# Justification

Gemeinsamer Bundesausschuss

## of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V - daratumumab (new therapeutic indication: newly diagnosed multiple myeloma)

of 22 March 2019

**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 studies 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 benefits,
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 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 was first placed on the market in Germany on 1 June 2016.

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. Proof 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 31 August 2018, 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 28 September 2018, i.e. at the latest within four weeks of notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has 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 is indicated in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant".

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 2 January 2019, 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 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 bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are in combination with for autologous stem cell transplant is:

- a combination therapy according to the doctor's instructions.

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 according to 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.

[1] General Methods, version 5.0 from 10.07.2017. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 benefit 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. According to the authorisation status, the following active ingredients are available for the first-line treatment of adult patients with multiple myeloma who are ineligible for autologous stem cell transplant: bendamustine, bortezomib, carmustine, cyclophosphamide, dexamethasone, doxorubicin, interferon alfa-2b, lenalidomide, melphalan, prednisone, prednisolone, thalidomide and vincristine. The marketing authorisation of bendamustine, carmustine, thalidomide, lenalidomide and bortezomib is linked to combination partners in each case.

on 2. For the present therapeutic indication, a non-medicinal treatment is not considered as an appropriate comparator therapy. According to the therapeutic indication, patients are ineligible for autologous stem cell transplant.

on 3. There are no resolutions or guidelines of the G-BA for administration of medical products or non-medicinal treatments regarding the therapeutic indication:

on 4. For the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, systematic reviews and relevant guidelines recommend combination therapies based on an immunomodulator or on the proteasome inhibitor bortezomib. This concerns the approved combination therapies bortezomib + melphalan + prednisone, thalidomide + melphalan + prednisone as well as lenalidomide + dexamethasone. The triple combination lenalidomide + melphalan + prednisone is also approved, but the overall evidence is poorer. Thus, in contrast to the triple combinations of bortezomib or thalidomide with melphalan + prednisone, no advantage compared to melphalan + prednisone was shown with regard to survival. In addition to the approved combinations, the triple combination of bortezomib + lenalidomide + dexamethasone, which is not approved in the present therapeutic indication, is also recommended. There is a discrepancy between medicinal products approved in the therapeutic indication and medicinal products recommended in the guidelines. In view of the available evidence, the combination therapies bortezomib + melphalan + prednisone, thalidomide + melphalan + prednisone, lenalidomide + dexamethasone as well as bortezomib + lenalidomide + dexamethasone are equally suitable comparators for the benefit assessment in the context of combination therapy according to the doctor's instructions. The additional benefit can be demonstrated over one of the treatment options in a single-comparator study.

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

Change of the appropriate comparator therapy

Originally, the appropriate comparator therapy was determined as follows:

The appropriate comparator therapy for daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant is:

- bortezomib in combination with melphalan and prednisone

*or*

- thalidomide in combination with melphalan and prednisone

*or*

- lenalidomide in combination with dexamethasone

After the start of the present benefit assessment procedure, a new situation arose that required a reassessment of the appropriate comparator therapy. As a result, combination therapy was determined to be the appropriate comparator therapy according to the doctor's instructions. This includes the originally determined appropriate comparator therapy. The pharmaceutical company and IQWiG were informed about this change in the ongoing benefit assessment procedure. The amended appropriate comparator therapy was published together with IQWiG's benefit assessment on the G-BA's website on 2 January 2019 and, thus made available for comment.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

### 2.1.3 Extent and probability of the additional benefit

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

There is hint for a considerable additional benefit for daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Justification:

The pharmaceutical company has submitted data from the open-label, randomised, controlled phase III ALCYONE study for benefit assessment.

This ongoing study compares daratumumab in combination with bortezomib + melphalan + prednisone (D-VMP regimen) versus bortezomib + melphalan + prednisone (VMP regimen). A total of 706 patients were included in the study in 162 study centres and randomised in a 1:1 ratio to the two study arms (N = 350 D-VMP; N = 356 VMP). Stratification was by International Staging System (ISS) stage (I vs II vs III), region (Europe vs other), and age (< 75 years vs ≥ 75 years). The mean age of the patients was 71.4 years.

