Gemeinsamer Bundesausschuss

# Justification

to 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 (reassessment after the deadline: systemic light chain (AL) amyloidosis, first-line, combination with cyclophosphamide, bortezomib and dexamethasone)

of 21 August 2025

**Contents**

## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 studies the pharmaceutical company have 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 € 30 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.

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient daratumumab (Darzalex) on 29 July 2021. The resolution of 20 January 2022

adopted by the G-BA in this procedure was set a deadline until 1 March 2025 for patient population a1) (adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy). The present reassessment after the deadline (resolution of 21 August 2025) only deals with patient population a1); the findings of the resolution of 20 January 2022 on patient population a2) remain unaffected.

In accordance with Section 4, paragraph 3, number 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Darzalex recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 28 February 2025.

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 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 have 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 cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

**Therapeutic indication of the resolution (resolution of 21.08.2025):**

See new therapeutic indication according to marketing authorisation.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

**Appropriate comparator therapy:**

– Bortezomib in combination with cyclophosphamide and dexamethasone

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.

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

On 1. Besides daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone, no other marketing authorisations are available.

On 2. In the present therapeutic indication, autologous stem cell transplantation is generally considered for eligible patients.

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

- Daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (resolution of 20 January 2022)

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

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. Written statements from the German Society for Haematology and Medical Oncology (DGHO) as well as the AkdÄ have been received.

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

The National Comprehensive Cancer Network (NCCN) guideline recommends various bortezomib, carfilzomib, daratumumab, lenalidomide or melphalan-based treatment regimens for the treatment of AL amyloidosis, whereby a fundamental distinction is made between Mayo staging and the presence of significant neuropathy. In Mayo stage I-IIIA, autologous stem cell transplantation (ASCT) is also recommended for eligible patients.

The bortezomib, daratumumab or melphalan-based therapy options mentioned in the written statements of the Drugs Commission of the German Medical Association (AkdÄ) and the German Society for Haematology and Medical Oncology (DGHO) on the question of comparator therapy are based on patient-individual criteria, including age, general condition, comorbidity and organ damage. In particular, the degree of heart and renal failure as well as the presence of amyloid-related polyneuropathy are mentioned. In this respect, the DGHO recommended that patients with pre-existing polyneuropathies should not be treated with bortezomib.

If there is a response to the initial treatment (induction therapy), the written statement of the AkdÄ recommended subsequent high-dose melphalan therapy with autologous stem cell transplantation in eligible patients. However, high-dose therapy is only indicated for a small number of patients due to their age or impaired organ function.

Besides the combination of active ingredients daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone assessed here, no other medicinal products are approved for the treatment of light chain (AL) amyloidosis.

According to the statements of the DGHO and the German Society of Amyloid Diseases (DGAK), the combination of active ingredients bortezomib in combination with cyclophosphamide and dexamethasone corresponds to the standard before the introduction of daratumumab-containing combination therapy in the present therapeutic indication.

For the above-mentioned reasons, bortezomib in combination with cyclophosphamide and dexamethasone is therefore determined to be the appropriate comparator therapy.

On the determination of an off-label use of medicinal products as the appropriate comparator therapy:

Besides the medicinal product Darzalex with the active ingredient daratumumab to be assessed, no other medicinal products are approved for the treatment of systemic light chain (AL) amyloidosis. According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy in this context must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed.

Bortezomib in combination with cyclophosphamide and dexamethasone is recommended in the guideline of the National Comprehensive Cancer Network (NCCN) based on the results of retrospective cohort studies.[1][2] This combination is also named as a treatment option by the Drugs Commission of the German Medical Association (AkdÄ) as part of its participation in accordance with Section 35a paragraph 7 SGB V. The use of bortezomib in combination with cyclophosphamide and dexamethasone is medically necessary. According to the generally recognised state of medical knowledge, the off-label use is considered the therapy standard with regard to the patient group to be assessed. With the medicinal product to be assessed, a medicinal product approved in the therapeutic indication and thus for the patient group to be assessed is available for the first time (Section 6, paragraph 2, sentence 3, number 1 AM-NutzenV).

