg	1 x 20 mg	104.0	104 x 20 mg
Cyclophosphamide monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)					
Cyclophosphamide	120 mg/m² – 240 mg/m²	229.2 mg – 458.4 mg	2 x 200 mg – 1 x 500 mg	365.0	730 x 200 mg – 365 x 500 mg
	400 mg/m² – 600 mg/m²	764 mg – 1,146 mg	1 x 1,000 mg – 1 x 1,000 mg + 1 x 200 mg	73.0 – 182.5	73 x 1,000 mg – 182.5 x 1,000 mg + 182.5 x 200 mg
	800 mg/m² – 1,600 mg/m²	1,528 mg – 3,506 mg	2 x 1,000 mg – 4 x 1,000 mg	13.0 - 17.4	26 x 1,000 mg – 69.6 x 1,000 mg
Cyclophosphamide in combination with dexamethasone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)					
No specification possible					
Daratumumab monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23.0	23 x 1,800 mg
Daratumumab in combination with pomalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23.0	23 x 1,800 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	29.0	29 x 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	21.0	21 x 1,800 mg
Bortezomib	1.3 mg/m²	2.5 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	53.0	53 x 20 mg
Daratumumab in combination with carfilzomib and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23.0	23 x 1,800 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 56 mg/m²	1st cycle day 1, 2 38.2 mg Thereafter 107 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78.0	154 x 10 mg + 78 x 30 mg + 76 x 60 mg
Dexamethasone	Day 1.2, 8, 9, 15, 16 20 mg Day 22 40 mg	Day 1.2, 8, 9, 15, 16 20 mg Day 22 40 mg	Day 1.2, 8, 9, 15, 16 1 x 20 mg Day 22 1 x 40 mg	68.0	57 x 20 mg + 11 x 40 mg
Elotuzumab in combination with pomalidomide and dexamethasone (only for subjects with at least 2 prior therapies)					
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22: 10 mg/kg From 3rd cycle Day 1: 20 mg/kg	1st - 2nd cycle Day 1, 8, 15, 22: 777 mg From 3rd cycle Day 1: 1,554 mg	1st - 2nd cycle Day 1, 8, 15, 22: 2 x 400 mg From 3rd cycle Day 1: 4 x 400 mg	19.0	60 x 400 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22: 28 mg From 3rd cycle Day 1: 28 mg Day 8, 15, 22: 40 mg	1st - 2nd cycle Day 1, 8, 15, 22: 28 mg From 3rd cycle Day 1 28 mg Day 8, 15, 22: 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52.0	19 x 8 mg + 19 x 20 mg + 33 x 40 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with at least 2 prior therapies)					
Isatuximab	10 mg/kg	777 mg	1 x 500 mg + 3 x 100 mg	28.0	28 x 500 mg + 84 x 100 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52.0 x 40 mg
Isatuximab in combination with carfilzomib and dexamethasone					
Isatuximab	10 mg/kg	777 mg	1 x 500 mg + 3 x 100 mg	28.0	28 x 500 mg + 84 x 100 mg
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 56 mg/m²	1st cycle day 1, 2 38.2 mg Thereafter 107 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78.0	154 x 10 mg + 78 x 30 mg + 76 x 60 mg
Dexamethasone PO	20 mg	20 mg	1 x 20 mg	25.0	25 x 20 mg
Dexamethasone IV	20 mg	20 mg	5 x 4 mg	79.0	395 x 4 mg
Melphalan monotherapy (only for at least triple-refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)					
Melphalan	0.4 mg/kg	31.1 mg	1 x 50 mg	13.0	13 x 50 mg
Melphalan in combination with prednisone or prednisolone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy and have received at least four prior therapies)					
Melphalan	Day 1: 15 mg/m²	Day 1: 28.7 mg	1 x 50 mg	8.7 – 13.0	8.7 x 50 mg – 13 x 50 mg
Prednisone	Day 1 – 4: 2 mg/kg	Day 1 – 4: 155.4 mg	3 x 50 mg + 1 x 5 mg	34.8 – 52.0	104.4 x 50 mg + 34.8 x 5 mg – 156 x 50 mg + 52 x 5 mg
Prednisolone	Day 1 – 4: 2 mg/kg	Day 1 – 4: 155.4 mg	3 x 50 mg + 1 x 5 mg	34.8 – 52.0	104.4 x 50 mg + 34.8 x 5 mg – 156 x 50 mg +