According to the inclusion criteria, patients must be aged 65 years and older or have significant comorbidities to be deemed ineligible for autologous stem cell transplant (ASCT). Since the start of the study, the criteria used to classify eligibility for ASCT have undergone change. Accordingly, biological age has become more important than chronological age, taking into account relevant comorbidities. As a result, patients who would be eligible for autologous stem cell transplant according to current criteria may have been included in the study. To address this issue, at the request of the EMA, the pharmaceutical company presented ASCT ineligibility data for a sub-population, which was operationalised based on the criteria of age < 65 years with significant comorbidities or age 65 - 69 years with an ECOG-PS = 2 or age ≥ 70 years. This includes 78% of patients in the total population in the D-VMP arm and 76% in the VMP arm.

Both populations are subject to the uncertainty about the percentage of patients who would have actually been ineligible for ASCT. The procedure chosen by the pharmaceutical company to operationalise the sub-population (ASCT ineligibility) is understandable and is considered to be a sufficient approximation to the target population. Nevertheless, the resulting sub-population, like the overall population, is subject to uncertainty, as the assessment of ASCT ineligibility would have to be patient-individual and independent of chronological age. The information required for this can no longer be determined post hoc. However, a comparison of the sub-population results with those of the total population shows that the magnitude of the effect for the decision-relevant endpoints is very similar in each case. Therefore, the overall population is used for the benefit assessment.

Although the 3rd data cut-off of 12.06.2018 has not been pre-specified, it is primarily used for the present benefit assessment due to its temporal proximity to the dossier preparation and due to the fact that it represents the longest available observation period. At the time of the 1 st data cut-off (12.06.2017), not enough events had occurred to assess the overall survival endpoint with sufficient certainty (93 deaths). At the time of the 3 rd data cut-off, 142 deaths occurred (approximately 43% of the planned events up to the final analysis).

Extent and probability of the additional benefit

Mortality

In terms of overall survival, there is a statistically significant advantage of daratumumab + bortezomib + melphalan + prednisone over bortezomib + melphalan + prednisone. The median time to onset of the event was not yet reached as of the 3 rd data cut-off. There were 59 events in the test arm compared with 83 events in the comparator arm (hazard ratio (HR): 0.68 [95% confidence interval (CI): 0.49; 0.95]; p-value < 0.023).

In terms of overall survival, there is an additional benefit of the daratumumab combination, the extent of which is classified as considerable.

Morbidity

*Progression-free survival (PFS)*

Progression-free survival is the primary endpoint of the ALCYONE study. It is operationalised as the time from randomisation to the onset of disease progression or death. In the daratumumab arm, 134 patients (38.3%) experienced the event, compared to 223 patients (62.6%) in the comparator arm. This difference was statistically significant (HR: 0.43 [0.35; 0.54]; p < 0.0001).

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is assessed according to IMWG criteria and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

*EORTC-QLQ C30 - Symptom scales*

In the ALCYONE study, disease symptomatology is assessed using the cancer-specific EORTC-QLQ C30 questionnaire. Of the symptom scales, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, and diarrhoea are assessed. There was a statistically significant difference of low magnitude between the treatment arms for the fatigue symptom: The number of patients who experienced a deterioration of ≥ 10 points was significantly smaller in the daratumumab arm than that in the control arm (n = 127 (36.3%) vs n = 147 (41.3%); HR = 0.74 [0.58; 0.94], p = 0.015).

Thus, there is an advantage of daratumumab combination therapy with regard to symptomatology.

*Health status according EQ-5D VAS*

Health status is assessed in the present study using the EQ-5D visual analogue scale (VAS). In the dossier, the pharmaceutical company presented responder analyses for improvement or deterioration by an MID of ≥ 7 or ≥ 10 points, respectively. IQWIG did not use these analyses in its dossier assessment. The reason given is that no MID can be derived from the cited work and, moreover, the MID was not pre-specified.

Instead of the responder analyses, IQWIG's dossier assessment uses the evaluation of the mean change of the VAS score from baseline in month 12. For the 3 rd data cut-off, no corresponding analyses are available, so that the 1 st data cut-off is used in this regard. The analysis in month 12 is the last possible time at which sufficiently high response rates are available for both study arms. No statistically significant difference was detected between the treatment arms in the analyses.