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 in combination with cyclophosphamide, bortezomib and dexamethasone is assessed as follows:

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

Hint for a considerable additional benefit

[1] Venner CP, Lane T, Foard D, Rannigan L, Gibbs SD, Pinney JH, Whelan CJ, Lachmann HJ, Gillmore JD, Hawkins PN, Wechalekar AD. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012 May 10;119(19):4387-90. doi: 10.1182/blood-2011-10-388462. Epub 2012 Feb 13. PMID: 22331187.

[2] Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, Stewart AK, Bergsagel PL, Fonseca R. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012 May 10;119(19):4391-4. doi: 10.1182/blood-2011-11-390930. Epub 2012 Feb 13. PMID: 22331188; PMCID: PMC3557400.

Justification:

For the benefit assessment, the pharmaceutical company submitted data from the open-label, randomised controlled phase III ANDROMEDA study, comparing daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone versus bortezomib in combination with cyclophosphamide and dexamethasone (VCd).

Adult patients with newly diagnosed systemic light chain amyloidosis (AL amyloidosis) who had at least one organ affected by AL amyloidosis and an ECOG-PS of no more than two were enrolled. Patients with abnormal cardiovascular conditions, for example New York Heart Association (NYHA) stage IIIb or IV heart failure and a planned autologous stem cell transplant (ASCT) within the first 6 cycles of treatment were excluded from enrolment in the study. Patients with grade 2 sensory peripheral neuropathy or grade 1 painful peripheral neuropathy were also excluded from enrolment in the study.

A total of 388 patients were enrolled, randomised in a 1:1 ratio and allocated to treatment either with daratumumab + VCd (N = 195) or with VCd (N = 193).

The ANDROMEDA study was conducted at 140 study sites in Asia, Australia, Europe, North America and South America from 10/2017 to 11/2024.

For the present benefit assessment, the results of the pre-specified final data cut-off from 15 November 2024 were used for the endpoint categories of mortality and side effects. The pre-specified data cut-off from 17 April 2024 was used for the endpoints in the categories of morbidity and health-related quality of life.

<u>On the implementation of the time limit requirements</u>

According to the justification of the resolution of 20 January 2022, the reason for the time limit for the patient population a1) was that further clinical data from the ANDROMEDA study were expected, which may be relevant for the benefit assessment. In particular, the final data on overall survival were not available due to a low number of events at the time of the used 1st data cut-off from the ANDROMEDA study, which is why the data on overall survival were assessed as less significant.

For the new benefit assessment after expiry of the deadline, evaluations for the patient population a1) for the expected final analysis of overall survival and especially the results for the endpoint of severe organ damage and all other patient-relevant endpoints, which are used for proving an additional benefit, from the ANDROMEDA study are to be presented.

In the dossier for the benefit assessment, the pharmaceutical company presented the results of the 2nd data cut-off from 17 April 2024 and also presented the relevant final evaluations at the data cut-off from 15 November 2024 for the mortality and side effects categories. For the categories of morbidity and health-related quality of life, results are not available for all endpoints at the relevant final data cut-off. Due to the collection of endpoints on side effects being linked to the treatment duration, these were only collected up to the 2nd data cut-off, and the results are therefore identical to the results for the final data cut-off. The endpoint of severe organ damage was only collected up to the 2nd data cut-off. For the patient-reported endpoints, the influence of the additional surveys on the results for the final data cut-off compared to the 2nd data cut-off was assessed as very minor, so that the 2nd data cut-off could be used for the new benefit assessment for the endpoints in the categories of morbidity and health-related quality of life. The time limit requirements are thus considered to have been implemented.

On the suitability of the patient population enrolled in the ANDROMEDA study

The present benefit assessment exclusively includes adults with newly diagnosed systemic light chain (AL) amyloidosis for whom VCd is the patient-individual appropriate therapy.

The therapy of patients with newly diagnosed systemic light chain (AL) amyloidosis depends on several individual factors. In addition to general condition, these are also existing comorbidity and organ damage of the patients. Accordingly, taking these factors into account, different treatment regimens, including high-dose melphalan therapy with autologous stem cell transplantation, are recommended in guidelines or the written statements of AkdÄ and scientific-medical societies on the question of the appropriate comparator therapy.

In the ANDROMEDA study, only VCd was used in the comparator arm. However, it is uncertain whether therapy with VCd is the patient-individual appropriate therapy for all patients in the ANDROMEDA study.

