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)
Idecabtagene vicleucel (reassessment of an orphan drug after exceeding the EUR 30 million limit: multiple myeloma, at least 3 prior therapies; new therapeutic indication: multiple myeloma, at least 2 prior therapies)

of 19 September 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. For medicinal products 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

Idecabtagene vicleucel (Abecma) was listed for the first time on 1 January 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Idecabtagene vicleucel is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

At its session on 16 June 2022, the G-BA decided on the benefit assessment of idecabtagene vicleucel in the therapeutic indication "treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an

immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy".

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

Abecma exceeded the EUR 30 million turnover limit on 1 July 2023 and has not yet been assessed with evidence of medical benefit and additional medical benefit in relation to the appropriate comparator therapy.

The pharmaceutical company has submitted the final dossier for the therapeutic indication of multiple myeloma after at least three prior therapies in due time to the G-BA on 29 February 2024 in accordance with Section 4, paragraph 3, number 6 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO. The benefit assessment procedure started on 1 March 2024.

On 19 March 2024, the European Commission issued the marketing authorisation for this new therapeutic indication:

"Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy."

The pharmaceutical company has submitted the final dossier for the new therapeutic indication of multiple myeloma after at least 2 prior therapies in due time to the G-BA on 27 March 2024 in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 VerfO. The benefit assessment procedure started on 1 April 2024.

Due to the submission of cumulative requirements in accordance with the resolution of 2 May 2024 to discontinue the "Reassessment of orphan drug > 30 million: multiple myeloma, at least 3 prior therapies" procedure, the G-BA merged the procedure started on 1 March 2024 with the procedure started on 1 April 2024 under the summary question of multiple myeloma after at least two prior therapies.

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

The G-BA came to a resolution on whether an additional benefit of idecabtagene vicleucel 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 idecabtagene vicleucel.

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 Idecabtagene vicleucel (Abecma) according to the product information

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Therapeutic indication of the resolution (resolution of 19.09.2024):

See new therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy; prior treatment includes an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody

Appropriate comparator therapy:

A patient-individual therapy under selection of:

- Carfilzomib in combination with lenalidomide and dexamethasone
- Elotuzumab in combination with lenalidomide and dexamethasone
- Elotuzumab in combination with pomalidomide and dexamethasone
- Daratumumab in combination with bortezomib and dexamethasone
- Daratumumab in combination with lenalidomide 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
  [only for subjects who are refractory to a CD38 antibody and lenalidomide]

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

- Ixazomib in combination with lenalidomide and dexamethasone [only for subjects who are refractory to bortezomib, carfilzomib and a CD38 antibody]
- Panobinostat in combination with bortezomib and dexamethasone
- Carfilzomib in combination with dexamethasone
- 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]
- Lenalidomide 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 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]

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 prior therapies

<u>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):</u>

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

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

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

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

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

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

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

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. A non-medicinal treatment is unsuitable as a comparator therapy in this therapeutic indication.

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
- 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.

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 generally refer to patient-individual 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 4 prior therapies, the general condition is also relevant for the selection of the most suitable patient-individual therapy option.

One criterion for patient-individual 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 and 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.

Patients with two to three prior therapies

With regard to the relapsed/refractory disease situation after two 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 patient-individual 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 carfilzomib in combination with lenalidomide and dexamethasone, elotuzumab in combination with lenalidomide and dexamethasone, elotuzumab in combination with pomalidomide and dexamethasone, daratumumab in combination with bortezomib and dexamethasone, daratumumab in combination with lenalidomide 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, ixazomib in combination with lenalidomide and dexamethasone as well as panobinostat in combination with brotezomib and dexamethasone were included in the patient-individual therapy of the appropriate comparator therapy.

The therapy options "pomalidomide in combination with bortezomib and dexamethasone (PVd) (only for subjects who are refractory to a CD38 antibody and lenalidomide)" and "ixazomib in combination with lenalidomide and dexamethasone (IRd) (only for subjects who are refractory to bortezomib, carfilzomib and a CD38 antibody)" are restricted to patients with a specific refractoriness to the active ingredients or combinations of active ingredients used in previous therapies.

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

Doublet therapy in patient-individual therapy

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

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 patient-individual 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 two to three prior therapies as part of patient-individual therapy (see above).

Other approved therapy options in patient-individual 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 patient-individual therapy.

For at least double-refractory patients who are ineligible for triplet therapy, the dual combinations of pomalidomide in combination with dexamethasone, lenalidomide in combination with dexamethasone, bortezomib in combination with pegylated liposomal doxorubicin and bortezomib in combination with dexamethasone can also be considered. Furthermore, according to the marketing authorisation, the dual combination of pomalidomide in combination with dexamethasone is only indicated for at least double-refractory subjects who have demonstrated disease progression on the last therapy.

