Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Daratumumab (new therapeutic indication: systemic light chain amyloidosis, first-line, combination with Cyclophosphamide, Bortezomib and Dexamethasone)

of 20 January 2022

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

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

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

On 21 June 2021, daratumumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number

2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 20 July 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient daratumumab with the new therapeutic indication (systemic light chain amyloidosis, first-line, combination with cyclophosphamide, bortezomib and dexamethasone).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 November 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

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

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Daratumumab (Darzalex) according to 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 20 January 2022):

- See new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed systemic light chain (AL) amyloidosis

Appropriate comparator therapy:

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- a patient-individual therapy, taking into account general condition, comorbidity and organ damage

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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 Federal Joint Committee has already determined the patient-relevant advantage 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Apart from daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone, there are no marketing authorisations of medicinal products for the treatment of light chain amyloidosis.

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

on 3. There are no relevant resolutions on medicinal applications or non-medicinal treatments.

on 4. The general state of medical knowledge in the present therapeutic indication was represented by a systematic search for guidelines and reviews of clinical studies. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

Accordingly, evidence is available on the basis of three systematic reviews. These reviews indicate that bortezomib or bortezomib-based regimens are treatment options for patients with systemic light chain (AL) amyloidosis. In the recommendations of international guidelines, various bortezomib, lenalidomide or melphalan-based treatment regimens are recommended, whereby a basic differentiation is made between patients who are eligible for autologous stem cell transplantation.

The treatment options mentioned in the written statements of the Drug Commission of the German Medical Profession (AkdÄ) and the scientific-medical societies are primarily based on patient-individual criteria, including age, general condition,

comorbidity and organ damage. In particular, the degree of cardiac and renal insufficiency and the presence of amyloid-related polyneuropathy are mentioned. In this respect, it is recommended that patients with pre-existing polyneuropathies should not be treated with bortezomib.

The following combination therapies, which are to be selected especially under consideration of general condition, comorbidity and organ damage, are named altogether as therapy options in guidelines and the available written statements of the AkdÄ and scientific-medical societies. These include:

- Bortezomib + cyclophosphamide + dexamethasone
- Bortezomib + dexamethasone
- Bortezomib + melphalan + dexamethasone
- Lenalidomide + cyclophosphamide + dexamethasone
- Lenalidomide + dexamethasone
- Melphalan + dexamethasone
- Lenalidomide + melphalan + dexamethasone.

If there is a response to this initial treatment (induction therapy), the written statements of the AkdÄ and the scientific-medical societies recommend that high-dose melphalan therapy with autologous stem cell transplantation (ASCT) be followed in eligible patients. However, immediate high-dose melphalan therapy with ASCT (i.e. without prior induction) may also be indicated, depending on the initial plasma cell percentage in the bone marrow, in particular. Accordingly, patients for whom ASCT may generally be considered at a later stage should not receive melphalan-based induction chemotherapy.

However, as mentioned under 1., there are no medicinal products approved for the treatment of light chain (AL) amyloidosis. Overall, it can therefore be stated in the present therapeutic indication that there is a discrepancy between the medicinal products approved in the indication and those used in care or recommended in guidelines and that no therapy option is as a rule preferable to all other therapy options according to the generally accepted state of medical knowledge. Rather, the treatment decision is made on the basis of the above-mentioned patient-individual criteria. Against this background, the G-BA specifies a patient-individual therapy, taking into account the general condition, comorbidity and organ damage as the appropriate comparator therapy in the present therapeutic indication. The combinations of active ingredients and interventions to be considered here are those discussed in accordance with the above justification.

However, the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

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

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:

Adults with newly diagnosed systemic light chain (AL) amyloidosis

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 minor additional benefit

a2) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom therapy other than Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy

An additional benefit is not proven.

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 two or less were enrolled. Patients with abnormal cardiovascular conditions such as 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). Randomisation was stratified by cardiac stage (Mayo stage I vs II vs IIIa), by country typically offering stem cell transplantation for patients with AL amyloidosis (list A: yes vs list B: no) and renal function status (creatinine clearance: < 60 ml/min vs ≥ 60 ml/min).