High-dose melphalan therapy followed by ASCT with or without prior induction therapy is recommended for eligible patients with a low risk profile (corresponding to a good performance status and mild impairment of organ function). VCd is suitable as induction therapy, which is why VCd is also a sufficiently suitable patient-individual therapy option for study participants with a low risk profile if this is followed by ASCT or ASCT can be dispensed with by achieving a complete remission with VCd. Uncertainties in the suitability of the patient population arise from the fact that the ANDROMEDA study was also conducted in countries that typically do not offer stem cell transplantation to patients with AL amyloidosis. A total of 24% of the patients in the comparator arm of the study were enrolled in such countries. For these patients, it is unclear how many of them would have been eligible for high-dose melphalan therapy, followed by ASCT. As part of the written statement procedure, the pharmaceutical company submitted an extrapolation regarding the number of patients in countries that do not offer ASCT but for whom ASCT would have been an option. This extrapolation is considered inappropriate in the present assessment.

Despite remaining uncertainties, the study population is considered suitable overall.

Extent and probability of the additional benefit

Mortality

The overall survival is defined in the ANDROMEDA study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of daratumumab in combination with Vcd compared to VCd.

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

Morbidity

*Severe organ damage*

The composite endpoint of severe organ damage is operationalised as the time from randomisation to the occurrence of one of the following events:

- Clinical manifestation of heart failure, defined as the need for a heart transplant, a left ventricular assist device, or an intra-aortic balloon pump

- Clinical manifestation of renal failure, defined as the development of end-stage renal disease (need for haemodialysis or kidney transplantation)

For the endpoint of severe organ damage, there was a statistically significant difference to the advantage of daratumumab + VCd. The results are influenced in particular by the component of clinical manifestation of renal failure. The magnitude of the effect is assessed as a relevant, but no more than a minor improvement against the background of the low event rates (1.5% vs 5.7%).

*Symptomatology (EORTC QLQ-C30)*

The symptomatology of the ANDROMEDA study patients is assessed using the symptom scales of the EORTC-QLQ-C30 questionnaire.

The pharmaceutical company submitted responder analyses with a change by ≥ 10 points for the time to 1st deterioration and for the time to 1st improvement in the dossier.

Due to the disease progression to be expected in the present therapeutic indication and taking into account the distribution of the absolute values of the scales at the start of the study, the responder analyses with a change by ≥ 10 points for the time to 1st deterioration was used for the present assessment.

There was a statistically significant advantage of daratumumab in combination with VCd for the time to deterioration of dyspnoea. There were no statistically significant differences in the other symptom scales.

*Symptomatology (individual items of the EORTC QLQ Ovarian Cancer 28 (OV28), Multiple Myeloma 20 (MY20) and Prostate Cancer 25 (PR25))*

In the dossier, the pharmaceutical company presented results of the EORTC QLQ-MY20 on the pre-specified EORTC individual items tingling in the hands and feet, of the EORTC QLQ-OV28 on fullness in the stomach/ abdomen and of the EORTC QLQ-PR25 on swelling of the legs or ankles, in addition to the results of the EORTC QLQ-C30.

The selection of the pre-specified individual items has been clearly justified by the pharmaceutical company. The results on the individual items are used for the benefit assessment.

The pharmaceutical company submitted responder analyses with a change by ≥ 10 points for the time to 1st deterioration and for the time to 1st improvement in the dossier.

Due to the disease progression to be expected in the present therapeutic indication and taking into account the distribution of the absolute values of the scales at the start of the study, the responder analyses with a change by ≥ 10 points for the time to 1st deterioration was used for the present assessment.

There was no statistically significant difference between the treatment arms for any of the evaluations presented.

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

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

For the benefit assessment, the pharmaceutical company submitted responder analyses with a change by ≥ 15 points of the VAS score from baseline in the dossier. In accordance with the

explanations on the "Symptomatology" section, the analyses for the time to 1st deterioration were used.

There was no statistically significant difference between the treatment arms.

Overall, in the endpoint category of morbidity, there was an advantage of daratumumab in combination with VCd compared to VCd, which results from the advantage in the endpoint of severe organ damage and is supported by the advantage in the symptom scale of dyspnoea. No significant differences between the study arms were found in the other symptom scales and in the EQ-5D VAS.

Quality of life

*EORTC QLQ-C30*

In the ANDROEMDA study, health-related quality of life was assessed using the functional scales and the global health status scale of the EORTC QLQ-C30.

In accordance with the explanations on the "Symptomatology" section, the analyses for the time to 1st deterioration were used.

There was no statistically significant difference between the treatment arms.

*Short Form 36 Health Survey (SF-36)*

Further data on health-related quality of life are collected in the ANDROMEDA study using the SF-36 questionnaire. The mental component summary (MCS) score and the physical component summary (PCS) score are considered separately.

For the benefit assessment, the pharmaceutical company submitted analyses with a change by ≥ 9.4 points (PCS) and ≥ 9.6 points (MCS) from baseline in the dossier. In accordance with the explanations on the "Symptomatology" section, the analyses for the time to 1st deterioration were used.

In the analyses for the time to 1st deterioration, there were no statistically significant differences between the treatment arms; for both the PCS and the MCS.

Side effects

*Adverse events (AEs) in total*

Nearly all patients in the ANDROMEDA study experienced an adverse event. The results for the endpoint were only presented additionally.

*Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs*

For the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs (discontinuation of at least 1 active ingredient component), there was no statistically significant difference between the treatment arms.

*Specific AE*

In detail, in the area of specific adverse events, there was a statistically significant difference to the disadvantage of daratumumab + VCd with respect to the endpoint of skin and

subcutaneous tissue disorders (SOC, AE); in contrast, there was a statistically significant advantage for the endpoint of hypokalaemia (PT, severe AE).

In the overall assessment of the results on side effects, the overall rates of serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs did not show any relevant difference between the treatment arms for the benefit assessment. In detail, the specific adverse events show a disadvantage for the endpoint of skin and subcutaneous tissue disorders (SOC, AE) as well as an advantage for the endpoint of hypokalaemia (PT, severe AE).

Overall assessment

For the assessment of the additional benefit of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone in adults with newly diagnosed systemic light chain (AL) amyloidosis, for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy, results are available from the ANDROMEDA study for the endpoint categories of mortality, morbidity, health-related quality of life and side effects. The study compared daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone with bortezomib in combination with cyclophosphamide and dexamethasone (VCd).

For the overall survival, this patient group showed a statistically significant difference to the advantage of daratumumab in combination with Vcd compared to VCd. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

In the endpoint category of morbidity, there was an advantage of daratumumab in combination with VCd in the endpoint of severe organ damage, which is supported by a further advantage in the symptom scale of dyspnoea.

With regard to health-related quality of life, the available data did not show any relevant differences between the treatment arms for the assessment overall.

For the side effects, the overall rates of serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs did not show any relevant difference between the treatment arms for the benefit assessment. In detail, the specific adverse events show a disadvantage for the endpoint of skin and subcutaneous tissue disorders (SOC, AE) as well as an advantage for the endpoint of hypokalaemia (PT, severe AE).

In the overall analysis of the available results, the advantage in the endpoint of overall survival and the advantage in the endpoint of severe organ damage, which is supported by a further advantage in the symptom scale of dyspnoea, were not offset by any disadvantage. As a result, the G-BA identified a considerable additional benefit of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone for the treatment of newly diagnosed systemic light chain (AL) amyloidosis in adult patients for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, controlled phase III ANDROMEDA study. The risk of bias is classified as low at study level.

With regard to the endpoint of severe organ damage, uncertainties relevant to the assessment result from the low event rates.

For the patient-reported endpoints of morbidity and health-related quality of life, the risk of bias is rated as high due to the lack of blinding in the subjective assessment.

A relevant uncertainty arises from the question on the study population as to whether therapy with VCd is the patient-individual appropriate therapy for all patients in the ANDROMEDA study.

Therefore, the reliability of data for the additional benefit determined is classified in the "hint" category overall.

### 2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone after expiry of the time limit of the resolution of 20 January 2022 on the therapeutic indication:

Darzalex is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

The patient population assessed here is:

"Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy"

Bortezomib in combination with cyclophosphamide and dexamethasone (VCd) was determined by the G-BA as the appropriate comparator therapy.

The pharmaceutical company submitted the results of the open-label, randomised, controlled phase III ANDROMEDA study, comparing daratumumab in combination with VCd versus VCd, for the benefit assessment.

For the overall survival, there was a statistically significant difference to the advantage of daratumumab in combination with VCd. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

In the endpoint category of morbidity, there was an advantage in the endpoint of severe organ damage, which is supported by a further advantage in the symptom scale of dyspnoea.

With regard to health-related quality of life, there were no relevant differences for the assessment.

For the side effects, there were no relevant differences between the treatment arms for the benefit assessment.

Uncertainties remain, particularly due to low event rates and the open-label study design, as well as the question regarding the study population as to whether therapy with VCd is the patient-individual appropriate therapy for all patients in the ANDROMEDA study.

In the overall assessment, a hint for a considerable additional benefit of daratumumab + VCd versus VCd is identified.

## 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 pharmaceutical company only provided information on patient numbers for the entire therapeutic indication. Information on the number of adults, for whom bortezomib in

combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy, was not provided. The patient numbers for the total population estimated by the pharmaceutical company in the dossier is subject to uncertainty, which is mainly due to the use of a higher incidence rate compared to the initial assessment of daratumumab in combination with VCd (resolution of 20 January 2022).

The patient numbers for the total population from the initial assessment (resolution of 20 January 2022) are considered more appropriate despite the uncertainties found. Therefore, this resolution does not make any changes to the patient numbers ascertained by resolution of 20 January 2022. It can be assumed that the number of patients in patient population a1) (patients for whom VCd is the patient-individual appropriate therapy) may also be lower.

## 2.3 Requirements for a quality-assured application

As a result of the present benefit assessment procedure, the requirements for a quality-assured application already established by resolution of 20 January 2022 remain in place.

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 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, cyclophosphamide and dexamethasone is based on the treatment regimen used in the AMY3001 study[3].

There are no approved medicinal products for the therapy options defined as appropriate comparator therapy in the present therapeutic indication. The cost representation for bortezomib, cyclophosphamide and dexamethasone (VCd) is based on the treatment regimen referenced in the NCCN guideline according to Mikhael JR et al.[4]

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

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

[3] Representation based on the information under 5.1 in the product information for daratumumab.

[4] Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, Stewart AK, Bergsagel PL, Fonseca R. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012 May 10;119(19):4391-4. doi: 10.1182/blood-2011-11-390930. Epub 2012 Feb 13. PMID: 22331188; PMCID: PMC3557400.

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, cyclophosphamide and dexamethasone* | | | | |
| Daratumumab | Week 1 - 8:<br>1 x every 7 days<br>Week 9 - 24:<br>1 x every 14 days<br>From week 25:<br>1 x every 28 days | 1st year:<br>23<br><br>Subsequent year:<br>13 | 1 | 1st year:<br>23 |
| Bortezomib | 1 x on day 1, 8, 15 and 22 of a 28-day cycle | 6 cycles | 4 | 24 |
| Cyclophosphamide | 1 x on day 1, 8, 15 and 22 of a 28-day cycle | 6 cycles | 4 | 24 |
| Dexamethasone | 1 x on day 1, 8, 15 and 22 of a 28-day cycle | 6 cycles | 1st year:<br>0 (cycle 1 - 2)<br>2 (cycle 3 - 6) | 1st year:<br>8[5] |
| Appropriate comparator therapy | | | | |
| *Bortezomib in combination with cyclophosphamide and dexamethasone* | | | | |
| Bortezomib | Day 1, 8, 15, 22 of a 28-day cycle | 6 cycles | 4 | 24 |
| | or | | | |
| | Day 1, 4, 8, 11 of a 28-day cycle | 6 cycles | 4 | 24 |
| Cyclophosphamide | Day 1, 8, 15, 22 of a 28-day cycle | 6 cycles | 4 | 24 |
| Dexamethasone | Day 1, 8, 15, 22 of a 28-day cycle | 6 cycles | 4 | 24 |

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

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)[6].