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 patient-individual 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 patient-individual therapy:

Among the approved active ingredients that have not been determined as appropriate comparator therapy as part of patient-individual 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 and ciltacabtagene autoleucel are approved for the treatment of patients who have undergone at least three prior therapies. For idecabtagene vicleucel (resolution of 16 June 2022) as well as ciltacabtagene autoleucel

(resolution of 17 August 2023), a hint for a non-quantifiable additional benefit was identified since the scientific data basis did not allow quantification. In the process, the indirect comparisons presented could not be used for both therapy options and the assessment was based on single-arm data in each case.

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 two prior therapies, have demonstrated disease progression on the last therapy and have received pretreatment with an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody, a patient-individual 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.

For the implementation of patient-individual therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned (multi-comparator study).

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 idecabtagene vicleucel is assessed as follows:

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy; prior treatment includes an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody

An additional benefit is not proven.

Justification:

About the KarMMa-3 study

For the benefit assessment, the pharmaceutical company presented the results of the ongoing, open-label, randomised and controlled KarMMa-3 study.

In the KarMMa-3 study, idecabtagene vicleucel was compared with a therapy according to doctor's instructions by selecting daratumumab + pomalidomide + dexamethasone (DPd), daratumumab + bortezomib + dexamethasone (DVd), ixazomib + lenalidomide + dexamethasone (IRd), carfilzomib + dexamethasone (Kd), elotuzumab + pomalidomide + dexamethasone (Epd), taking into account the last treatment regime.

The study enrolled adults with relapsed and refractory multiple myeloma who had received two to four prior therapies, including daratumumab, an immunomodulator and a proteasome inhibitor, and who demonstrated disease progression on the last therapy or 60 days after the end of a therapy. At the time of enrolment in the study, the patients had to have an ECOG-PS of 0 or 1.

A total of 386 patients were enrolled in the study and randomised in a 2:1 ratio to either treatment with idecabtagene vicleucel (n = 254) or therapy according to doctor's instructions (n = 132). A total of 261 (68%) patients had undergone 2 to 3 and 125 (32%) patients 4 prior therapies.

Treatment with idecabtagene vicleucel and with the respective combinations of active ingredients in the control arm was carried out largely in accordance with the corresponding product information.

Patients in the control arm were able to switch to treatment with idecabtagene vicleucel from amendment 2 to the study protocol dated 17.12.2019 after disease progression and eligibility, at the request of the principal investigator, and could receive a bridge therapy to stabilise their disease until infusion.

Overall, there were many study discontinuations. In addition, there are differential differences between the treatment groups in terms of the study discontinuations, with significantly more discontinuations in the intervention group compared to the control group. The most common reasons for discontinuation were death and withdrawal of consent.

The primary endpoint of the KarMMa-3 study is progression-free survival (PFS). Patient-relevant secondary endpoints include endpoints in the categories of mortality, morbidity, health-related quality of life and side effects.

The still ongoing study was conducted in study sites in Europe, North America and Japan and was initiated in April 2019. No information is available on the end of study.

For the benefit assessment, the results of the most recent data cut-off from 28 April 2023 are used.

Limitations of the study:

The majority of patients in the KarMMa-3 study are under 75 years of age (approx. 95%). In contrast, the median age of onset for multiple myeloma in healthcare is 72 years for men and 74 years for women.

In addition, the patients in the study are in a good general condition (ECOG-PS ≤ 1).

On the implementation of the appropriate comparator therapy in the KarMMa-3 study

The 5 therapy options offered in the KarMMa-3 study (daratumumab + pomalidomide + dexamethasone (DPd), daratumumab + bortezomib + dexamethasone (DVd), ixazomib + lenalidomide + dexamethasone (IRd), carfilzomib + dexamethasone (Kd), elotuzumab + pomalidomide + dexamethasone (Epd)) are included in the determined appropriate comparator therapy and represent relevant therapy options in the present therapeutic indication. It is therefore assumed that the majority of patients enrolled in the KarMMa-3 study received adequate patient-individual therapy in line with the appropriate comparator therapy. However, uncertainties remain because statements on the additional benefit of idecabtagene vicleucel based on the results of the KarMMa-3 study can only be made for patients in this therapeutic indication for whom treatment with DPd, DVd, IPd, Kd or Epd represents the optimum patient-individual therapy. Since only patients with 2, 3 and 4 prior therapies were enrolled in the study, the available data only allows statements to be made on the additional benefit for patients with 2, 3 or 4 prior therapies.

The information on patient characteristics subsequently submitted by the pharmaceutical company for the written statement procedure shows that both sub-populations (patients with 2 and 3 prior therapies vs patients with 4 prior therapies) differed at the start of the study, particularly with regard to the time since the initial diagnosis and the refractoriness status.

The G-BA estimates these differences to be inadequate to carry out a differentiated evaluation of the data according to the corresponding sub-populations and therefore uses the total population (patients with at least 2 prior therapies) for the benefit assessment.

Extent and probability of the additional benefit

Mortality

The overall survival was defined in the KarMMa-3 study as the time from randomisation to occurrence of death from any cause.

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the KarMMa-3 study.

PFS is defined as the time from randomisation to the time of first disease progression or death from any cause. PFS was assessed using the International Myeloma Working Group (IMWG) criteria, based on laboratory parameters as well as haematological and imaging methods.

There is a statistically significant prolonged PFS in favour of idecabtagene vicleucel compared to the appropriate comparator therapy.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". The morbidity component "disease progression" was assessed according to the IMWG criteria and thus, not in a symptom-related manner but only 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.

Results on morbidity and quality of life are potentially relevant for the interpretation of the PFS results in the present case since disease progression determined by laboratory parametric, imaging and haematological procedures may be associated with effects on morbidity and/or health-related quality of life.

Reliable analyses of morbidity and quality of life data are required in order to assess any effects on morbidity and health-related quality of life.

The evaluations presented on morbidity and quality of life data are unsuitable for the benefit assessment (see justification below the endpoints of the endpoint categories of morbidity and quality of life). Thus, it cannot be assessed whether the prolonged PFS with idecabtagene vicleucel in the KarMMa-3 study is associated with an advantage in terms of morbidity or health-related quality of life.

In summary, the available data do not indicate that the statistically significant prolonged time of progression-free survival with idecabtagene vicleucel – disease progression determined by laboratory parametric, imaging and haematological procedures according to IMWG criteria – is associated with an improvement in morbidity or health-related quality of life.

The results for the PFS endpoint are not used in the present assessment. The overall statement on the additional benefit therefore remains unaffected by the different opinions within the G-BA regarding the patient relevance of the PFS endpoint.

Symptomatology

Disease symptomatology was assessed in the KarMMa-3 study using the symptom scales of the EORTC-QLQ-C30 questionnaire and the myeloma-specific additional module EORTC-QLQ-MY20.

The pharmaceutical company presented all time-to-event analyses (time to first/ confirmed/ permanent improvement/ deterioration) planned according to PRO-SAP for the benefit assessment. The company also presented sensitivity analyses on the time-to-event analyses (time to first deterioration), in which an earlier survey before chemotherapy for lymphocyte depletion is taken into account for the intervention arm.

For the patient-reported endpoints, the first survey after randomisation was conducted on the day of the infusion of idecabtagene vicleucel in the intervention arm and on the day of the 1st administration of the comparator therapy in the control arm. In these evaluations, the median time from randomisation to this survey was 54 days in the intervention arm and 5

days in the control arm. In the evaluations in which an earlier survey at the time of chemotherapy for lymphocyte depletion is also taken into account, the median time from randomisation to chemotherapy for lymphocyte depletion in the intervention arm was 49 days. This means that the sensitivity analyses shorten the unobserved period in the intervention arm only insignificantly by approx. 5 days. This design also means that the patient-reported endpoints in the control arm were already surveyed twice after randomisation, before they were surveyed at the time of chemotherapy for lymphocyte depletion in the intervention arm. This meant that a change in the symptomatology of patients in the control arm could be surveyed much earlier, while in the intervention arm an event could only occur much later due to the delayed survey time periods. In addition, the unobserved period from randomisation to chemotherapy for lymphocyte depletion in the intervention group is a period in which the corresponding patients are exposed to high levels of burdens. In the KarMMa-3 study, for example, more than 80% of patients received bridge therapy for multiple myeloma during this period. Overall, the time-to-event analyses (time to first/ confirmed/ permanent deterioration/ improvement) presented by the pharmaceutical company and the sensitivity analyses mentioned are therefore unsuitable for the benefit assessment.

In addition to the time-to-event analyses, the pharmaceutical company presented results from longitudinal analyses using constrained Longitudinal Data Analysis (cLDA) over the entire course of the study and cLDA sensitivity analyses up to month 6 and thus, analyses with the same observation periods in the treatment groups in the written statement procedure.

Irrespective of the structural problems of the collection (important therapy phases prior to chemotherapy for lymphocyte depletion are not assessed in the intervention arm), the cLDA evaluations cannot be used simply because the difference in the return rates between the study arms at month 6 was greater than 25%.

Overall, the results on disease symptomatology (EORTC-QLQ-C30; EORTC-QLQ-MY20) cannot be interpreted meaningfully for the reasons mentioned and therefore cannot be used for the benefit assessment.

Health status (EQ-5D VAS)

The health status was surveyed using the VAS of the EQ-5D questionnaire.

The pharmaceutical company presented evaluations of time-to-event analyses (time to first/ confirmed/ permanent improvement/ deterioration) as well as sensitivity analyses of the time-to-event analyses (time to first deterioration), in which they consider the survey prior to chemotherapy for lymphocyte depletion in the intervention arm. In addition to the time-to-event analyses, the pharmaceutical company presented results from longitudinal analyses using constrained Longitudinal Data Analysis (cLDA) over the entire course of the study in the written statement procedure. They also presented cLDA sensitivity analyses up to month 6 and thus, analyses with equal observation periods in the treatment groups.

In line with the above statements on symptomatology, the results on health status can also not be meaningfully interpreted and therefore cannot be used for the benefit assessment.

<u>Quality of life</u>

Health-related quality of life was assessed using the functional scales of the EORTC-QLQ-C30 questionnaire and the myeloma-specific additional module EORTC-QLQ-MY20.

The pharmaceutical company presented evaluations of time-to-event analyses (time to first/ confirmed/ permanent improvement/ deterioration) as well as sensitivity analyses of the time-to-event analyses (time to first deterioration), in which they consider the survey prior to chemotherapy for lymphocyte depletion in the intervention arm. In addition to the time-to-event analyses, the pharmaceutical company presented results from longitudinal analyses using constrained Longitudinal Data Analysis (cLDA) over the entire course of the study in the written statement procedure. They also presented cLDA sensitivity analyses up to month 6 and thus, analyses with equal observation periods in the treatment groups.

In line with the above statements on symptomatology, the results on health-related quality of life cannot be meaningfully interpreted and therefore cannot be used for the benefit assessment.

Side effects

In the study, all events in the endpoints on side effects were systematically collected in both study arms in the period up to 6 months after randomisation. These evaluations are used for the endpoints of serious adverse events (SAEs) and severe AEs.

Adverse events (AEs) in total

In the KarMMa-3 study, 100% of patients in the intervention arm experienced an adverse event, compared to 99% of patients in the comparator arm.

Serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference in the KarMMa-3 study for the endpoint of serious adverse events.

For the endpoint of severe AEs (CTCAE ≥ 3), there was a statistically significant difference to the disadvantage of idecabtagene vicleucel.

Discontinuation due to AEs

No suitable evaluations are available for the endpoint of discontinuation due to AEs. The pharmaceutical company presented the therapy discontinuation due to AEs collected in the KarMMa-3 study in the dossier only descriptively and justifies this with the single administration of idecabtagene vicleucel, which means that no therapy discontinuation due to AEs after an infusion with idecabtagene vicleucel is possible.

The descriptions show that only a few therapy discontinuations due to AEs occurred in both treatment groups.

Due to the available data constellation with only a few treatment discontinuations due to AEs, the missing analyses have no consequences for the assessment.

Specific AEs

The analyses subsequently submitted by the pharmaceutical company in the written statement procedure are used for the presentation of the specific AEs. These show the uncertainty that potentially selectively recorded events are included in the evaluation after month 6.

For the specific AEs severe neurological toxicity, severe infections and secondary malignancies, there was no statistically significant difference between the treatment groups.

Overall assessment

For the assessment of the additional benefit of idecabtagene vicleucel for the treatment of relapsed and refractory multiple myeloma in adults who have received at least two prior therapies and have shown disease progression under the last therapy and have been pretreated with an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody, results are available from the KarMMa-3 study in the endpoint categories mortality, morbidity, health-related quality of life and adverse events compared with patient-individual therapy.

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

The evaluations presented on disease symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-MY20) and health status (collected using EQ 5D-VAS) cannot be meaningfully interpreted and therefore cannot be used for the benefit assessment. This is due in particular to the design of the collection, which meant that no collection was conducted in the intervention arm of the study in the period after randomisation, during which the patients were treated with intensive bridge therapies.

With regard to health-related quality of life, assessed using the scales of the EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-MY-20 (functional scales), there are no data - for the same reasons - that can be meaningfully interpreted and thus cannot be used for the benefit assessment.

With regard to side effects, there is a statistically significant disadvantage for idecabtagene vicleucel compared to patient-individual therapy with regard to the endpoint severe AEs (CTCAE grade ≥ 3). In detail, there were neither advantages nor disadvantages for the specific adverse events. The overall results on side effects show a disadvantage in favour of idecabtagene vicleucel compared to patient-individual therapy.

In the overall assessment, the G-BA concludes that there is no evidence of additional benefit for idecabtagene vicleucel for the treatment of relapsed and refractory multiple myeloma in adults who have received at least two prior therapies and have shown disease progression under the last therapy and have been pretreated with an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody, compared with a patient-individual therapy.

2.1.4 Summary of the assessment

The present assessment is a joint benefit assessment of a new therapeutic area and a new benefit assessment of idecabtagene vicleucel due to exceeding the 30 million euro turnover limit. Idecabtagene vicleucel was approved as an orphan drug.

The therapeutic indication assessed here is as follows:

"Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy."

The G-BA determined a patient-individual therapy as an appropriate comparator therapy, taking into account the 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.