In the intervention arm, patients received daratumumab in combination with VCd for the first six 28 day cycles and daratumumab as monotherapy from cycle seven onwards up to a maximum of cycle 24. Treatment in the comparator arm was a maximum of six 28 day cycles of VCd. Treatment with daratumumab + VCd was administered subcutaneously according to the product information. Treatment with VCd in the comparator arm was equivalent to the administration of VCd in the intervention arm.

Patients were treated until disease progression, initiation of subsequent therapy, unacceptable toxicity or withdrawal of consent. Subsequent therapies including therapy with daratumumab were allowed without restriction.

The primary endpoint of the ANDROMEDA study was complete haematological response (CHR). Patient-relevant endpoints were overall survival, endpoints for morbidity and health-related quality of life and adverse events (AEs).

The pre-specified interim data cut-off from 14 February 2020 is used for the present benefit assessment. Further results from the ongoing study are pending. The final analysis of overall survival is planned after occurrence of 156 events.

Implementation of the appropriate comparator therapy

The treatment of adult 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, different treatment regimes, including high-dose melphalan therapy with autologous stem cell transplantation, are recommended in guidelines or the written statements of AkdÄ and scientific-medical societies, while taking these factors into account. In the ANDROMEDA study, only VCd was used in the comparator arm. There is no study comparing multiple treatment options.

According to the product information for bortezomib, patients with pre-existing severe neuropathy should only be treated with bortezomib after due risk-benefit assessment. In this regard, patients with grade 2 sensory peripheral neuropathy or grade 1 painful peripheral neuropathy were excluded from enrolment in the ANDROMEDA study. Furthermore, the ANDROMEDA study population mainly comprises patients in good general condition. In addition, patients with abnormal cardiovascular conditions, for whom bortezomib-based dual combinations are primarily considered, were excluded from the study. Thus, it is assumed that for the ANDROMEDA study population, on the one hand, bortezomib is generally a possible therapy option and, on the other, the triple combination VCd represents the patient-individual appropriate therapy for the majority of the study population.

The significance of a melphalan-based therapy in the ANDROMEDA study population is also considered to be low overall, as the study predominantly included patients with a good general condition, for whom ASCT would generally be an option and for whom a melphalan-based therapy is therefore not indicated in the first line. The same applies to treatment regimens containing lenalidomide, which are not recommended for cardiac involvement of AL amyloidosis or, according to the product information, are to be used with caution in renal insufficiency. This applies to 71% and 32% of the patients in the comparator arm of the ANDROMEDA study, respectively.

Uncertainties in the implementation of the appropriate comparator therapy arise from the fact that the ANDROMEDA study is also being conducted in countries that typically do not offer stem cell transplantation for 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 a patient-individual therapy within the scope of the appropriate comparator therapy.

Overall, despite remaining uncertainties, VCd is considered to be a sufficient implementation of patient-individual therapy for the ANDROMEDA study population, taking into account general condition, comorbidity and organ damage. However, on the basis of the study, only statements on the additional benefit of daratumumab in combination with VCd compared to a patient-individual therapy are possible for the patient group for which VCd represents the patient-individual appropriate therapy. A division of the population covered by the therapeutic indication into patients for whom VCd is the patient-individual appropriate

therapy (a1) and patients for whom a therapy other than VCd is the patient-individual appropriate therapy (a2) is therefore appropriate.

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom Bortezomib in combination with Cyclophosphamide andDdexamethasone is the patient-individual appropriate therapy

Extent and probability of the additional benefit

Mortality

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

An additional benefit of daratumumab in combination with VCd with regard to overall survival is therefore not proven.

Morbidity

Severe organ damage

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

The endpoint of severe organ damage is considered patient-relevant in the present operationalisation. There is a statistically significant difference in favour of daratumumab + VCd. 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 (0.5% vs 3.6%).

Symptomatology (EORTC QLQ-C30)

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

The pharmaceutical company submits responder analyses with a change by ≥ 10 points and ≥ 15% of the scale range for time to the 1st deterioration and for 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 study, the responder analyses are reduced by ≥ 10 points for time to 1st deterioration for the present assessment.

There is a statistically significant advantage for 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 presents results of the EORTC QLQ-MY20 questionnaire on the individual items tingling in the hands and feet, of EORTC QLQ-OV28 on fullness in the stomach/abdomen and of EORTC QLQ-PR25 on swelling of the legs or ankles in addition to results of the EORTC QLQ-C30 questionnaire.

