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 (new therapeutic indication: smouldering multiple myeloma (SMM))

of 19 February 2026

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 decide 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.

On 18 July 2025, 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 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 from 12.12.2008, sentence 7).

On 15 August 2025, i.e. at the latest within four weeks of informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company submitted a dossier in due time 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 as monotherapy is indicated for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma."

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 November 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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA have 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 have made 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 as monotherapy is indicated for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma.

Therapeutic indication of the resolution (resolution of 19.02.2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with smouldering multiple myeloma at high risk of developing multiple myeloma

Appropriate comparator therapy for daratumumab as monotherapy:

- Monitoring wait-and-see approach

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 they determine 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. No medicinal products are explicitly approved for the treatment of smouldering multiple myeloma.
Bendamustine, carmustine, cyclophosphamide, doxorubicin, melphalan, vincristine, bortezomib, daratumumab, lenalidomide, isatuximab, thalidomide, dexamethasone, prednisolone and prednisone are approved for multiple myeloma.

On 2. No non-medicinal treatments are considered for smouldering multiple myeloma.

Both autologous and allogeneic stem cell transplants are considered for transplantable subjects with multiple myeloma.

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

- Isatuximab – resolution of 7 August 2025 (combination with bortezomib, lenalidomide and dexamethasone)
- Daratumumab – resolution of 15 May 2025 (combination with bortezomib, lenalidomide and dexamethasone)
- Daratumumab – resolution of 16 May 2024 (combination with bortezomib, melphalan and prednisone)
- Daratumumab – resolution of 18 March 2022 (combination with lenalidomide and dexamethasone)
- Daratumumab – resolution of 20 August 2020 (in combination with bortezomib, thalidomide and dexamethasone)

Annex VI to Section K of the Pharmaceuticals Directive – Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use):

- Bortezomib plus cyclophosphamide plus dexamethasone for the induction therapy of newly diagnosed multiple myeloma (resolution of 20 May 2021)

For transplantable patients, there are also two resolutions on the Directive on Inpatient Treatment Methods (last revised 4 June 2025) – Annex II: Methods whose assessment procedures are suspended (resolutions of 19 December 2024, both resolutions valid until 31 December 2026):

- Autologous multiple transplants (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 systematic 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.

Based on the available evidence, a watch-and-wait strategy, among others, is recommended for patients with smouldering multiple myeloma.

Lenalidomide is listed as a possible medicinal intervention in the available evidence. Studies are available on the treatment of smouldering multiple myeloma with

lenalidomide as monotherapy and in combination with dexamethasone. However, the treatment of smouldering multiple myeloma with lenalidomide assumes unclear significance in healthcare and does not represent a standard therapy option in the present therapeutic indication.

According to written statements by the Drugs Commission of the German Medical Association (AkdÄ) and the German Society for Haematology and Medical Oncology (DGHO), monitoring wait-and-see approach is standard practice for patients with smouldering multiple myeloma.

Taking into account the present treatment setting as well as the overall assessment of evidence and clinical practice, the G-BA determined "monitoring wait-and-see approach" as the appropriate comparator therapy.

The relevant findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

2.1.3 Extent and probability of the additional benefit

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

Adults with smouldering multiple myeloma at high risk of developing multiple myeloma

Hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submitted the results of the pre-specified data cut-off from 1 May 2024 from the ongoing open-label, randomised, controlled phase III AQUILA study, which compared daratumumab as monotherapy to no intervention.

The study has been conducted in a total of 140 study sites in Asia, Australia, Europe, North America and South America since November 2017. 390 adult patients with smouldering multiple myeloma at a high risk of developing multiple myeloma were enrolled in the study.

The high risk of developing multiple myeloma is defined as ≥ 10% clonal plasma cells in the bone marrow, with at least one of the following risk criteria also applying: Serum M protein ≥ 3 g/dl, clonal plasma cells in bone marrow > 50% to < 60%, FLC ratio ≥ 8 to < 100, IgA subtype or immunoparesis with reduction of 2 unaffected Ig isotypes.

