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
Daratumumab (new therapeutic indication: multiple myeloma, first-line, suitable for stem cell transplantation, combination with bortezomib, lenalidomide and dexamethasone)

of 15 May 2025

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient daratumumab (Darzalex) was listed for the first time on 1 June 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Daratumumab is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indications, the sales volume of daratumumab with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 50 million. Evidence must therefore be provided for daratumumab in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 21 October 2024, daratumumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for

medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 19 November 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient daratumumab with the new therapeutic indication ("Darzalex is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 March 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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 Daratumumab (Darzalex) in accordance with the product information

Darzalex is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Therapeutic indication of the resolution (resolution of 15.05.2025):

See the approved therapeutic indication.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

Appropriate comparator therapy for daratumumab in combination with bortezomib, lenalidomide and dexamethasone:

- An induction therapy consisting of:
  - bortezomib + thalidomide + dexamethasone (VTd)

    or
  - bortezomib + cyclophosphamide + dexamethasone (VCd) [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive]

    or
  - daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)
- followed by a high-dose therapy with melphalan and subsequent autologous stem cell transplant
- followed by a consolidation therapy with D-VTd (only if an induction therapy with D-VTd is administered)
- followed by maintenance treatment with lenalidomide

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

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

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal

product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

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. In terms of authorisation status, the chemotherapeutic agents carmustine, cyclophosphamide, doxorubicin, melphalan and vincristine, the proteasome inhibitor bortezomib, the CD38 antibody daratumumab, the immunomodulatory substances lenalidomide and thalidomide, as well as the glucocorticoids dexamethasone, prednisolone and prednisone are available for the treatment of adults with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

On 2. In principle, autologous and allogeneic stem cell transplants can be considered in this therapeutic indication.

On 3. In the therapeutic indication of newly diagnosed multiple myeloma, the following resolutions on the benefit assessment of medicinal products with new active ingredients (Section 35a SGB V) are available:
- Daratumumab in combination with bortezomib, thalidomide and dexamethasone (resolution of 20 August 2020)
- Daratumumab in combination with lenalidomide and dexamethasone (resolution 18 March 2022)
- Daratumumab in combination with bortezomib, melphalan and prednisone (resolution of 16 May 2024)

Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex VI (off-label use):
Bortezomib plus cyclophosphamide plus dexamethasone for the induction therapy of newly diagnosed multiple myeloma (resolution of 20 May 2021).

There is also a resolution dated 19.01.2017 on the Directive on Inpatient Treatment Methods (last revised 17 June 2021) - Annex II: Methods whose assessment procedures have been suspended (resolution of 19.01.2017):

- Autologous multiple transplantation (tandem transplantation) for multiple myeloma
- Allogeneic stem cell transplant for multiple myeloma in first-line therapy

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

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

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

Overall, the research revealed extensive evidence from systematic reviews and relevant guidelines on treatment options for adults with newly diagnosed multiple myeloma that are suitable for autologous stem cell transplant.

Accordingly, patients were given induction therapy as standard prior to autologous stem cell transplant. In the available evidence, the induction therapy is based on a triple or quadruple combination, which should contain a proteasome inhibitor. The approved combinations of bortezomib with thalidomide and dexamethasone (VTd) and daratumumab with bortezomib and thalidomide and dexamethasone (D-VTd) are eligible for this. For the combination therapy of daratumumab with bortezomib and thalidomide and dexamethasone, the G-BA determined a non-quantifiable additional benefit compared to bortezomib + thalidomide + dexamethasone by resolution of 20 August 2020. The two combination therapies of D-VTd and VTd are considered to be equally appropriate comparator therapies for the treatment phase of induction therapy.

The combination of bortezomib, cyclophosphamide and dexamethasone can also be considered as induction therapy. The latter is only indicated for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy in accordance with Annex VI to Section K of the Pharmaceuticals Directive.

The present guidelines and the statements of the clinical experts in the written statement procedure also refer to the triple combination consisting of bortezomib, lenalidomide and dexamethasone. As part of a completed marketing authorisation procedure by the European Medicines Agency (EMA) for lenalidomide (Revlimid) for the treatment of newly diagnosed multiple myeloma, it was however found that no conclusions regarding either superiority or non-inferiority to standard therapy can be drawn on the basis of the presented evidence for adults eligible for autologous stem cell transplant[2]. Accordingly, the combination therapy of bortezomib + lenalidomide + dexamethasone is not determined as an appropriate comparator therapy for the induction therapy phase.

[2] European Medicines Agency (EMA). Assessment report: Revlimid. 28 March 2019 URL: https://www.ema.europa.eu/en/documents/variation-report/revlimid-h-c-717-ii-0102-g-epar-assessment-report-variation_en.pdf

Induction therapy is followed by high-dose therapy with subsequent autologous stem cell transplant. According to guidelines, melphalan is the standard for high-dose therapy.

Antineoplastic consolidation therapy following autologous stem cell transplant has not yet shown any advantage in terms of overall survival and cannot be considered the standard based on the available evidence. Here, the concept of "consolidation" therapy must be distinguished from that of "maintenance treatment", which address different therapeutic goals. Only when D-VTd-based induction therapy is administered does consolidation therapy with 2 cycles of D-VTd following high-dose therapy and autologous stem cell transplant correspond to the dosage regimen according to the product information for daratumumab and is part of the appropriate comparator therapy.

With regard to maintenance treatment, the guidelines are clearly in favour of maintenance treatment with lenalidomide, which is the only medicinal product with explicit marketing authorisation for this therapy phase.

The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately.

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 daratumumab is assessed as follows:

Adults with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

An additional benefit is not proven.

Justification:

About the PERSEUS study

For the assessment of the additional benefit of daratumumab in combination with bortezomib, lenalidomide and dexamethasone compared with the appropriate comparator therapy, the pharmaceutical company submitted the ongoing, open-label, randomised PERSEUS study.

The study treatment was divided into the 3 phases of induction, consolidation and maintenance. As induction therapy, patients in both study arms received treatment with bortezomib, lenalidomide and dexamethasone for 4 cycles (28 days each). In the intervention arm, treatment was also given in combination with daratumumab. This is followed by stem cell mobilisation, high-dose chemotherapy with melphalan and an autologous stem cell transplant. The autologous stem cell transplant is followed by consolidation therapy (combination of active ingredients identical to the induction phase) with 2 cycles (28 days each). In maintenance treatment, a combination therapy of daratumumab + lenalidomide in the intervention arm or monotherapy with lenalidomide in the comparator arm is

administered in 28-day cycles until disease progression or the occurrence of unacceptable toxicity.

Adult patients with newly diagnosed multiple myeloma for whom high-dose therapy and autologous stem cell transplant was indicated were enrolled. Patients had to have a general condition according to ECOG-PS ≤ 2.

The primary endpoint of the study is progression-free survival. Secondary endpoints include overall survival, morbidity and health-related quality of life endpoints and adverse events.

The still ongoing study was conducted in study sites in Europe and Australia and was initiated in December 2018. The end of the study is currently estimated to be November 2029.

Implementation of the appropriate comparator therapy:

The induction therapy with bortezomib + lenalidomide + dexamethasone (VRd) used in the comparator arm of the PERSEUS study does not correspond to any of the options for induction therapy specified in the appropriate comparator therapy.

With regard to induction therapy with VRd, as part of a completed EMA marketing authorisation procedure for lenalidomide (Revlimid) for the treatment of newly diagnosed multiple myeloma, it was found that no conclusions regarding either superiority or non-inferiority to standard therapy can be drawn on the basis of the presented evidence for adults eligible for autologous stem cell transplant[3]. The EMA has therefore not made a positive recommendation for a marketing authorisation of VRd for patients who are eligible for an autologous stem cell transplant and has limited the positive recommendation to patients who are ineligible for an autologous stem cell transplant. The corresponding European Public Assessment Report (EPAR)[3] stated in this regard that the EMA will revisit the question of marketing authorisation of VRd for patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant as soon as new suitable evidence is available for this research question. However, since this decision by the EMA on the facts presented, no suitable new studies that would allow reassessment of this research question are available. Accordingly, the combination therapy of bortezomib + lenalidomide + dexamethasone is not determined as an appropriate comparator therapy for the induction therapy phase.

In contrast, clinical experts stated in the written statement procedure that VRd is a relevant therapy option in induction therapy and that induction therapy with VRd also corresponds to the German healthcare context.