According to the authors, the use of individual items as an item list is only intended in conjunction with the EORTC QLQ-C30 questionnaire and an already validated additional module, but not, as was done in the ANDROMEDA study, alone in conjunction with the EORTC QLQ-C30 questionnaire. The individual items are therefore not used for the present assessment.

In the overall assessment of the results on symptomatology, there is a single advantage of daratumumab in combination with VCd in the dyspnoea scale. The advantage in the dyspnoea scale supports the result for the endpoint of severe organ damage.

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 submits responder analyses with a change by ≥ 7, ≥ 10, and ≥ 15 points of the VAS score from baseline in the dossier. In accordance with the explanations on the section "Symptomatology", the analyses for the time to 1st deterioration are used.

According to IQWiG's current methodological approach (Methods 6.0, published on 5 November 2020), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) to be necessary for patient-reported endpoints to represent a noticeable change with sufficient certainty. For the EQ-5D VAS, the G-BA has recognised response thresholds of ≥ 7 and ≥ 10 points as a clinically relevant change in previous benefit assessment procedures in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% (here ≥ 15 points) and the responder analyses with a response threshold of ≥ 7 and ≥ 10 points are used to assess the additional benefit.

There is no statistically significant difference between the treatment groups in all of the three responder analyses (≥ 7, ≥ 10 and ≥ 15 points).

Overall, there is an additional benefit for daratumumab in combination with VCd compared to VCd in the endpoint category of morbidity, which results from the advantage in the endpoint of severe organ damage and is supported by the advantage in the symptom scale dyspnoea.

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 questionnaire.

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

There is a statistically significant advantage of daratumumab in combination with VCd for the time to deterioration of emotional functioning. There are no statistically significant differences in the other functional scales and the global health status scale.

Short Form 36 Health Survey (SF-36)

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

According to IQWiG's current methodological approach (Methods 6.0, published on 5 November 2020), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) to be necessary for patient-reported endpoints to represent a noticeable change with sufficient certainty. For the SF-36, the G-BA has recognised a response threshold of ≥ 5 points as a clinically relevant change in previous benefit assessment procedures in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% (here ≥ 10.05 points for the PCS or ≥ 10.80 points for the MCS) as well as the responder analysis with a response threshold of ≥ 5 points are used to assess the additional benefit.

In the analyses for the time to 1st deterioration, there are no statistically significant differences between the treatment arms when considering the response threshold of ≥ 5 points or the response threshold of 15%; for both the PCS and the MCS.

In the overall assessment of health-related quality of life, there are no statistically significant differences between the treatment arms for the MCS and the PCS of the SF-36. In the EORTC QLQ-C30 results, there is a single advantage of daratumumab in combination with VCd only in the emotional functioning scale. When interpreting this result, uncertainties relevant to the assessment must be taken into account, which result from the wide interval limits of the 95% confidence interval of the effect estimator and the differences in the survey intervals of the patient-reported endpoints between the treatment arms during the course of the study. Against this background, no relevant difference was found in the overall results for health-related quality of life.

Side effects

Adverse events (AEs) in total

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

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

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

Specific AEs

In detail, in the area of specific adverse events, there is a statistically significant difference to the disadvantage of daratumumab in combination with VCd with respect to the endpoint of

skin and subcutaneous tissue disorders (SOC, AE); however, there is a statistically significant advantage for the endpoint of hypokalaemia (PT, severe AE).

In the overall assessment of the results on side effects, there are no relevant difference for the benefit assessment between the treatment arms. In detail, the specific adverse events alone 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, results from the ANDROMEDA study are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects. In the ongoing study, daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone are being compared with bortezomib in combination with cyclophosphamide and dexamethasone (VCd).

Despite remaining uncertainties, VCd is considered to be a sufficient implementation of the appropriate comparator therapy (patient-individual therapy, taking into account general condition, comorbidity and organ damage) for the ANDROMEDA study population. However, on the basis of the study, only statements on the additional benefit of daratumumab in combination with VCd compared to a patient-individual therapy are possible for the patient group for which VCd represents the patient-individual appropriate therapy.

However, there were no statistically significant differences between the treatment arms in this patient group for the overall survival. An additional benefit for overall survival is therefore not proven.

In the endpoint category of morbidity, there is 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 dyspnoea.

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

In the overall assessment of the results on side effects, there are no relevant differences for the benefit assessment between the treatment arms. In detail, the specific adverse events alone 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 assessment of the present results, the advantage in the endpoint of severe organ damage, which is supported by a further advantage in the symptom scale dyspnoea, is not offset by a disadvantage. As a result, the G-BA identified a minor additional benefit for 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 appropriate patient-individual 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 subjective assessment.

Overarching limitations arise due to the uncertainty of the albeit small percentage of patients in the ANDROMEDA study for whom a therapy other than VCd would potentially have represented the appropriate patient-individual therapy.

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

a2) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom therapy other than Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy

For the sub-population of adult patients with newly diagnosed systemic, light chain (AL) amyloidosis, for whom a therapy other than bortezomib in combination with cyclophosphamide and dexamethasone represents the appropriate patient-individual therapy, no statements on the additional benefit can be made on the basis of the ANDROMEDA study. Since only results with a comparison to VCd were presented for the benefit assessment, no usable data are available overall.

An additional benefit of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone are therefore not proven for the sub-population a2).

2.1.4 Limitation of the period of validity of the 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

The limitation of the period of validity of the resolution on the benefit assessment of daratumumab finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

The overall survival data of the patient population a1) available for this assessment from the ANDROMEDA study are less significant due to a small number of events at the time of this data cut-off used. According to the pharmaceutical company, the final overall survival data from the ANDROMEDA study, which must also be submitted to the European Medicines Agency (EMA), are expected in December 2024.

Since further clinical data concerning the overall survival are expected to be relevant for the assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of daratumumab. The limitation enables the inclusion of the expected final results from the phase ANDROMEDA study in the benefit assessment of the medicinal product according to Section 35a SGB V. For this purpose, a time limit of the resolution until 1 March 2025 is considered appropriate.

Conditions for the limitation:

For the new benefit assessment after expiry of the deadline, the expected results from the final analysis of overall survival and especially the results for the endpoint of serious 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 patient group a1).

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 1 number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of daratumumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of daratumumab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for daratumumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Darzalex with the active ingredient daratumumab. This medicinal product was approved as an orphan drug but has exceeded the EUR 50 million turnover limit.

The therapeutic indication assessed here is as follows:

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

A patient-individual therapy, taking into account general condition, comorbidity and organ damage was determined as the appropriate comparator therapy.

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

This results in the following patient groups:

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

and

a2) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom therapy other than Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy.

On patient group a1)

However, there were no statistically significant differences between the treatment arms in this patient group for the overall survival.

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

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

In the overall assessment of the results on side effects, there are no relevant differences for the benefit assessment between the treatment arms.

Uncertainties remain, especially due to still low event rates and the open-label study design.

In the overall assessment, a hint of minor additional benefit is identified.

The findings for patient group a1) are limited until 1 March 2025.

On patient group a2)

No data are available for adult patients with newly diagnosed, systemic, light chain (AL) amyloidosis for whom therapy other than bortezomib in combination with cyclophosphamide and dexamethasone is the patient-individual appropriate therapy. An additional benefit for this sub-population is therefore not proven.

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

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The procedure of the pharmaceutical company is mathematically comprehensible. Uncertainties arise, in particular, from the fact that it cannot be ruled out that the sources used by the pharmaceutical company for the calculation also included patients with other forms of amyloidosis in some cases and that the pharmaceutical company transfers the incidence rate calculated by it for adults to the total population (i.e., without restriction to adults).

However, the overall assessment is based on the assumption that the stated range lies in a largely plausible order of magnitude.

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: 8 December 2021):

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 doctors experienced in treating adults with light chain (AL) amyloidosis.

In accordance with the European Medicines Agency (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 indirect Coombs test). Interference with blood typing induced by daratumumab may persist for up to 6 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 6 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: 1 January 2022).

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

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual 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.

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: 1 x every 7 days Week 9 - 24: every 14 days From week 25: every 28 days	1st year: 23 Subsequent year: 13	1	1st year: 23
Bortezomib	Day 1, 8, 15, 22 28 day cycle	6 cycles	4	24
Cyclophosphamide	Day 1, 8, 15, 22 28 day cycle	6 cycles	4	24

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone	Day 1, 8, 15, 22 28 day cycle	6 cycles	1st year: 0 (cycle 1 - 2) 2 (cycle 3 - 6)	1st year: 8[2]
Appropriate comparator therapy				
Patient-individual therapy, taking into account general condition, comorbidity and organ damage	Different from patient to patient			

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[3]

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	1800 mg	1800 mg	1 x 1800 mg	1st year: 23	23 x 1800 mg
Bortezomib	1.30 mg/m² = 2.47 mg	2.47 mg	1 x 2.5 mg	24	24 x 2.5 mg
Cyclophosphamide	300 mg/m² = 570 mg	500 mg[4]	1 x 500 mg	24	24 x 500 mg

[2] 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.

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[4] According to the product information of daratumumab, the maximum dosage of cyclophosphamide is 500 mg.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 8	1st year 8 x 40 mg[2]
Appropriate comparator therapy					
Patient-individual therapy, taking into account general condition, comorbidity and organ damage	Different from patient to patient				

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 usage. 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.

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	€ 5,809.83	€ 1.77	€ 0.00	€ 5,808.06
Bortezomib 2.5 mg	1 PSI	€ 1,039.63	€ 1.77	€ 48.80	€ 989.06
Cyclophosphamide 500 mg	6 PSI	€ 82.22	€ 1.77	€ 8.98	€ 71.47
Dexamethasone 40 mg[5]	10 TAB	€ 46.26	€ 1.77	€ 0.00	€ 44.49

[5] Fixed reimbursement rate

Appropriate comparator therapy	
Patient-individual therapy, taking into account general condition, comorbidity and organ damage	Different from patient to patient
Abbreviations: TAB = tablets; SFI = solution for injection; PSI = powder for solution for injection	

LAUER-TAXE® last revised: 1 January 2022

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.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[6]	Treatment days per year	Costs/ patient/ year
Medicinal product to be assessed: Daratumumab in combination with Bortezomib, Cyclophosphamide and Dexamethasone					
Premedication[7]					
Dexamethasone 40 mg[2]	€ 81.55[5] 20 x 40 mg	€ 79.78 [€ 1.77; € 0.00]	€ 3.99	1st year 16	1st year € 63.82
Dexamethasone 20 mg	€ 32.38[5] 10 x 20 mg	€ 30.61 [€ 1.77; € 0.00]	€ 3.06	1st year 7	1st year € 21.43
Paracetamol[8] 500 - 1,000 mg, oral	€ 1.50[9] 20 x 500 mg € 1.06[9] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 23	1st year € 1.56 - € 2.23

[6] Proportionate share of cost per pack for consumption per treatment day. Rounded interim result.
[7] According to the product information for Darzalex (last revised: July 2021)
[8] The dosage of 650 mg paracetamol in premedication stated in the product information cannot be achieved by tablets. Because of this, a dosage of 500 - 1,000 mg is used.
[9] Fixed reimbursement rate. Non-prescription medicinal products which, in accordance with Section 12, paragraph 7, AM-RL (information as concomitant medication in the product information of the prescription medicinal product) are reimbursable at the expense of the statutory health insurance, are not subject to the current Pharmaceutical Price Ordinance. Instead, pursuant to Section 129 paragraph 5a SGB V, sold non-prescription medicinal products when billing according to Section 300 are subject to a medicinal product sales price in the amount of the sales price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[6]	Treatment days per year	Costs/ patient/ year
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 23	1st year € 139.75

Patients receiving therapy with daratumumab should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[10]. 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. If HBs antigen is positive, an active HBV infection is detected.

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

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed				
Daratumumab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for

[10] "Update of the S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Hepatitis_B_Virusinfektionen_Prophylaxe_Diagnostik_Therapie_2011-abgelaufen.pdf

the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 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.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 6 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 20 July 2021, 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 26 July 2021 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 28 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2021. The deadline for submitting written statements was 22 November 2021.

The oral hearing was held on 6 December 2021.

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 11 January 2022, and the proposed resolution was approved.

At its session on 20 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	6 October 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	1 December 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 December 2021	Conduct of the oral hearing
Working group Section 35a	15 December 2021 5 January 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	11 January 2022	Concluding discussion of the draft resolution
Plenum	20 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 January 2022

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

Prof. Hecken