On the implementation of the appropriate comparator therapy:

In the comparator arm of the study, active monitoring visits were made every 12 weeks until disease progression. This is considered sufficient implementation of the appropriate comparator therapy "monitoring wait-and-see approach".

On the definition of risk in the AQUILA study

The EMA has restricted the marketing authorisation of daratumumab to patients who are at high risk according to the inclusion criteria of the AQUILA study. Of the patients enrolled in the study, 40.5% were at high risk of developing multiple myeloma according to the Mayo criteria. The risk criteria applied in the study do not correspond to the updated Mayo risk criteria established in healthcare[2].

[2] Lakshman A, Rajkumar SV, Buadi FK et al. Risk stratification of smouldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J 2018; 8(6): 59. https://doi.org/10.1038/s41408-018-0077-4.

Extent and probability of the additional benefit

Mortality

In the AQUILA study, overall survival is operationalised as the time between randomisation and death from any cause.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of daratumumab compared to the monitoring wait-and-see approach. However, this effect and the transferability of this result from the AQUILA study to the reality of care are subject to significant uncertainty for the reasons stated below. Firstly, the statistically significant difference is based on a small number of events in both study arms at the time of the current data cut-off, with the median survival time not yet reached in either study arm. The subgroup analyses show an effect modification by the "region" characteristic. No statistically significant difference between daratumumab and the monitoring wait-and-see approach was observed for the subgroup of patients in the "Western Europe and USA" region.

Furthermore, the data on subsequent therapies show that only a relatively small percentage of patients in the comparator arm of the AQUILA study, who received first-line therapy for multiple myeloma, were treated with a CD-38 antibody. However, trio and tetra combination therapies with a CD-38 antibody represent a highly effective treatment option for patients with multiple myeloma, according to the generally accepted state of medical knowledge. The information on the subsequent therapies submitted in the written statement procedure shows that 43.9% of patients eligible for autologous stem cell transplant (ASCT) and 53.1% of patients ineligible for ASCT in the comparator arm received therapy in line with the recommendations for the treatment of newly diagnosed multiple myeloma.

It can therefore be assumed that the subsequent therapies in the AQUILA study do not adequately reflect the current standard of care.

As a result, the statistically significant difference in the endpoint of overall survival from the AQUILA study is used. However, the advantage is based on a small number of events and there is relevant uncertainty regarding its transferability to the reality of care.

Morbidity

Progression-free survival (PFS)

Progression-free survival is operationalised in the AQUILA study as the time from randomisation to the time of disease progression to multiple myeloma according to IMWG criteria or the time of death from any cause, whichever occurs first.

For the PFS endpoint, there was a statistically significant advantage of daratumumab.

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The mortality endpoint component is already assessed via the overall survival endpoint as an independent endpoint. The morbidity component "disease progression to multiple myeloma" was assessed according to IMWG criteria and thus, not in a symptom-related manner but only by means of laboratory parametric, imaging, and haematological procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-MY20)

Symptomatology was assessed in the AQUILA study using the EORTC QLQ-C30 questionnaire and the "disease symptoms" symptom scale of the disease-specific additional module EORTC QLQ-MY20.

The selective collection of data on the "disease symptoms" symptom scale of the EORTC QLQ-MY20 was justified by the pharmaceutical company in the written statement procedure. The pharmaceutical company's statement does not indicate that the selective collection of data on the "disease symptoms" symptom scale in the AQUILA study is appropriate. The results of the "disease symptoms" symptom scale are therefore not used for the benefit assessment.

The pharmaceutical company submitted analyses of the time to first deterioration and the time to first improvement in the dossier. The time to first deterioration is used for the benefit assessment due to the expected course of the disease in the present therapeutic indication and taking into account the distribution of the absolute values of the scales at the start of the study.

For the endpoints of pain and dyspnoea assessed using the EORTC QLQ-C30, there was a statistically significant advantage of daratumumab in each case. For the endpoints of fatigue, nausea and vomiting, insomnia, appetite loss, constipation and diarrhoea, there was no statistically significant difference between the study arms.