For the assessment of the additional benefit of idecabtagene vicleucel for the treatment of relapsed and refractory multiple myeloma in adults who have received at least two prior therapies, results are available from the KarMMa-3 study in the endpoint categories mortality, morbidity, health-related quality of life and side effects compared with patient-individual therapy.

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

The evaluations presented on morbidity and health-related quality of life cannot be interpreted in a meaningful way. This is due in particular to the design of the collection, which meant that no collection was conducted in the intervention arm of the study in the period after randomisation, during which the patients were treated with intensive bridge therapies.

The overall results on side effects show a disadvantage in favour of idecabtagene vicleucel compared to patient-individual therapy.

In the overall assessment, the G-BA concludes that there is no evidence of additional benefit for idecabtagene vicleucel for the treatment of relapsed and refractory multiple myeloma in adults who have received at least two prior therapies and have shown disease progression under the last therapy and have been pretreated with an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody, compared with a patient-individual therapy.

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

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company.

The pharmaceutical company calculated the number of patients in the SHI target population using five derivation steps.

In comparison with earlier procedures in a similar therapeutic indication (resolution on pomalidomide (D-193) and the resolutions on isatuximab (D-675) and elotuzumab (D-708)), the patient numbers stated by the pharmaceutical company in the dossier are almost doubled in the present procedure. This is mainly due to the reduced restriction of the therapeutic indication with regard to previous therapies, the use of more up-to-date prevalence data, the expansion of treatment options and the inclusion of patients who became ill more than 5 years ago in the current procedure compared to the older procedures.

The information from the pharmaceutical company's dossier is subject to uncertainties due to the following aspects:

- With regard to the exclusion of cases with ICD-10 C90.1, C90.2 and C90.3, the transfer of the proportions obtained from newly diagnosed patients (incidence data) to the

patients diagnosed in previous years (prevalence data) leads to uncertainty in the categorisation of the target population.

- With regard to the exclusion of patients with smouldering multiple myeloma (SMM), the corresponding percentages are incidence figures. Transferring these to a prevalent population results in uncertainties.
- There are uncertainties regarding the percentage (19%) of patients who have received at least 2 prior therapies, including an immunomodulator, a proteasome inhibitor and an anti-CD38 antibody, as determined by the pharmaceutical company from the healthcare research analysis.

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 Abecma (active ingredient: idecabtagene vicleucel) at the following publicly accessible link (last access: 22 May 2024):

https://www.ema.europa.eu/en/documents/product-information/abecma-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 idecabtagene vicleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of 1 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, the need to report symptoms immediately to the treating physician, to remain close to the treatment facility for at least 4 weeks after infusion of idecabtagene vicleucel, and to carry the patient emergency card at all times.

Idecabtagene vicleucel must be used in a qualified treatment centre. For the infusion of idecabtagene vicleucel in multiple myeloma diagnosed with C90.00 and C90.01, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

There is limited experience of re-treatment of patients with a second dose of Abecma. The response to re-treatment with Abecma was irregular and of shorter duration compared to the first treatment. In addition, fatal courses were observed in patients who were retreated.

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: 1 September 2024).

Idecabtagene vicleucel

Idecabtagene vicleucel 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 these active ingredients.

Idecabtagene vicleucel 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.

Idecabtagene vicleucel are autologous T cells genetically modified to express a chimeric antigen receptor directed against BCMA (B-cell maturation antigen). Accordingly, the concentration of viable CAR-positive T cells may vary between patient-individual batches. One or more infusion bags contain a total of 260 x 10^6 to 500 x 10^6 viable CAR+ T cells.

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.

Idecabtagene vicleucel is administered as a single intravenous infusion according to the requirements in the product information.

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

Treatment with ixazomib in combination with lenalidomide and dexamethasone for more than 24 cycles should be based on an individual risk-benefit assessment, as data on tolerability and toxicity beyond 24 cycles are limited.

Treatment with carfilzomib in combination with lenalidomide and dexamethasone spanning beyond 18 cycles should be based on an individual risk-benefit assessment, as data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited.

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.

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy; prior treatment includes an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Idecabtagene vicleucel				
Idecabtagene vicleucel	Single dose	1	1	1
Appropriate comparator therapy				
A patient-individual therapy under selection of:				
Bortezomib in combination with pegylated liposomal doxorubicin (only for at least double-refractory subjects who are ineligible for triplet therapy)				
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)				
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 lenalidomide and dexamethasone				
Carfilzomib	1st - 12th cycle: Day 1, 2, 8, 9, 15, 16 From 13th cycle: Day 1, 2, 15, 16 28-day cycle	13.0	1st - 12th cycle: 6 From 13th cycle: 4	76.0
Lenalidomide	Day 1 – 21: 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22:	13.0	4	52.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	28-day cycle			
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
Daratumumab in combination with lenalidomide 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
Lenalidomide	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**Fehler! Textmarke nicht definiert.**
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	29.0**Fehler! Textmarke nicht definiert.**

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
			From cycle 7 onwards: 3	
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
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**Fehler! Textmarke nicht definiert.**
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**Fehler! Textmarke nicht definiert.**
Daratumumab monotherapy (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)				
Daratumumab	Week 1 - 8:	23.0	1	23.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days			
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	1st - 2nd cycle: Day 1, 8, 15, 22 From 3rd cycle: Day 1, 15 28-day cycle	13.0	1st - 2nd cycle 4 From 3rd cycle 2	30.0
Lenalidomide	Day 1 – 21: 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22: 28-day cycle	13.0	4	52.0
Elotuzumab + pomalidomide + dexamethasone				
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
Dexamethasone	Day 1, 8, 15, 22: 28-day cycle	13.0	4	52.0
Isatuximab in combination with pomalidomide 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
Pomalidomide	Day 1 - 21: 28-day cycle	13.0	21	273.0

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
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**Fehler! Textmarke nicht definiert.**
Ixazomib in combination with lenalidomide and dexamethasone (only for subjects who are refractory to bortezomib, carfilzomib and an anti-CD38 antibody)				
Ixazomib	Day 1, 8, 15 of a 28-day cycle	13.0	3	39.0
Lenalidomide	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
Lenalidomide in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy)				
Lenalidomide	Day 1 - 21 of a 28-day cycle	13.0	21	273.0
Dexamethasone	1st - 4th cycle: Day 1 - 4, 9 - 12, 17 - 20 From 5th cycle: Day 1 - 4 28-day cycle	13.0	1st - 4th cycle: 12 From 5th cycle: 4	84.0
Panobinostat in combination with bortezomib and dexamethasone				
Panobinostat	1st - 16th cycle: Day 1, 3, 5, 8, 10, 12 21-day cycle	8 – 16	6	48 – 96

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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 and lenalidomide)				
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
Pomalidomide in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy)				
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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cyclophosphamide monotherapy (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)				
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)				
No specification possible				
Melphalan monotherapy (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)				
Melphalan	Continuously, 1 x every 28 days	13.0	1	13.0
Melphalan in combination with prednisolone or prednisone (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)				
Melphalan	Day 1 of a 28 – 42-day cycle	8.7 – 13.0	1	8.7 – 13.0
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

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)[2].

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.

The consumption of infusion bags is presented for the medicinal product to be assessed, idecabtagene vicleucel, according to the requirements in the product information. These are administered to the patient in a single infusion depending on the number of cells per infusion bag. The annual treatment costs of idecabtagene vicleucel are independent of the specific number of infusion bags used.

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy; prior treatment includes an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody

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					
Idecabtagene vicleucel					
Idecabtagene vicleucel	260 x 10^6 - 500 x 10^6 viable CAR+ T cells	260 x 10^6 - 500 x 10^6 viable CAR+ T cells	1 or more infusion bag(s)	1	1 or more infusion bag(s)
Appropriate comparator therapy					
A patient-individual therapy under selection of:					
Bortezomib in combination with pegylated liposomal doxorubicin (only for at least double-refractory subjects who are ineligible for triplet therapy)					
Bortezomib	1.3 mg/m²	2.5 mg	1 x 2.5 mg	32	32 x 2.5 mg
Doxorubicin (pegylated, liposomal)	30 mg/m²	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)					
Bortezomib	1.3 mg/m²	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

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 27 mg/m²	1st cycle day 1, 2 38.2 mg Thereafter 51.57 mg	1st cycle Day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 1 x 60 mg	76.0	2 x 10 mg + 2 x 30 mg + 74 x 60 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Carfilzomib in combination with dexamethasone					
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	20 mg	20 mg	1 x 20 mg	104.0	104 x 20 mg
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23.0	23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	29.0	29 x 40 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

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	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
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
Daratumumab monotherapy (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23.0	23 x 1,800 mg
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	10 mg/kg	777 mg	2 x 400 mg	30.0	60 x 400 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22: 28 mg From 3rd cycle Day 1, 15: 28 mg Day 8, 22: 40 mg	1st - 2nd cycle Day 1, 8, 15, 22: 28 mg From 3rd cycle Day 1, 15: 28 mg Day 8, 22: 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52.0	30 x 8 mg + 30 x 20 mg + 22 x 40 mg
Elotuzumab + pomalidomide + dexamethasone					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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
Isatuximab in combination with pomalidomide 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
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	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
			2 x 10 mg + 1 x 30 mg + 1 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
Ixazomib in combination with lenalidomide and dexamethasone (only for subjects who are refractory to bortezomib, carfilzomib and an anti-CD38 antibody)					
Ixazomib	4 mg	4 mg	1 x 4 mg	39.0	39 x 4 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Lenalidomide in combination with dexamethasone (only for at least double-refractory subjects who are ineligible for triplet therapy)					
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	84.0	84 x 40 mg
Panobinostat in combination with bortezomib and dexamethasone					
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 and lenalidomide)					
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)					
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
Cyclophosphamide monotherapy (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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)					
No specification possible					
Melphalan monotherapy (only for at least triple refractory subjects who are ineligible for triplet or doublet therapy)					
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)					
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 + 52 x 5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

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				
Idecabtagene vicleucel	1 or more infusion bag(s) (260 x 10^6 - 500 x 10^6 viable CAR+ T cells)	€ 240,000	€ 0 [3]	€ 240,000

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	€ 2.00	€ 8.26	€ 175.11
Carfilzomib 10 mg	1 PIS	€ 197.03	€ 2.00	€ 10.28	€ 184.75
Carfilzomib 30 mg	1 PIS	€ 568.43	€ 2.00	€ 30.84	€ 535.59
Carfilzomib 60 mg	1 PIS	€ 1,125.54	€ 2.00	€ 61.69	€ 1,061.85
Cyclophosphamide 1,000 mg	6 PSI	€ 127.45	€ 2.00	€ 6.43	€ 119.02
Cyclophosphamide 500 mg	6 PSI	€ 84.44	€ 2.00	€ 9.25	€ 73.19
Cyclophosphamide 200 mg	10 PSI	€ 62.80	€ 2.00	€ 2.85	€ 57.95
Daratumumab 1,800 mg	1 SFI	€ 5,809.87	€ 2.00	€ 0.00	€ 5,807.87
Dexamethasone 4 mg[4]	10 SFI	€ 16.92	€ 2.00	€ 0.44	€ 14.48
Dexamethasone 8 mg[4]	100 TAB	€ 123.41	€ 2.00	€ 8.87	€ 112.54
Dexamethasone 20 mg[4]	10 TAB	€ 32.42	€ 2.00	€ 0.00	€ 30.42
Dexamethasone 20 mg[4]	20 TAB	€ 54.09	€ 2.00	€ 0.00	€ 52.09

[3] The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.
[4] Fixed reimbursement rate

Dexamethasone 20 mg[4]	50 TAB	€ 118.88	€ 2.00	€ 0.00	€ 116.88
Dexamethasone 40 mg[4]	50 TAB	€ 188.03	€ 2.00	€ 0.00	€ 186.03
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 721.49	€ 2.00	€ 89.87	€ 629.62
Pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,778.90	€ 2.00	€ 224.69	€ 1,552.21
Elotuzumab 400 mg	1 PIC	€ 1,557.91	€ 2.00	€ 85.68	€ 1,470.23
Isatuximab 100 mg	1 CIS	€ 333.96	€ 2.00	€ 17.86	€ 314.10
Isatuximab 500 mg	1 CIS	€ 1,621.58	€ 2.00	€ 89.32	€ 1,530.26
Ixazomib 4 mg	3 HC	€ 6,431.30	€ 2.00	€ 364.00	€ 6,065.30
Lenalidomide 25 mg[4]	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Melphalan 50 mg	1 DSS	€ 50.49	€ 2.00	€ 2.17	€ 46.32
Panobinostat 20 mg	6 HC	€ 4,656.41	€ 2.00	€ 262.64	€ 4,391.77
Pomalidomide 4 mg	21 HC	2,781.42	€ 2.00	€ 133.33	€ 2,646.09
Prednisolone 5 mg[4]	100 TAB	€ 15.43	€ 2.00	€ 0.33	€ 13.10
Prednisolone 50 mg[4]	50 TAB	€ 31.44	€ 2.00	€ 1.59	€ 27.85
Prednisone 5 mg[4]	100 TAB	€ 16.74	€ 2.00	€ 0.43	€ 14.31
Prednisone 50 mg[4]	50 TAB	€ 68.06	€ 2.00	€ 4.49	€ 61.57
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: 1 September 2024

Costs for additionally required SHI services:

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

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

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

According to the product information of idecabtagene vicleucel, lymphocyte-depleting chemotherapy should be administered before the CAR-T cells are administered. To this end, cyclophosphamide (300 mg/m^2 = 573 mg) and fludarabine (30 mg/m^2 = 57.3 mg) should be administered daily for 3 days.

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 idecabtagene vicleucel. 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[5]. 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, daratumumab and lenalidomide 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[6]. 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 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.

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[5] 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

[6] 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

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							
Idecabtagene vicleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide IV 300 mg/m² = 573 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 2.85	€ 57.95	3.0	€ 57.95
Fludarabine IV 30 mg/m² = 57.3 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 668.70
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
HCV screening							
Hepatitis C HCV antibody status (GOP 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV screening							
Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies (GOP number 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Appropriate comparator therapy							
Daratumumab *in combination with lenalidomide and dexamethasone*							
Premedication							
Dexamethasone 40 mg, PO[4]	50 TAB x 40 mg	€ 188.03	€ 2.00	€ 0.00	€ 186.03	23.0	€ 85.57
Paracetamol 500 - 1,000 mg, PO[4,7]	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	€ 23.72	€ 2.00	€ 5.02	€ 16.70	23.0	€ 153.64
Daratumumab *in combination with bortezomib and dexamethasone*							
Premedication							

[7] 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
Dexamethasone 20 mg, PO [4]	50 TAB x 20 mg	€ 118.88	€ 2.00	€ 0.00	€ 116.88	21.0	€ 49.09
Paracetamol 500 - 1,000 mg, PO [7,4]	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	€ 23.72	€ 2.00	€ 5.02	€ 16.70	21.0	€ 140.28
Daratumumab *in combination with pomalidomide and dexamethasone*							
Premedication							
Dexamethasone 40 mg, PO [4]	50 TAB x 40 mg	€ 188.03	€ 2.00	€ 0.00	€ 186.03	23.0	€ 85.57
Paracetamol 500 - 1,000 mg, PO [7,4]	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	€ 23.72	€ 2.00	€ 5.02	€ 16.70	23.0	€ 153.64
Daratumumab *in combination with carfilzomib and dexamethasone*							
Dexamethasone 20 mg, PO [4]	50 TAB x 20 mg	€ 118.88	€ 2.00	€ 0.00	€ 116.88	21.0	€ 49.09
Dexamethasone 40 mg, PO [4]	50 TAB x 40 mg	€ 188.03	€ 2.00	€ 0.00	€ 186.03	2.0	€ 7.44
Paracetamol 500 - 1,000 mg, PO [7,4]	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	€ 23.72	€ 2.00	€ 5.02	€ 16.70	23.0	€ 153.64
Daratumumab *monotherapy*							
Premedication							
Methyl prednisolone 60 mg - 100 mg, IV	3 PII x 32 mg	€ 26.14	€ 2.00	€ 6.73	€ 17.41	23.0	€ 266.95 - € 533.91
Postmedication							

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
Methyl prednisolone 20 mg, PO[4]	100 TAB x 4 mg 100 TAB x 16 mg	€ 29.35 € 73.84	€ 2.00 € 2.00	€ 1.43 € 4.95	€ 25.92 € 66.89	46.0 46.0	€ 42.69
Elotuzumab *in combination with lenalidomide and dexamethasone*							
Premedication in combination with lenalidomide and dexamethasone							
Dexamethasone 8 mg, IV [4]	10 SFI x 8 mg	€ 20.38	€ 2.00	€ 0.72	€ 17.66	30.0	€ 52.98
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 23.72	€ 2.00	€ 5.02	€ 16.70	30.0	€ 200.40
Famotidine 20 mg, PO [4]	100 TAB x 20 mg	€ 20.18	€ 2.00	€ 0.70	€ 17.48	30.0	€ 5.24
Paracetamol 500 – 1,000 mg, PO[4]	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	30.0	€ 4.73 - € 9.03
Elotuzumab *in combination with pomalidomide and dexamethasone*							
Premedication in combination with pomalidomide and dexamethasone							
Dexamethasone 8 mg, IV[4]	10 SFI x 8 mg	€ 20.38	€ 2.00	€ 0.72	€ 17.66	19.0	€ 33.55
Dimetindene 1 mg/10 kg BW, IV	5 SFI x 4 mg	23.72	€ 2.00	€ 5.02	€ 16.70	19.0	€ 126.92
Famotidine 20 mg, PO[4]	100 TAB x 20 mg	€ 20.18	€ 2.00	€ 0.70	€ 17.48	19.0	€ 3.32
Paracetamol 500 – 1,000 mg, PO[4]	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 Lenalidomide Pomalidomide							
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Abbreviations:							

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
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 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs 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 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:

Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy; prior treatment includes an immunomodulator, a proteasome inhibitor and an anti-CD-38 antibody

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 idecabtagene vicleucel (Abecma); ABECMA® 260 - 500 × 10^6 cells infusion dispersion; last revised: June 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

At its session on 24 January 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 March 2024.

On 27 March 2024, the pharmaceutical company submitted a dossier for the benefit assessment of idecabtagene vicleucel to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 27 March 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 idecabtagene vicleucel.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 June 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 July 2024. The deadline for submitting statements was 22 July 2024.

The oral hearing was held on 5 August 2024.

By letter dated 6 August 2024, 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 29 August 2024.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 September 2024, and the proposed draft resolution was approved.

At its session on 19 September 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 January 2023	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	26 March 2024	New determination of the appropriate comparator therapy
Working group Section 35a	30 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 August 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 August 2024 3 September 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	10 September 2024	Concluding discussion of the draft resolution

Plenum	19 September 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 September 2024

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

Prof. Hecken