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

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| *Daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone* | | | | | |
| Daratumumab | 1,800 mg | 1,800 mg | 1 x 1,800 mg | 1st year: 23 | 23 x 1,800 mg |
| Bortezomib | 1.30 mg/m² = 2.48 mg | 2.48 mg | 1 x 2.5 mg | 24 | 24 x 2.5 mg |
| Cyclophosphamide | 300 mg/m² = 573 mg | 500 mg[7] | 1 x 500 mg | 24 | 24 x 500 mg |
| Dexamethasone | 40 mg | 40 mg | 1 x 40 mg | 1st year: 8 | 1st year 8 x 40 mg[5] |
| Appropriate comparator therapy | | | | | |
| *Bortezomib in combination with cyclophosphamide and dexamethasone* | | | | | |
| Bortezomib | 1.50 mg/m² = 2.48 mg | 2.87 mg | 1 x 3.5 mg | 24 | 24 x 3.5 mg |
| | or | | | | |
| | 1.30 mg/m² = 2.48 mg | 2.48 mg | 1 x 2.5 mg | 24 | 24 x 2.5 mg |
| Cyclophosphamide | 300 mg/m² = 573 mg | 500 mg[4] | 1 x 500 mg | 24 | 24 x 500 mg |
| Dexamethasone | 40 mg | 40 mg | 1 x 40 mg | 24 | 24 x 40 mg |

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

[7] According to the product information of daratumumab, the maximum dosage of cyclophosphamide is 500 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 reference prices shown in the cost representation may not represent the cheapest available alternative.

**Costs of the medicinal products:**

| Designation of the therapy | Packaging size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Daratumumab 1,800 mg | 1 SFI | € 5,809.87 | € 1.77 | € 0.00 | € 5,808.10 |
| Bortezomib 2.5 mg | 1 PSI | € 185.37 | € 1.77 | € 8.26 | € 175.34 |
| Cyclophosphamide 500 mg | 50 TAB | € 56.83 | € 1.77 | € 17.65 | € 37.41 |
| Dexamethasone 40 mg[8] | 10 TAB | € 46.29 | € 1.77 | € 0.00 | € 44.52 |
| Appropriate comparator therapy | | | | | |
| Bortezomib 2.5 mg | 1 PSI | € 185.37 | € 1.77 | € 8.26 | € 175.34 |
| Bortezomib 3.5 mg | 1 PSI | € 255.31 | € 1.77 | € 11.58 | € 241.96 |
| Cyclophosphamide 500 mg | 50 TAB | € 56.83 | € 1.77 | € 17.65 | € 37.41 |
| Dexamethasone 40 mg[8] | 10 TAB | € 46.29 | € 1.77 | € 0.00 | € 44.52 |
| Dexamethasone 40 mg[8] | 20 TAB | € 81.59 | € 1.77 | € 0.00 | € 79.82 |
| Abbreviations: TAB = tablets; SFI = solution for injection; PSI = powder for solution for injection | | | | | |

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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.

As the appropriate comparator therapy in the present case was exceptionally determined as

[8] Fixed reimbursement rate

the off-label use of medicinal products, no statement can be made as to whether there are regular differences in the necessary use of medical treatment or in the prescription of other services when using the medicinal product to be assessed compared with the appropriate comparator therapy according to the product information. Therefore, no costs for additionally required SHI services are taken into account here.

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 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 designate 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 have 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 have 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 have 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:

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy

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 daratumumab (Darzalex); Johnson&Johnson; DARZALEX® 1,800 mg solution for injection; last revised: August 2025

## 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 7 October 2020, 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 11 February 2025.

On 28 February 2025, 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 5 VerfO.

By letter dated 28 February 2025 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 27 May 2025, and the written statement procedure was initiated with publication on the G-BA website on 2 June 2025. The deadline for submitting statements was 23 June 2025.

The oral hearing was held on 7 July 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 12 August 2025, and the proposed draft resolution was approved.

At their session on 21 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 7 October 2020 | Determination of the appropriate comparator therapy |
| Subcommittee on Medicinal Products | 11 February 2025 | New determination of the appropriate comparator therapy |
| Working group Section 35a | 2 July 2025 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 7 July 2025 | Conduct of the oral hearing |
| Working group Section 35a | 16 July 2025;<br>6 August 2025 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 12 August 2025 | Concluding discussion of the draft resolution |
| Plenum | 21 August 2025 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 21 August 2025

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

Prof. Hecken