Subgroup analyses show effect modifications for the endpoints "nausea and vomiting" and "appetite loss".

For the endpoint of nausea and vomiting, there was an effect modification by the "risk according to Mayo criteria" characteristic. There was a statistically significant difference to the advantage of daratumumab for patients at a high risk according to Mayo criteria. There were no statistically significant differences for patients at low or medium risk according to Mayo criteria.

For the endpoint of appetite loss, there was an effect modification due to the "age" characteristic. For patients < 65 years of age, there was a statistically significant difference to the advantage of daratumumab. For patients ≥ 65 years of age, there was no statistically significant difference.

As no reliable conclusions could be drawn from the effect modifications for the overall statement on additional benefit, the result of the total population is used.

Health status (assessed using EQ-5D VAS)

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

For the benefit assessment, the pharmaceutical company submitted analyses of the time to first deterioration and the time to first improvement in the dossier. The analyses of the time to first deterioration are used in accordance with the explanations on the "Symptomatology" section.

There was no statistically significant difference between the study arms.

The overall analysis of the results on morbidity shows a moderate advantage in favour of daratumumab.

Quality of life

Health-related quality of life was assessed in the AQUILA study using EORTC QLQ-C30 and the "Future prospects" functional scale of the EORTC QLQ-MY20.

The analyses of the time to first deterioration are used in accordance with the explanations on the "Symptomatology" section. The "Future prospects" functional scale of the EORTC QLQ-MY20 is also not used for the reasons stated in the "Symptomatology" section.

For the endpoints of global health status and emotional functioning, the EORTC QLQ-C30 showed a statistically significant advantage of daratumumab. For the endpoints of physical functioning, role functioning, cognitive functioning and social functioning, there was no statistically significant difference.

The overall analysis of the results on health-related quality of life shows a moderate advantage in favour of daratumumab.

Side effects

Total adverse events (AEs) (presented additionally)

In the AQUILA study, adverse events occurred in 96.9% of patients in the intervention arm and 82.7% of patients in the control arm. The results are only presented additionally.

Serious AEs (SAEs) and severe AEs (CTCAE grade ≥ 3)

For the endpoints of SAEs and severe AEs, there was no statistically significant difference between the study arms in each case.

For the "severe AEs" endpoint, subgroup analyses show an effect modification by the "sex" characteristic. A statistically significant difference to the disadvantage of daratumumab was observed here for men. There was no statistically significant difference for women.

Therapy discontinuation due to AEs

No suitable data were available for the endpoint of therapy discontinuation due to AEs. In the AQUILA study, no intervention was administered in the comparator arm, which is why no therapy discontinuation can occur in that arm. The results on the endpoint of therapy discontinuation due to AEs are therefore unsuitable for the benefit assessment.

Specific AEs

In detail, for the specific AEs, there was a statistically significant difference to the disadvantage of daratumumab for all endpoints: General disorders and administration site conditions (SOC, AEs), gastrointestinal disorders (SOC, AEs), nervous system disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), insomnia (PT, AEs), vascular disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs) as well as infections and infestations (SOC, severe AEs).

For the "Respiratory, thoracic and mediastinal disorders (SOC, AEs)" endpoint, subgroup analyses show an effect modification by the "sex" characteristic. A statistically significant difference to the disadvantage of daratumumab was observed here for women. There was no statistically significant difference for men.

Conclusion on side effects

For the overall rate of severe AEs and SAEs in the endpoint category of side effects, there were no statistically significant differences between the study arms. No suitable data were available for the endpoint of discontinuation due to AEs. In detail, for the specific AEs, there were several disadvantages of daratumumab therapy.

As no reliable conclusions could be drawn from the aforementioned effect modifications for the overall statement on additional benefit, the result of the total population is used.

In the overall analysis of the results on side effects, there were neither advantages nor disadvantages of treatment with daratumumab.