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					52 x 5 mg
Panobinostat in combination with bortezomib and dexamethasone (only for subjects who have received at least four prior therapies)					
Panobinostat	20 mg	20 mg	1 x 20 mg	48 – 96	48 x 20 mg – 96 x 20 mg
Bortezomib	1.3 mg/m^2	2.5 mg	1 x 2.5 mg	32 – 48	32 x 2.5 mg – 48 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	64 – 96	64 x 20 mg – 96 x 20 mg
Pomalidomide in combination with bortezomib and dexamethasone (only for subjects who are refractory to an anti-CD38 antibody)					
Pomalidomide	4 mg	4 mg	1 x 4 mg	243.6	243.6 x 4 mg
Bortezomib	1.3 mg/m^2	2.5 mg	1 x 2.5 mg	50.8	50.8 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	101.6	101.6 x 20 mg
Pomalidomide in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy and have received at least four prior therapies)					
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
High-dose therapy with autologous stem cell transplant (only for subjects who have undergone 1 prior therapy and are eligible for an autologous stem cell transplant; after achieving remission)					
	once				
High-dose therapy with allogeneic stem cell transplant (only for subjects who have undergone 1 prior therapy and are eligible for an allogeneic stem cell transplant; after achieving remission)					
	once				

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 reference prices shown in the cost representation may not represent the cheapest available alternative.

Inpatient treatments:

The costs of high-dose chemotherapy with allogeneic stem cell transplant cannot be quantified, as the DRGs in question exclude plasmacytomas, which also include multiple myeloma.

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Appropriate comparator therapy									
High-dose chemotherapy with allogeneic stem cell transplant									
No specification possible									
High-dose chemotherapy with autologous stem cell transplant									
2025	A15D	19	3.823	€ 4,394.22	1.0538	€ 250	€ 16,799.10	€ 5,005.55	€ 21,804.65
2025	A42C	4.2	0.809	€ 4,394.22	0.843	€ 250	€ 3,554.92	€ 885.15	€ 4,440.07

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Ciltacabtagene autoleucel	1 single infusion bag	€ 285,000	€ 0[10]	€ 285,000

[10] The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.

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
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 1.77	€ 8.26	€ 175.34
Carfilzomib 10 mg	1 PIS	€ 197.03	€ 1.77	€ 10.28	€ 184.98
Carfilzomib 30 mg	1 PIS	€ 568.43	€ 1.77	€ 30.84	€ 535.82
Carfilzomib 60 mg	1 PIS	€ 1,125.54	€ 1.77	€ 61.69	€ 1,062.08
Cyclophosphamide 1,000 mg	6 PSI	€ 142.80	€ 1.77	€ 7.28	€ 133.75
Cyclophosphamide 500 mg	6 PSI	€ 84.44	€ 1.77	€ 9.25	€ 73.42
Cyclophosphamide 200 mg	10 PSI	€ 69.60	€ 1.77	€ 3.23	€ 64.60
Daratumumab 1,800 mg	1 SFI	€ 5,953.27	€ 1.77	€ 0.00	€ 5,951.50
Dexamethasone 4 mg[11]	10 SFI	€ 16.92	€ 1.77	€ 0.44	€ 14.71
Dexamethasone 8 mg[11]	100 TAB	€ 123.41	€ 1.77	€ 8.87	€ 112.77
Dexamethasone 20 mg[11]	10 TAB	€ 32.42	€ 1.77	€ 0.00	€ 30.65
Dexamethasone 20 mg[11]	20 TAB	€ 54.09	€ 1.77	€ 0.00	€ 52.32
Dexamethasone 20 mg[11]	50 TAB	€ 118.88	€ 1.77	€ 0.00	€ 117.11
Dexamethasone 40 mg[11]	50 TAB	€ 188.03	€ 1.77	€ 0.00	€ 186.26
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 721.49	€ 1.77	€ 89.87	€ 629.85
Pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,778.90	€ 1.77	€ 224.69	€ 1,552.44
Elotuzumab 400 mg	1 PIC	€ 1,557.91	€ 1.77	€ 85.68	€ 1,470.46
Isatuximab 100 mg	1 CIS	€ 333.96	€ 1.77	€ 17.86	€ 314.33
Isatuximab 500 mg	1 CIS	€ 1,621.58	€ 1.77	€ 89.32	€ 1,530.49
Melphalan 50 mg	1 DSS	€ 50.49	€ 1.77	€ 2.17	€ 46.55
Panobinostat 20 mg	6 HC	€ 4,656.41	€ 1.77	€ 262.64	€ 4,392.00
Pomalidomide 4 mg	21 HC	€ 2,752.90	€ 1.77	€ 131.94	€ 2,619.19
Prednisolone 5 mg[11]	100 TAB	€ 15.43	€ 1.77	€ 0.33	€ 13.33
Prednisolone 50 mg[11]	50 TAB	€ 31.44	€ 1.77	€ 1.59	€ 28.08
Prednisone 5 mg[11]	100 TAB	€ 16.74	€ 1.77	€ 0.43	€ 14.54
Prednisone 50 mg[11]	50 TAB	€ 68.06	€ 1.77	€ 4.49	€ 61.80
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection; PIS = powder for the preparation of an infusion solution; PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets; DSS = dry substance with solvent					

LAUER-TAXE® last revised: 15 April 2025

[11] Fixed reimbursement rate

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.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

According to the product information of ciltacabtagene autoleucel, lymphodepleting chemotherapy should be administered before the CAR-T cells are administered. For this, cyclophosphamide (300 mg/m^2 = 573 mg) and fludarabine (30 mg/m^2 = 57.3 mg) should be administered daily for 3 days, with infusion of ciltacabtagene autoleucel 5 to 7 days after the start of lymphocyte depletion.

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with ciltacabtagene autoleucel. These examinations are not required for all therapy options (of the appropriate comparator therapy). Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, hepatitis C and HIV, the costs of additionally required SHI services are presented in the resolution.

Diagnostics to rule out hepatitis C requires sensibly coordinated steps[12]. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-RNA detection to confirm the diagnosis of an HCV infection.

Patients receiving therapy with pomalidomide and daratumumab should be tested for the presence of HBV infection before initiating the respective treatment.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps[13]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations.

In deviation from this, additional required SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the medicinal product to be evaluated and the appropriate comparator therapy and are consequently considered as

[12] S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf

[13] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

additionally required SHI services in the resolution.

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.

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							
Ciltacabtagene autoleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide IV 300 mg/m² = 573 mg	10 PSI at 200 mg	€ 69.60	€ 1.77	€ 3.23	€ 64.60	3.0	€ 64.60
Fludarabine IV 30 mg/m² = 57.3 mg	1 CII at 50 mg	€ 118.54	€ 1.77	€ 5.09	€ 111.68	3.0	€ 670.08
Premedication							
Paracetamol 500 - 1,000 mg, PO[11,14]	10 TAB x 500 mg 10 TAB x 1,000 mg	€ 2.96 € 3.32	€ 0.15 € 0.17	€ 0.13 € 0.14	€ 2.68 € 3.01	1.0	€ 2.68 – € 3.01
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	1.0	€ 17.45
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43
HCV screening							
Hepatitis C HCV antibody status (GOP 32618)	-	-	-	-	€ 9.02	1.0	€ 9.02
HIV screening							

[14] The dosage of 650 mg paracetamol in premedication stated in the product information cannot be achieved by tablets. Because of this, a dosage of 500 - 1,000 mg is used.

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
Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies (GOP number 32575)	-	-	-	-	€ 4.09	1.0	€ 4.09
Appropriate comparator therapy							
Daratumumab *in combination with bortezomib and dexamethasone*							
Premedication							
Dexamethasone 20 mg, PO[11]	50 TAB x 20 mg	€ 118.88	€ 1.77	€ 0.00	€ 117.11	21.0	€ 49.19
Paracetamol 500 - 1,000 mg, [11,14] PO	20 TAB x 500 mg 10 TAB x 1,000 mg	€ 3.47 € 3.32	€ 0.17 € 0.17	€ 0.15 € 0.14	€ 3.15 € 3.01	21.0	€ 3.31 – € 6.32
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	21.0	€ 146.58
Daratumumab *in combination with pomalidomide and dexamethasone*							
Premedication							
Dexamethasone 40 mg, PO[11]	50 TAB x 40 mg	€ 188.03	€ 1.77	€ 0.00	€ 186.26	23.0	€ 85.68
Paracetamol 500 - 1,000 mg, PO[11,14]	20 TAB x 500 mg 10 TAB x 1,000 mg	€ 3.47 € 3.32	€ 0.17 € 0.17	€ 0.15 € 0.14	€ 3.15 € 3.01	23.0	€ 3.62 – € 6.92
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	23.0	€ 160.54
Daratumumab *in combination with carfilzomib and dexamethasone*							
Dexamethasone 20 mg, PO[11]	50 TAB x 20 mg	€ 118.88	€ 1.77	€ 0.00	€ 117.11	21.0	€ 49.19
Dexamethasone 40 mg, PO[11]	50 TAB x 40 mg	€ 188.03	€ 1.77	€ 0.00	€ 186.26	2.0	€ 7.45
Paracetamol 500 - 1,000 mg, PO[11,14]	20 TAB x 500 mg 10 TAB x 1,000 mg	€ 3.47 € 3.32	€ 0.17 € 0.17	€ 0.15 € 0.14	€ 3.15 € 3.01	23.0	€ 3.62 – € 6.92
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	23.0	€ 160.54

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
Daratumumab *monotherapy*							
Premedication							
Methyl prednisolone 60 mg - 100 mg, IV	3 PII x 32 mg	€ 26.14	€ 1.77	€ 6.73	€ 17.64	23.0	€ 270.48 - € 540.96
Postmedication							
Methyl prednisolone 20 mg, PO[11]	100 TAB x 4 mg 100 TAB x 16 mg	€ 29.35 € 73.84	€ 1.77 € 1.77	€ 1.43 € 4.95	€ 26.15 € 67.12	46.0	€ 42.91
Elotuzumab *in combination with pomalidomide and dexamethasone*							
Premedication in combination with pomalidomide and dexamethasone							
Dexamethasone 8 mg, IV[11]	10 SFI x 8 mg	€ 20.38	€ 1.77	€ 0.72	€ 17.89	19.0	€ 33.99
Dimetindene 1 mg/10 kg BW, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	19.0	€ 132.62
Famotidine 20 mg, PO[11]	100 FCT x 20 mg	€ 20.18	€ 1.77	€ 0.70	€ 17.71	19.0	€ 3.36
Paracetamol 500 – 1,000 mg, PO[11,14]	20 TAB x 500 mg 10 TAB x 1,000 mg	€ 3.47 € 3.32	€ 0.17 € 0.17	€ 0.15 € 0.14	€ 3.15 € 3.01	19.0	€ 2.99 – € 5.72
Daratumumab, Pomalidomide							
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43

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: FCT = film-coated tablets; SFI = solution for injection; CII = concentrate for the preparation of a solution for injection or infusion; PSI = powder for solution for injection; PII = powder and solvent for solution for injection or infusion; TAB = tablets							

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 1 October 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 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 requirements 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:

a) Adults with relapsed and refractory multiple myeloma, who have received at least one prior therapy, have demonstrated disease progression on the last therapy and are refractory to lenalidomide; pretreatment includes an immunomodulator and a proteasome inhibitor

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for ciltacabtagene autoleucel (Carvykti); Carvykti infusion dispersion; last revised: July 2024

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 27 November 2024, the pharmaceutical company submitted a dossier for the benefit assessment of ciltacabtagene autoleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

The Subcommittee on Medicinal Products determined the appropriate comparator therapy for the assessment procedure at its session on 7 January 2025.

By letter dated 29 November 2024 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 ciltacabtagene autoleucel. The appropriate comparator therapy determined for the assessment procedure was submitted to IQWiG on 9 January 2025 in addition to the letter of 29 November 2024.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2025, and the written statement procedure was initiated with publication on the G-BA website on 3 March 2025. The deadline for submitting written statements was 24 March 2025.

The oral hearing was held on 7 April 2025.

By letter dated 8 April 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 25 April 2025.

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 6 May 2025, and the proposed draft resolution was approved.

At their session on 15 May 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 January 2025	Determination of the appropriate comparator therapy
Working group Section 35a	1 April 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 April 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 April 2025 29 April 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 May 2025	Concluding discussion of the draft resolution
Plenum	15 May 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 May 2025

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

Prof. Hecken