In view of the fact that responder analysis based on an MID for a clinical assessment of effects generally have advantages over an analysis of mean differences, and taking into account that the validation study in question has already been used in previous evaluations, the G-BA still uses the responder analysis for the evaluation of the effects on symptomatology in the present assessment. These do not show a significant difference between the treatment arms under neither the operationalisation based on an MID of 7 points, nor of 10.

An additional benefit of daratumumab has not been proven for this endpoint.

Quality of life

*EORTC-QLQ-C30 - Functional scales*

Health-related quality of life will be assessed in the ALCYONE study using the functional scales of the EORTC-QLQ C30. There was no statistically significant difference between the test and control arms in any of the scales (general health status, role functioning, emotional functioning, physical functioning, cognitive functioning, or social functioning).

An additional benefit of daratumumab in the category of quality of life is therefore not proven.

Side effects

In both the test arm and the control arm, almost every patient suffered an adverse event. The results for the "Total adverse events" endpoint are only presented additionally.

Serious adverse events occurred in 43.6% of patients receiving daratumab combination therapy versus 32.5% in the control arm. The difference between the two treatment arms was not statistically significant.

There was also no statistically significant difference in terms of serious adverse events (CTCAE grade ≥ 3) between the daratumumab arm (79.2%) and the control arm (78.0%).

Regarding the endpoint "Therapy discontinuations of all active ingredient components due to adverse events", there is a statistically significant difference in favour of daratumumab combination therapy (HR: 0.48 [0.26; 0.86]; p = 0.013). With daratumumab, 22 patients (6.4%) discontinued therapy with all active ingredient components, compared to 33 patients (9.3%) in the comparator arm.

In specific adverse events, there are both advantages and disadvantages of daratumumab in combination with bortezomib, melphalan and prednisone compared to the triple combination of bortezomib, melphalan and prednisone. Statistically significant disadvantages to the disadvantage of the daratumumab quadruple combination exist for the endpoint "Infections and infestations (SAEs)" (D-VMP: n = 83 (24.0%), VMP: n = 42 (11.9%); HR: 1.85 [1.27; 2.71], p = 0.001), "Vascular disorders (severe AEs [CTCAE grade ≥ 3]" (D-VMP: n = 20

(5.8%), VMP: n = 8 (2.3%); HR: 2.38 [1.04; 5.44], p = 0.040) and "Respiratory, thoracic and mediastinal disorders (AEs)" (D-VMP: n = 140 (40.5%), VMP: n = 74 (20.9%); HR: 1.91 [1.43; 2.55], p < 0.001). There is a statistically significant benefit of low magnitude, in favour of daratumumab for the endpoint "Peripheral neuropathies (AEs)" (D-VMP: n = 110 (31.8%), VMP: n = 133 (37.6%); HR: 0.75 [0.58; 0.96]; p = 0.025).

Overall, in the category of side effects, there are thus advantages of the daratumumab combination with regard to therapy discontinuations as well as advantages and disadvantages with regard to the specific side effects. As the disadvantages associated with some specific AEs are not reflected in the overall rates of AE, SAE and AE (CTCAE grade 3-4), they are not used for downgrading of the additional benefit.

Overall assessment / conclusion

Results on mortality, morbidity, quality of life and side effects are available from the ALCYONE study, compared to the combination therapy bortezomib + melphalan + prednisone for the assessment of the additional benefit of daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

With regard to mortality, there is a statistically significant advantage in favour of daratumumab combination therapy, which is assessed as moderate prolongation of life.

In the area of morbidity, there is a statistically significant difference of low magnitude in terms of the fatigue symptom in favour of daratumumab combination therapy.

Results for health-related quality of life showed no statistically significant difference between the daratumumab quadruple combination and the triple combination.

With regard to side effects, there is an advantage with regard to the endpoint of "Therapy discontinuations". As the advantages and disadvantages for some specific AEs are not reflected in the overall rates of AE, SAE and AE (CTCAE grade 3-4), they are not used for downgrading of the additional benefit in the side effects category.

In summary, considerable additional benefit is identified for daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT due to an overall survival benefit, which is classified as moderate prolongation of life, compared with the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III ALCYONE study. At the study level, the risk of bias is considered low.

The risk of bias at the endpoint level is considered high except for the endpoints of overall survival and severe AEs (CTCAE grade ≥ 3). This is based on a lack of blinding.

In the ALCYONE study, uncertainties arise from the study population on the one hand: The total population also includes patients who could be assigned to such treatment according to current eligibility criteria for ASCT. The results of the total population are used for the benefit assessment as the magnitude of the effects in the ASCT eligibility sub-population defined post hoc (77% of the total population) is similar to that in the total population.

In addition, uncertainties result from the reduced bortezomib dosage applied in the comparator arm compared to that specified in the product information. However, this is considered to be a sufficient approximation to the dosage compliant with the marketing authorisation.

Taking into account the uncertainties mentioned above, an overall hint for an additional benefit of daratumumab can be derived.

### 2.1.4 Limitation of the period of validity of the resolution

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 pursuant to Section 35a paragraph 1 SGB V.

This benefit assessment is based on the analyses of the data cut-off of 12 June 2018. At this time, the median duration of observation was 25.5 months in the intervention arm and 24.0 months in the control arm. The data, in particular on overall survival, are not yet considered conclusive at this time of observation.

The end of study will be reached when 330 overall survival endpoint events have occurred or 5 years after the last patient has been randomised. According to the current state, the final data cut-off of the ALCYONE study is scheduled for the end of 2021.

Since further clinical data from the ALCYONE study are expected, which may be relevant for evaluating of the benefits of the medicinal product, it is justified to limit the validity of the present resolution.

Conditions for the limitation:

For the renewed benefit assessment after the expiry of the deadline, the dossier should be submitted with the final results of the ALCYONE study on all patient-relevant endpoints.

For this purpose, the G-BA considers a limitation for the resolution until 1 March 2022 to be appropriate.

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 (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). 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 benefit assessment is the benefit assessment of a new therapeutic indication for the active ingredient daratumumab. The therapeutic indication assessed here is as follows: "Daratumumab is indicated in combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant."

Daratumumab has received marketing authorisation as an orphan drug.

The G-BA determined a combination therapy as an appropriate comparator therapy according to the doctor’s instructions. The pharmaceutical company presented the results of the ALCYONE study, comparing daratumumab in combination with bortezomib, melphalan and prednisone versus the combination bortezomib + melphalan + prednisone. For the benefit assessment, the 3 rd data cut-off was used.

A statistically significant advantage of daratumumab combination therapy exists for the endpoint of overall mortality, which is rated as having considerable magnitude. There is a minor benefit in morbidity for the fatigue endpoint. There is no statistically significant

difference in the area of quality of life. In terms of side effects, there are advantages and disadvantages.

Due to the lack of blinding, the bias for the results of morbidity, quality of life and side effects (except severe AEs CTCAE grade ≥ 3) is considered high. Uncertainties with regard to the probability result, on the one hand, from the fact that the total population contains patients who are eligible for ASCT according to current criteria, and on the other, from a dosage of bortezomib in the control arm that is not compliant with marketing authorisation, but is classified as sufficiently approximate to it.

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

The validity of the resolution is limited to 1 March 2022.

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

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

The resolution is based on the information provided by the pharmaceutical company in the written statement procedure.

## 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: 13 February 2019):

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

Treatment with daratumumab in combination with bortezomib, melphalan and prednisone 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 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 March 2019).

The costs for the first year of treatment are shown for the cost representation in the resolution. The treatment costs for the following years are listed in the following derivation if different from the therapy costs for the first year of treatment shown.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or shorter on average.

| 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 | First year of treatment:<br>Week 1 - 6:<br>1 x weekly<br>Week 7 - 54:<br>1 x every 3 weeks | 22 treatments[2] | 1 | 22 |
| | Subsequent year:<br>1 x every 4 weeks | 13 treatments[2] | 1 | 13 |
| Bortezomib | 2x weekly in the weeks 1, 2, 4, 5 of the first 6-week cycle<br>Subsequently per cycle:<br>1x weekly in the weeks 1, 2, 4, 5 | 9 cycles | 8 (cycle 1)<br>4 (cycle 2-9) | 40 |
| Melphalan | Day 1 - 4 of the 6-week cycles | 9 cycles | 4 | 36 |
| Prednisone | Day 2 - 4 of the 6-week cycles | 9 cycles | 3 | 27 |
| Appropriate comparator therapy[a] | | | | |
| *Bortezomib + melphalan + prednisone* | | | | |
| Bortezomib | 6-week cycle<br>Cycles 1 - 4:<br>on the days 1, 4, 8, 11, 22, 25, 29, 32<br>Cycles 5 - 9:<br>on the days 1, 8, 22, 29 | 9 cycles | 8 (cycle 1-4)<br>4 (cycle 5-9) | 52 |
| Melphalan | Day 1 - 4 of the 6-week cycles | 9 cycles | 4 | 36 |
| Prednisone | Day 1 - 4 of the 6-week cycles | 9 cycles | 4 | 36 |
| *Thalidomide + melphalan + prednisone* | | | | |

[2] Treatments

| | | | | |
|---|---|---|---|---|
| Thalidomide | First year of treatment:<br>Day 1 - 42 of the<br>6-week cycles | 9 cycles | 42 | 378 |
| | Subsequent year:<br>Day 1 - 42 of the<br>6-week cycles | 3 cycles | 42 | 126 |
| Melphalan | First year of treatment:<br>Day 1 - 4 of the<br>6-week cycles | 9 cycles | 4 | 36 |
| | Subsequent year:<br>Day 1 - 4 of the<br>6-week cycles | 3 cycles | 4 | 12 |
| Prednisone | First year of treatment:<br>Day 1 - 4 of the<br>6-week cycles | 9 cycles | 4 | 36 |
| | Subsequent year:<br>Day 1 - 4 of the<br>6-week cycles | 3 cycles | 4 | 12 |
| *Lenalidomide + dexamethasone* | | | | |
| Lenalidomide | Day 1 - 21 of the<br>28-day cycles | 13 cycles | 21 | 273 |
| Dexamethasone | Day 1, 8, 15 and 22 of the<br>28-day cycles | 13 cycles | 4 | 52 |
| [a] In addition to the combination therapies listed, the triple combination of bortezomib + lenalidomide + dexamethasone also represents a suitable comparator for the present benefit assessment in the context of combination therapy according to the doctor's instructions. This triple combination is not approved in the present therapeutic indication and therefore, the costs are not represented. | | | | |

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).

| Designation of the therapy | Dosage | Dosage/ patient/ treatment days | Usage by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Daratumumab | 16 mg/kg | 1232 mg | 3 x 400 mg<br>1 x 100 mg | 1st year<br>22 | 1st year<br>66 VIA<br>400 mg<br>22 VIA |

| Designation of the therapy | Dosage | Dosage/ patient/ treatment days | Usage by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | | | | Subsequent year<br>13 | 100 mg<br>Subsequent year<br>39 VIA<br>400 mg<br>13 VIA<br>100 mg |
| Bortezomib | 1.3 mg/m$^2$ | 2.5 mg | 1 x 3.5 mg | 40 | 40 VIA<br>3.5 mg |
| Melphalan | 9 mg/m$^2$ | 17.1 mg | 9 x 2 mg | 36 | 325 FCT,<br>2 mg |
| Prednisone | 60 mg/m$^2$ | 114 mg | 6 x 20 mg | 27 | 200 TAB,<br>20 mg |
| Appropriate comparator therapy[a] | | | | | |
| *Bortezomib + melphalan + prednisone* | | | | | |
| Bortezomib | 1.3 mg/m$^2$ | 2.5 mg | 1 x 3.5 mg | 52 | 52 VIA<br>3.5 mg |
| Melphalan | 9 mg/m$^2$ | 17.1 mg | 9 x 2 mg | 36 | 325 FCT,<br>2 mg |
| Prednisone | 60 mg/m$^2$ | 114 mg | 6 x 20 mg | 36 | 220 TAB<br>20 mg |
| *Thalidomide + melphalan + prednisone* | | | | | |
| Thalidomide | 200 mg | 200 mg | 4 x 50 mg | 1st year<br>378<br>Subsequent year<br>126 | 1st year<br>1,512 HC,<br>50 mg<br>Subsequent year<br>504 HC |
| Melphalan | 0.25 mg/kg | 19.25 mg | 10 x 2 mg | 1st year<br>36<br>Subsequent year<br>12 | 1st year<br>360 FCT,<br>2 mg<br>Subsequent year<br>120 FCT |
| Prednisone | 2 mg/kg | 154 mg | 3 x 50 mg | 1st year<br>36 | 1st year<br>108 TAB |

| Designation of the therapy | Dosage | Dosage/ patient/ treatment days | Usage by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | | | | Subsequent year<br>12 | 50 mg<br><br>Subsequent year<br>36 TAB |
| *Lenalidomide + dexamethasone* | | | | | |
| Lenalidomide | 25 mg | 25 mg | 1 x 25 mg | 273 | 273 HC,<br>25 mg |
| Dexamethasone | 40 mg | 40 mg | 1 x 40 mg | 52 | 52 TAB,<br>40 mg |
| [a] In addition to the combination therapies listed, the triple combination of bortezomib + lenalidomide + dexamethasone also represents a suitable comparator for the present benefit assessment in the context of combination therapy according to the doctor's instructions. This triple combination is not approved in the present therapeutic indication and therefore, the costs are not represented. | | | | | |
| VIA: Vials, FCT: Film-coated tablets; HC: Hard capsule; TAB: Tablets | | | | | |

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 130 a SGB V. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. 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.

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

**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 | 400 mg,<br>1 VIA | € 1,979.51 | € 1.77 | € 109.78 | € 1,867.96 |
| | 100 mg,<br>1 VIA | 506.67 | € 1.77 | € 27.44 | € 477.46 |
| Bortezomib | 3.5 mg,<br>1 VIA | € 1,643.25 | € 1.77 | € 104.10 | € 1,537.38 |

| | | | | | |
|---|---|---|---|---|---|
| Melphalan | 2 mg,<br>50 FCT | € 162.70 | € 1.77 | € 73.80 | € 87.13 |
| Prednisone | 20 mg,<br>100 TAB | € 28.95[3] | € 1.77 | € 1.42 | € 25.76 |
| Appropriate comparator therapy | | | | | |
| Bortezomib | 3.5 mg,<br>1 VIA | € 1,643.25 | € 1.77 | € 104.10 | € 1,537.38 |
| Melphalan | 2 mg,<br>50 FCT | € 162.70 | € 1.77 | € 73.80 | € 87.13 |
| Melphalan | 2 mg,<br>25 FCT | € 94.43 | € 1.77 | € 42.18 | € 50.48 |
| Prednisone | 20 mg,<br>100 TAB | € 28.95[3] | € 1.77 | € 1.42 | € 25.76 |
| Prednisone | 20 mg,<br>20 TAB | € 15.08[3] | € 1.77 | € 0.32 | € 12.99 |
| Prednisone | 50 mg,<br>50 TAB | € 67.72[3] | € 1.77 | € 4.49 | € 61.46 |
| Thalidomide | 50 mg,<br>28 HC | € 499.25 | € 1.77 | € 27.93 | € 469.55 |
| Lenalidomide | 25 mg<br>21 HC | € 8,054.46 | € 1.77 | € 459.41 | € 7,593.28 |
| Dexamethasone | 40 mg<br>50 TAB | € 187.70[3] | € 1.77 | € 13.98 | € 171.95 |

LAUER-TAXE® last revised: 1 March 2019

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 standard expenditure in the course of the treatment are not shown.

[3] Fixed reimbursement rate (phase I)

| Type of service | Cost per pack | Costs after deduction of statutory rebates [Section 130; Section 130a SGB V] | Costs per service[4] | Treatment days / year | Costs/ patient/ year |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| ***Premedication***[5] | | | | | |
| Dexamethasone 20 mg, IV | € 16.59[6]<br>10 x 4 mg | € 14.38<br>[€ 1.77; € 0.44] | € 7.19 | 1st year<br>22<br>Subsequent year<br>13 | 1st year<br>€ 158.18<br>Subsequent year<br>€ 93.47 |
| Paracetamol[7]<br>500 – 1,000 mg, oral | € 1.50[8]<br>20 x 500 mg<br><br>€ 1.06[8]<br>10 x 1,000 mg | € 1.36<br>[€ 0.08; € 0.06]<br><br>€ 0.97<br>[€ 0.05; € 0.04] | € 0.07 -<br><br><br>€ 0.10 | 1st year<br>22<br>Subsequent year<br>13<br>1st year<br>22<br>Subsequent year<br>13 | 1st year<br>€ 1.50 -<br>Subsequent year<br>€ 0.88 -<br>1st year<br>€ 2.13<br>Subsequent year<br>€ 1.26 - |
| Dimetindene 1 mg/10 kg KG, IV[9] | € 18.56<br>5 x 4 mg | € 14.76<br>[€ 1.77; € 2.03] | € 5.90 | 1st year<br>22<br>Subsequent year<br>13 | 1st year<br>€ 129.89<br>Subsequent year<br>€ 76.75 |
| ***Postmedication***[5] | | | | | |
| Prednisone | € 28.95[6]<br>100 x 20 mg | € 25.76<br>[€ 1.77; € 1.42] | € 0.26 | 1st year<br>22<br>Subsequent year<br>13 | 1st year<br>€ 5.67<br>Subsequent year<br>€ 3.35 |

LAUER-TAXE® last revised: 1 March 2019

[4] Proportionate share of cost per pack for consumption per treatment day.
[5] According to the product information for Darzalex (last revised: September 2018)
[6] Fixed reimbursement rate (phase I)
[7] The dosage of 650 mg paracetamol in premedication stated in the product information cannot be achieved by tablets. Because of this, a dosage of 500 - 1,000 mg is used.
[8] Fixed reimbursement rate (phase I)
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 medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the non-prescription medicinal products.
[9] For dosages depending on body weight or body surface area, 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).

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (last revised: 7: Supplementary Agreement to the Contract on the Pricing of Substances and Preparations of Substances of 1 March 2016) is not fully used for the calculation of costs, as it (1) is dynamically negotiated, (2) is not representative of care due to the large number of existing billing modalities for preparations of cytostatic agents in SHI care, most of which are regulated in non-public contracts and are not bound to the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), (3) may not include all relevant active ingredients at a certain point in time and for these reasons, is not suitable overall for a standardised cost estimate. In comparison, 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 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 € 81, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These amounts may be underestimated in contracts. These additional other costs are not added to the pharmacy sales price but follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy sales 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 and the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

## 3. Bureaucratic costs

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

By letter dated 20 April 2018, received on 20 April 2018, the pharmaceutical company requested for consultation pursuant to Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), inter alia, on the question of the appropriate comparator therapy. At its session on 29 May 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy. The consultation meeting was held on 28 May 2018.

There was a review of the appropriate comparator therapy defined by the G-BA at the time of the consultation on the basis of the planned/requested therapeutic indication. The Subcommittee on Medicinal Products again determined the appropriate comparator therapy at its session on 27 November 2018.

On 28 September 2018, 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 1 October 2018 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient daratumumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 20 December 2018, and the written statement procedure was initiated with publication on the website of the G-BA on 2 January 2019. The deadline for submitting written statements was 23 January 2019.

The oral hearing was held on 11 February 2019.

By letter dated 12 February 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 1 March 2019.

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 were discussed at the session of the subcommittee on 12 March 2019, and the proposed resolution was approved.

At its session on 22 March 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal product | 22 May 2018 | Determination of the appropriate comparator therapy |
| Subcommittee Medicinal product | 27 November 2018 | Change of the appropriate comparator therapy |
| Working group Section 35a | 5 February 2019 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal product | 11 February 2019 | Conduct of the oral hearing<br>Commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 19 February 2019<br>5 March 2019 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee Medicinal product | 12 March 2019 | Concluding discussion of the draft resolution |
| Plenum | 22 March 2019 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 22 March 2019

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

Prof. Hecken