Overall assessment

The pharmaceutical company presented the results of the AQUILA study, which compared daratumumab with monitoring wait-and-see approach for the assessment of the additional benefit of daratumumab as monotherapy for the treatment of adults with smouldering multiple myeloma who are at high risk of developing multiple myeloma. Results in the endpoint categories of mortality, morbidity, health-related quality of life and side effects are available from the study.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of daratumumab compared to the monitoring wait-and-see approach. However, there is relevant uncertainty regarding the transferability of this result from the AQUILA study to the reality of care. In this regard, subgroup analyses show an effect modification by the "region" characteristic. No statistically significant difference between daratumumab and the monitoring wait-and-see approach was observed for the subgroup of patients in the "Western Europe and USA" region. Furthermore, with regard to the information on subsequent therapies, it is to be assumed that the subsequent therapies in the AQUILA study do not adequately reflect the current standard of care. In addition to this uncertainty, the statistically significant result in the overall survival endpoint is based on a small number of events in both study arms at the time of the present data cut-off.

In the endpoint category of morbidity, results on patient-reported symptomatology (EORTC QLQ-C30; "disease symptoms" symptom scale of the EORTC QLQ-MY20) and health status (EQ-5D VAS) were available. The results on the "disease symptoms" symptom scale of the EORTC QLQ-MY20 are not used for the benefit assessment due to selective data collection.

Overall, for the morbidity endpoint category, there was a moderate advantage in favour of daratumumab, taking into account the significant advantages in the "pain" and "dyspnoea" symptom scales of the EORTC QLQ-C30.

There were results for patient-reported endpoints (EORTC QLQ-C30; "future prospects" functional scale of the EORTC QLQ-MY20) in the endpoint category of health-related quality of life. The results of the "future prospects" functional scale of the EORTC QLQ-MY20 are not used for the benefit assessment due to selective data collection.

Overall, there was a moderate advantage in favour of daratumumab for the endpoint category of health-related quality of life, taking into account the significant advantages in the "global health status" and "emotional functioning" functional scales of the EORTC QLQ-C30.

For the side effects, there were no relevant differences between the study arms for the benefit assessment, based on the overall rates of serious AEs (SAEs) und severe AEs (CTCAE grade ≥ 3). No suitable data were available for the endpoint of discontinuation due to AEs. In detail, there were disadvantages in the specific AEs.

As a result, a minor additional benefit of daratumumab compared with the monitoring wait-and-see approach is identified, particularly due to the moderate advantages in the endpoint categories of morbidity and health-related quality of life.

Reliability of data (probability of additional benefit)

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

There is relevant uncertainty regarding the result for the endpoint of overall survival.

For all endpoints of morbidity, health-related quality of life and non-severe/ non-serious specific AEs, the risk of bias is classified as high due to the lack of blinding in subjective collection.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient daratumumab as monotherapy for the treatment of adults with smouldering multiple myeloma who are at high risk of developing multiple myeloma.

The G-BA determined the "monitoring wait-and-see approach" as the appropriate comparator therapy. For the benefit assessment, the pharmaceutical company submitted the results of the pre-specified data cut-off from 1 May 2024 from the ongoing open-label, randomised, controlled phase III AQUILA study, which compared daratumumab as monotherapy to the monitoring wait-and-see approach.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of daratumumab compared to the monitoring wait-and-see approach. However, there is relevant uncertainty regarding the transferability of this result from the AQUILA study to the reality of care. In this regard, subgroup analyses show an effect modification by the "region" characteristic. No statistically significant difference between daratumumab and the monitoring wait-and-see approach was observed for the subgroup of patients in the "Western Europe and USA" region. Furthermore, with regard to the information on subsequent therapies, it is to be assumed that the subsequent therapies in the AQUILA study do not adequately reflect the current standard of care. In addition to this uncertainty, the statistically significant result in the overall survival endpoint is based on a small number of events in both study arms at the time of the present data cut-off.

In the endpoint categories of morbidity and health-related quality of life, results on patient-reported symptomatology (EORTC QLQ-C30; "disease symptoms" symptom scale of the EORTC QLQ-MY20), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30; "future prospects" functional scale of the EORTC QLQ-MY20) were available.