In addition, the consolidation therapy with VRd used in the comparator arm of the PERSEUS study does not correspond to the appropriate comparator therapy determined by the G-BA.

In this regard, antineoplastic consolidation therapy following autologous stem cell transplant has not yet shown any advantage in terms of overall survival and cannot be considered the standard based on the available evidence. Here, the concept of "consolidation" therapy must be distinguished from that of "maintenance treatment", which address different therapeutic goals. Only when D-VTd-based induction therapy is administered does consolidation therapy with 2 cycles of D-VTd following high-dose therapy and autologous stem cell transplant correspond to the dosage regimen according to the product information for daratumumab and is part of the appropriate comparator therapy.

Conclusion:

[3] European Medicines Agency (EMA). Assessment report: Revlimid. 28 March 2019 URL: https://www.ema.europa.eu/en/documents/variation-report/revlimid-h-c-717-ii-0102-g-epar-assessment-report-variation_en.pdf

Overall, the induction and consolidation therapy with VRd conducted in the comparator arm of the PERSEUS study does not correspond to the appropriate comparator therapy determined by the G-BA. Thus, the appropriate comparator therapy was not implemented in the PERSEUS study. Thus, the PERSEUS study is not suitable for the assessment of the additional benefit of daratumumab + bortezomib + lenalidomide + dexamethasone compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient daratumumab.

Daratumumab (Darzalex) is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

The G-BA determined the following as appropriate comparator therapy:

- an induction therapy consisting of bortezomib + thalidomide + dexamethasone (VTd), or bortezomib + cyclophosphamide + dexamethasone (VCd) [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive], or daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)
- followed by a high-dose therapy with melphalan and subsequent autologous stem cell transplant
- followed by a consolidation therapy with D-VTd (only if an induction therapy with D-VTd is administered)
- followed by maintenance treatment with lenalidomide

For the assessment of the additional benefit of daratumumab in combination with bortezomib, lenalidomide and dexamethasone, the pharmaceutical company submitted the ongoing, open-label, randomised PERSEUS study, which compared daratumumab + bortezomib + lenalidomide + dexamethasone with bortezomib + lenalidomide + dexamethasone for newly diagnosed multiple myeloma in patients who are eligible for autologous stem cell transplant.

The induction therapy with bortezomib + lenalidomide + dexamethasone (VRd) used in the comparator arm of the PERSEUS study does not correspond to any of the options for induction therapy specified in the appropriate comparator therapy.

With regard to induction therapy with VRd, as part of a completed EMA marketing authorisation procedure for lenalidomide (Revlimid) for the treatment of newly diagnosed multiple myeloma, it was found that no conclusions regarding either superiority or non-inferiority to standard therapy can be drawn on the basis of the presented evidence for adults eligible for autologous stem cell transplant. Accordingly, the combination therapy of bortezomib + lenalidomide + dexamethasone is not determined by the G-BA as an appropriate comparator therapy for the induction therapy phase.

In addition, the consolidation therapy with VRd used in the comparator arm of the PERSEUS study does not correspond to the appropriate comparator therapy determined.

In summary, the PERSEUS study is not suitable for the assessment of the additional benefit of daratumumab + bortezomib + lenalidomide + dexamethasone compared with the appropriate comparator therapy.

Thus, no suitable data are available to enable an assessment of the additional benefit, which is why an additional benefit of dartumumab in combination with bortezomib and lenalidomide and dexamethasone in the treatment of patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant is not proven.

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

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

The resolution is based on the information from the dossier of the pharmaceutical company.

The number of patients estimated by the pharmaceutical company is subject to uncertainties, which mainly result from the determination of the number of patients with newly diagnosed multiple myeloma who are eligible for autoSCT from the reported sample sizes of autologous first transplants from the German Registry for Haematopoietic Stem Cell Transplantation and Cell Therapy (DRST). In this respect, it is conceivable that:

- The DRST sample sizes also include patients whose disease was not newly diagnosed in the year under review.
- Those patients, who were eligible for an autoSCT at least initially, but did not receive it, were not included.

In the overall assessment, it is however assumed that these uncertainties are sufficiently small for the patient numbers to be considered plausible in terms of size.

In addition, the number of patients in the SHI target population in the present procedure is of a similar size as in the benefit assessment procedure on daratumumab from 2020 in the same therapeutic indication, despite a different methodological approach. The number of patients determined for this assessment is favoured due to the more recent data.

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 Darzalex (active ingredient: daratumumab) at the following publicly accessible link (last access: 21 February 2025):

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

Treatment with daratumumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with multiple myeloma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for medical professionals and blood banks contains instructions on how to manage the risk of daratumumab interfering with blood typing (indirect antihuman globulin test or Coombs test). Interference with blood typing induced by daratumumab may persist for up to six months after the last infusion of the medicinal product; therefore, medical professionals should advise patients to carry their patient identification card with them for up to six months after the end of the treatment.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2025).

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.

The cost representation for daratumumab in combination with bortezomib, lenalidomide and dexamethasone is based on the treatment regimen used in the MMY3014 study.

The cost representation for daratumumab in combination with bortezomib, thalidomide and dexamethasone (VTd) is based on the treatment regimen used in the MMY3006 study.

Inpatient treatments

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

To calculate the treatment duration for the maintenance treatments, the treatment duration of the induction therapies plus any consolidation therapy and the treatment duration (23.2 days) of high-dose chemotherapy with subsequent autologous stem cell transplant were taken into account. The DRG case flat fees used and the corresponding mean lengths of stay result in a mean total treatment duration of 23.2 days for high-dose chemotherapy with melphalan followed by autologous stem cell transplant. The actual treatment duration and the haematological recovery phase following autologous stem cell transplant is different from patient to patient and is not taken into account in the calculation.

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)[4].

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

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Daratumumab in combination with bortezomib, lenalidomide and dexamethasone				
Induction				
Daratumumab	Cycle 1 - 2 Day 1, 8, 15 and 22 Cycle 3 - 4 Day 1 and 15 of a 28-day cycle	4	Cycle 1 – 2: 4 Cycle 3 – 4: 2	12
Bortezomib	Day 1, 4, 8 and 11 of a 28-day cycle	4	4	16
Lenalidomide	Day 1 – 21 of a 28-day cycle	4	21	84
Dexamethasone[5]	On the days 1 – 4 and 9 – 12 of a 28-day cycle	4	7	28
High-dose chemotherapy and subsequent autologous stem cell transplant				
Bone marrow transplantation/ stem cell transfusion, autogenous, for plasmacytoma, without specific collection	once		19.0 (average length of stay)	19.0
Stem cell collection from autologous donors without chemotherapy, age > 15 years, without most severe CC, without sepsis, without complicating constellation	once		4.2 (average length of stay)	4.2
Consolidation				
Daratumumab	Day 1 and 15 of a 28-day cycle	2	2	4
Bortezomib	Day 1, 4, 8 and 11 of a 28-day cycle	2	4	8

[5] On the days of daratumumab administration, the dexamethasone dose is administered orally or intravenously as premedication

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lenalidomide	Day 1 – 21 of a 28-day cycle	2	21	42
Dexamethasone[5]	On the days 1 – 4 and 9 – 12 of a 28-day cycle	2	7	14
Maintenance treatment				
Daratumumab	1 x every 28 days	6.2	1	6.2
Lenalidomide	Day 1 – 28 of a 28-day cycle	6.2	28	173.6
Appropriate comparator therapy				
Bortezomib + thalidomide + dexamethasone (VTd)				
Induction				
Bortezomib	On the days 1, 4, 8 and 11 of a 28-day cycle	4 – 6	4	16 – 24
Thalidomide	Day 1 – 28 of a 28-day cycle	4 – 6	28	112 – 168
Dexamethasone PO	On the days 1, 2, 3, 4, 8, 9, 10 and 11 of a 28-day cycle	4 – 6	8	32 – 48
High-dose therapy with melphalan and subsequent autologous stem cell transplant				
Bone marrow transplantation/ stem cell transfusion, autogenous, for plasmacytoma, without specific collection	once		19.0 (average length of stay)	19.0
Stem cell collection from autologous donors without chemotherapy, age > 15 years, without most severe CC, without sepsis, without complicating constellation	once		4.2 (average length of stay)	4.2
Maintenance treatment with lenalidomide				
Lenalidomide	Day 1 – 28 of a 28-day cycle	6.2 – 8.2	28	173.6 – 229.6

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bortezomib + cyclophosphamide + dexamethasone (VCd) (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive)				
Induction				
Bortezomib	Day 1, 4, 8, 11 of a 21-day cycle	3 – 4	4	12 – 16
Cyclophosphamide	Day 1 of a 21-day cycle	3 – 4	1	3 – 4
Dexamethasone	On the days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle	3 – 4	8	24 – 32
High-dose therapy with melphalan and subsequent autologous stem cell transplant				
Bone marrow transplantation/ stem cell transfusion, autogenous, for plasmacytoma, without specific collection	once		19.0 (average length of stay)	19.0
Stem cell collection from autologous donors without chemotherapy, age > 15 years, without most severe CC, without sepsis, without complicating constellation	once		4.2 (average length of stay)	4.2
Maintenance treatment with lenalidomide				
Lenalidomide	Day 1 – 28 of a 28-day cycle	9.2 – 10.0	28	257.6 – 280.0
daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)				
Induction				
Daratumumab	28-day cycle: Cycle 1 - 2 1 x every 7 days Cycle 3 - 4 1 x every 14 days	4	Cycle 1 – 2: 4 Cycle 3 – 4: 2	12
Bortezomib	Day 1, 4, 8 and 11 of a 28-day cycle	4	4	16

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Thalidomide	Day 1 – 28 of a 28-day cycle	4	28	112
Dexamethasone[6]	Cycle 1 – 2: Day 1, 2, 8, 9, 15, 16, 22 and 23 Cycle 3 – 4: Day 1, 2, 8, 9, 15 and 16 of a 28-day cycle	4	4	16
High-dose therapy with melphalan and subsequent autologous stem cell transplant				
Bone marrow transplantation/ stem cell transfusion, autogenous, for plasmacytoma, without specific collection	once		19.0 (average length of stay)	19.0
Stem cell collection from autologous donors without chemotherapy, age > 15 years, without most severe CC, without sepsis, without complicating constellation	once		4.2 (average length of stay)	4.2
Consolidation				
Daratumumab	28-day cycle: 1 x every 14 days	2	2	4
Bortezomib	Day 1, 4, 8 and 11 of a 28-day cycle	2	4	8
Thalidomide	Day 1 – 28 of a 28-day cycle	2	28	56
Dexamethasone[6]	Cycle 5 – 6: Day 1, 2, 8, 9, 15 and 16 of a 28-day cycle	2	4	8
Maintenance treatment with lenalidomide				

[6] On the days of daratumumab injection, the dexamethasone dose is administered as premedication.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lenalidomide	Day 1 – 28 of a 28-day cycle	6.2	28	173.6

Consumption:

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					
Daratumumab in combination with bortezomib, lenalidomide and dexamethasone					
Induction					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	12	12 x 1,800 mg
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	16	16 x 2.5 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	84	84 x 20 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	28	28 x 40 mg
High-dose therapy with melphalan and subsequent autologous stem cell transplant					
	once				
Consolidation					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	4	4 x 1,800 mg
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	8	8 x 2.5 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	42	42 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	14	14 x 40 mg
Maintenance treatment					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	6.2	6.2 x 1,800 mg
Lenalidomide	10 mg	10 mg	1 x 10 mg	173.6	173.6 x 10 mg
Appropriate comparator therapy					
Bortezomib + thalidomide + dexamethasone (VTd)					
Induction					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	16 – 24	16 x 2.5 mg – 24 x 2.5 mg
Thalidomide	Cycle 1 Day 1 – 14:	Cycle 1 Day 1 – 14:	Cycle 1 Day 1 - 14	112 – 168	112 x 50 mg – 602 x 50 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	50 mg <u>Day 15 - 28</u> 50 mg – 100 mg <u>Cycle 2 - 6</u> 50 mg – 200 mg	50 mg <u>Day 15 - 28</u> 50 mg – 100 mg <u>Cycle 2 - 6</u> 50 mg – 200 mg	1 x 50 mg <u>Day 15 - 28</u> 1 x 50 mg – 2 x 50 mg <u>Cycle 2 - 6</u> 1 x 50 mg – 4 x 50 mg		
Dexamethasone PO	40 mg	40 mg	1 x 40 mg	32 – 48	32 x 40 mg – 48 x 40 mg
High-dose therapy with melphalan and subsequent autologous stem cell transplant					
	once				
Maintenance treatment with lenalidomide					
Lenalidomide	<u>Cycle 1 - 3</u> 10 mg <u>From cycle 3 onwards</u> 10 mg – 15 mg	<u>Cycle 1 - 3</u> 10 mg <u>From cycle 3 onwards</u> 10 mg – 15 mg	<u>Cycle 1 - 3</u> 1 x 10 mg <u>From cycle 3 onwards</u> 1 x 10 mg – 1 x 15 mg	173.6 – 229.6	173.6 x 10 mg – 84 x 10 mg + 145.6 x 15 mg
Bortezomib + cyclophosphamide + dexamethasone (VCd) (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive)					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	12 – 16	12 x 2.5 mg – 16 x 2.5 mg
Cyclophosphamide	900 mg/m^2 = 1,719 mg	1,719 mg	2 x 1,000 mg	3 – 4	6 x 1,000 mg – 8 x 1,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	24 – 32	24 x 40 mg – 32 x 40 mg
High-dose therapy with melphalan and subsequent autologous stem cell transplant					
	once				
Maintenance treatment with lenalidomide					
Lenalidomide	<u>Cycle 1 - 3</u> 10 mg <u>From cycle 3 onwards</u> 10 mg – 15 mg	<u>Cycle 1 - 3</u> 10 mg <u>From cycle 3 onwards</u> 10 mg – 15 mg	<u>Cycle 1 - 3</u> 1 x 10 mg <u>From cycle 3 onwards</u> 1 x 10 mg – 1 x 15 mg	257.6 –280.0	257.6 x 10 mg – 84 x 10 mg + 196 x 15 mg
daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Induction					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	12	12 x 1,800 mg
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	16	16 x 2.5 mg
Thalidomide	100 mg	100 mg	2 x 50 mg	112	224 x 50 mg
Dexamethasone [6]	Cycle 1 - 2 Day 1, 2, 8, 9, 15, 16, 22 and 23 and cycle 3 – 4 Day 1 and 2: 40 mg	40 mg	1 x 40 mg	10	10 x 40 mg
Dexamethasone [6]	Cycle 3 – 4 day 8, 9, 15 and 16: 20 mg	20 mg	1 x 20 mg	6	6 x 20 mg
High-dose therapy with melphalan and subsequent autologous stem cell transplant					
	once				
Consolidation					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	4	4 x 1,800 mg
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	8	8 x 2.5 mg
Thalidomide	100 mg	100 mg	2 x 50 mg	56	112 x 50 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	8	8 x 20 mg
Maintenance treatment with lenalidomide					
Lenalidomide	Cycle 1 - 3 10 mg From cycle 3 onwards 10 mg – 15 mg	Cycle 1 - 3 10 mg From cycle 3 onwards 10 mg – 15 mg	Cycle 1 - 3 1 x 10 mg From cycle 3 onwards 1 x 10 mg – 1 x 15 mg	173.6	173.6 x 10 mg – 84 x 10 mg + 89.6 x 15 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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction

of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Inpatient treatments:

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Medicinal product to be assessed									
High-dose chemotherapy and subsequent autologous stem cell transplant									
2025	A15D	19	3.823	€ 4,394.22	1.0538	€ 250	€ 16,799.10	€ 5,005.55	€ 21,804.65
2025	A42C	4.2	0.809	€ 4,394.22	0.843	€ 250	€ 3,554.92	€ 885.15	€ 4,440.07
Appropriate comparator therapy									
High-dose therapy with melphalan and subsequent autologous stem cell transplant									
2025	A15D	19	3.823	€ 4,394.22	1.0538	€ 250	€ 16,799.10	€ 5,005.55	€ 21,804.65
2025	A42C	4.2	0.809	€ 4,394.22	0.843	€ 250	€ 3,554.92	€ 885.15	€ 4,440.07

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Daratumumab 1,800 mg	1 SFI	€ 5,953.27	€ 1.77	€ 0.00	€ 5,951.50
Dexamethasone 40 mg[7]	50 TAB	€ 188.03	€ 1.77	€ 0.00	€ 186.26
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 1.77	€ 8.26	€ 175.34
Lenalidomide 25 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Lenalidomide 10 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Appropriate comparator therapy					
Daratumumab 1,800 mg	1 SFI	€ 5,953.27	€ 1.77	€ 0.00	€ 5,951.50
Dexamethasone 20 mg[7]	20 TAB	€ 54.09	€ 1.77	€ 0.00	€ 52.32
Dexamethasone 40 mg[7]	10 TAB	€ 46.29	€ 1.77	€ 0.00	€ 44.52
Dexamethasone 40 mg[7]	20 TAB	€ 81.59	€ 1.77	€ 0.00	€ 79.82
Dexamethasone 40 mg[7]	50 TAB	€ 188.03	€ 1.77	€ 0.00	€ 186.26
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 1.77	€ 8.26	€ 175.34
Cyclophosphamide 1,000 mg	6 PSI	€ 142.80	€ 1.77	€ 7.28	€ 133.75

[7] Fixed reimbursement rate

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
Cyclophosphamide 1,000 mg	1 PSI	€ 33.24	€ 1.77	€ 1.21	€ 30.26
Lenalidomide 25 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Lenalidomide 15 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Lenalidomide 10 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Thalidomide 50 mg	28 HC	€ 620.42	€ 1.77	€ 77.09	€ 541.56
Abbreviations: HC = hard capsules; SFI = solution for injection; PSI = powder for solution for injection; TAB = tablets					

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Costs for additionally required SHI services:

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

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

Screening for hepatitis B virus (HBV)

Patients receiving therapy with daratumumab, thalidomide 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[8]. 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

[8] 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

surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Daratumumab *in combination with bortezomib, lenalidomide and dexamethasone*							
Premedication							
Dexamethasone 20 mg, PO[7]	50 TAB x 20 mg	€ 118.88	€ 1.77	€ 0.00	€ 117.11	16.2	€ 37.94
Dexamethasone 40 mg, PO[7]	10 TAB x 40 mg	€ 46.29	€ 1.77	€ 0.00	€ 44.52	6.0	€ 44.52
Paracetamol 500 - 1,000 mg, PO [9,7]	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	22.2	€ 3.50 – € 6.68
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	22.2	€ 154.96
HBV screening (daratumumab, lenalidomide)							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43
Appropriate comparator therapy							
Daratumumab + *bortezomib + thalidomide + dexamethasone (D-VTd)*							
Premedication							
Dexamethasone 40 mg, PO[7]	10 TAB x 40 mg	€ 46.29	€ 1.77	€ 0.00	€ 44.52	10	€ 44.52
Dexamethasone 20 mg, PO[7]	10 TAB x 20 mg	€ 32.42	€ 1.77	€ 0.00	€ 30.65	6	€ 30.65
Paracetamol 500 - 1,000 mg, PO [7,9]	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	16	€ 3.15 – € 6.02
Dimetindene 1 mg/10 kg = 7.8 mg, IV	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	16	€ 122.15
Daratumumab Lenalidomide Thalidomide							
HBV screening							
HBV test	-	-	-	-	€ 5.06	1.0	€ 5.06

[9] 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
Hepatitis B surface antigen status (GOP 32781)							
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43
Abbreviations: SFI = solution for injection; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

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

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

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

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication)

and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

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

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

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

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

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

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

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication

according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

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

References:
Product information for daratumumab (Darzalex); DARZALEX® 1,800 mg solution for injection; last revised: October 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 their session on 22 May 2018, 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 their session on 26 November 2024.

On 19 November 2024, the pharmaceutical company submitted a dossier for the benefit assessment of daratumumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 21 November 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 daratumumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 20 February 2025, and the written statement procedure was initiated with publication on the G-BA website on 3 March 2025. The deadline for submitting statements was 24 March 2025.

The oral hearing was held on 7 April 2025.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 May 2025, and the proposed draft resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	22 May 2018	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	26 November 2024	Last new implementation of the appropriate comparator therapy
Working group Section 35a	1 April 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 April 2025	Conduct of the oral hearing
Working group Section 35a	15 April 2025 29 April 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 May 2025	Concluding discussion of the draft resolution
Plenum	15 May 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 May 2025

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

Prof. Hecken