The results of the EORTC QLQ-MY20 are not used for the benefit assessment due to the selective collection of individual scales.

Overall, there was a moderate advantage in favour of daratumumab for the endpoint categories of morbidity and health-related quality of life, taking into account the statistically significant advantages in the "pain" and "dyspnoea" symptom scales as well as the "global health status" and "emotional functioning" functional scales of the EORTC QLQ-C30.

For the side effects, there were no relevant differences between the study arms for the benefit assessment, based on the overall rates of serious AEs (SAEs) und severe AEs (CTCAE grade ≥ 3). No suitable data were available for the endpoint of discontinuation due to AEs. In detail, there were disadvantages in the specific AEs.

As a result, a minor additional benefit of daratumumab compared with the monitoring wait-and-see approach is identified, particularly due to the moderate advantages in the endpoint categories of morbidity and health-related quality of life.

The significance of the evidence is classified in the "hint" category.

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

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

The G-BA base their resolution on the patient numbers from the dossier submitted by the pharmaceutical company.

Although the patient number determined by the pharmaceutical company is mathematically plausible, it must be classified as an underestimate in consideration of the uncertainty. This underestimate is largely due to the fact that only newly diagnosed patients with smouldering multiple myeloma are included in the calculation of the target population. Patients diagnosed with smouldering multiple myeloma that only progresses to smouldering multiple myeloma at a high risk of developing multiple myeloma during the course of the disease were not included in the calculation.

Furthermore, the risk criteria used in the studies to identify the percentage of patients at high risk of developing multiple myeloma differ from the definition of high risk according to the AQUILA study and, accordingly, the marketing authorisation.

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: 12 January 2026):

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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 December 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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 is

different from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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

Treatment period:

Adults with smouldering multiple myeloma at high risk of developing multiple myeloma

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	Week 1 – 8: (weekly dosage regimen): 1 x per 7-day cycle	8.0	1	8.0
	Week 9–24: (biweekly dosage regimen): 1 x per 14-day cycle	8.0	1	8.0
	From week 25: (four-weekly dosage regimen): 1 x per 28-day cycle	7.0	1	7.0
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

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)[3].

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

Adults with smouldering multiple myeloma at high risk of developing multiple myeloma

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	1,800 mg	1,800 mg	1 x 1,800 mg	8.0	8.0 x 1,800 mg
				8.0	8.0 x 1,800 mg
				7.0	7.0 x 1,800 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

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
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

LAUER-TAXE® last revised: 15 December 2025

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.

The calculation of the additionally required SHI services is based on packs in distribution with the LAUER-TAXE® last revised on 15 September 2025 and fee structure items (FSI) - last revised in the 3rd quarter of 2025 of the uniform value scale (UVS 2025/Q3).

Hepatitis B diagnostics

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. 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.[4]

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
HBV screening							
HBV test Hepatitis B surface antigen status (FSI 32781)	–	–	–	–	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (FSI 32614)	–	–	–	–	€ 5.43	1.0	€ 5.43

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.

[4] 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] .

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:

Adults with smouldering multiple myeloma at high risk of developing multiple myeloma

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient approved in monotherapy.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at their session on 9 February 2016.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products newly determined the appropriate comparator therapy at their session on 26 August 2025.

On 15 August 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 2 VerfO.

By letter dated 18 August 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient daratumumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 November 2025, and the written statement procedure was initiated with publication on the G-BA website on 17 November 2025. The deadline for submitting written statements was 8 December 2025.

The oral hearing was held on 12 January 2026.

By letter dated 13 January 2026, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 31 January 2026.

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 subcommittee session on 10 February 2026, and the draft resolution was approved.

At their session on 19 February 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 February 2016	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	26 August 2025	New determination of the appropriate comparator therapy
Working group Section 35a	7 January 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents

Working group Section 35a	21 January 2026 4 February 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	10 February 2026	Concluding discussion of the draft resolution
Plenum	19 February 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 February 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken