Justification

Gemeinsamer Bundesausschuss

to 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: Multiple Myeloma, Newly Diagnosed, Patients Ineligible for Autologous Stem Cell Transplant, Combination with Lenalidomide and Dexamethasone)

of 20 August 2020

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 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 German market on 1 June 2016.

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

In its previously approved therapeutic indications, the sales of daratumumab within the German statutory health insurance system at pharmacy sales prices including VAT exceeded € 50 million, necessitating the submission of evidence for daratumumab in accordance with Section 5, paragraphs 1 to 6 of the Rules of Procedure (VerfO) of the G-BA to demonstrate its additional benefit compared with the appropriate comparator therapy.

On 19 November 2019, daratumumab received the marketing authorisation for a new therapeutic indication classified as a major type 2 variation according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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 December 2008, p. 7).

On 8 October 2019, the pharmaceutical company filed an application to consolidate the assessment procedures for daratumumab according to Section 35a, paragraph 5b SGB V. At its session on 22 November 2019, the G-BA approved the application for consolidation.

On 14 February 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient daratumumab with the new therapeutic indication (multiple myeloma, newly diagnosed, patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone) in due time.

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 15 May 2020, 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 addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed 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 arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of daratumumab (Darzalex®) in accordance with the product information

Darzalex® is indicated in combination with lenalidomide and dexamethasone or 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 was determined as follows:

Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Appropriate comparator therapy:

- Daratumumab in combination with bortezomib, melphalan, and prednisone

  or

- Bortezomib in combination with melphalan and prednisone

  or

- Bortezomib in combination with lenalidomide and dexamethasone

  or

- Thalidomide in combination with melphalan and prednisone

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

or

- Lenalidomide in combination with dexamethasone

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.

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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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. In principle, the chemotherapeutic agents bendamustine, carmustine, cyclophosphamide, doxorubicin, melphalan, and vincristine; the proteasome inhibitor bortezomib; the immunomodulators lenalidomide and thalidomide; the CD-38 antibody daratumumab; the immunostimulant interferon alfa-2b; and the glucocorticoids dexamethasone, prednisolone, and prednisone are approved for the present therapeutic indication. The approvals are partly bound to (specified) combination partners.

On 2. In accordance with the therapeutic indication, patients ineligible for autologous stem cell transplant. A non-medicinal treatment is not an appropriate comparator therapy for the therapeutic indication in question.

On 3. Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V:

- Daratumumab, resolution of 22 March 2019

On 4. Systematic reviews and relevant guidelines for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant result in a general recommendation for combination therapies containing an immunomodulator or protease inhibitor (bortezomib). In this respect, according to the authorisation status, the combination therapies bortezomib + melphalan + prednisone, thalidomide + melphalan + prednisone, and lenalidomide + melphalan + prednisone, lenalidomide + dexamethasone as well as the combination therapy bortezomib + lenalidomide + dexamethasone may be considered. The evidence for combination therapy lenalidomide + melphalan + prednisone is worse overall. In contrast to bortezomib or thalidomide + melphalan + prednisone, no survival benefit was shown compared with melphalan + prednisone. In contrast to the other approved therapeutic options mentioned above, lenalidomide + melphalan + prednisone is therefore not determined to be an appropriate comparator therapy in the present therapeutic indication.

In addition, the combination therapy daratumumab + bortezomib + melphalan + prednisone is a relatively new therapeutic option. In its resolution of 22 March 2019, the G-BA established a considerable additional benefit for this combination therapy compared with a combination therapy according to the doctor's instructions. There was a statistically significant benefit of considerable magnitude for the overall survival endpoint as well as a small advantage for one morbidity endpoint. There was no statistically significant difference in quality of life. There were both advantages and disadvantages in the side effects category.

Overall, all the combinations mentioned in the appropriate comparator therapy represent equally appropriate therapy options.

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

2.1.3 Extent and probability of the additional benefit

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

For daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, there is a hint for a minor additional benefit.

Justification:

The benefit assessment is based on the results of the open, randomised, controlled MAIA study. In the study, daratumumab in combination with lenalidomide and dexamethasone is compared with the dual combination of lenalidomide and dexamethasone.

A total of 737 patients were randomised to the two treatment arms (test arm: N = 368, control arm: N = 369). Patients were stratified by international staging system (ISS stage) (I vs II vs III), region (North America vs others), and age (< 75 years vs ≥ 75 years).

The study included patients who were ineligible for high-dose chemotherapy followed by autologous stem cell transplant (ASCT). In order to be classified as ineligible, patients had to be at least 65 years old. If younger than 65, they had to have the corresponding comorbidities. At the time of study planning, this operationalisation was suitable to reflect the ineligibility for an ASCT. However, since then, the criteria for assessing the (in)eligibility for an ACCT have changed. Compared with chronological age, biological age has grown in importance. Accordingly, the eligibility for ASCT is assessed on a patient-individual basis, taking into account the patient's general condition, existing comorbidities, and organ functions. Against this background, post hoc sub-populations were formed within the approval procedure to assess ASCT (in)eligibility based on age, comorbidities, and ECOG-PS (Eastern Cooperative Oncology Group-Performance Status).

The sub-population 1 - "ASCT" ineligibility (age < 65 years with significant comorbidities or age 65 to 69 years with an ECOG-PS = 2 or age ≥ 70 years) accounts for 83% of the total population. In the decision-relevant endpoints, the magnitude of the effect between the total population and the sub-population "ASCT ineligibility" is very similar. In view of this, the total population is used for the benefit assessment. This is analogous to the procedure of the EMA, which had also based its recommendation for marketing authorisation on the total population.

The patient characteristics were balanced between both study arms. In both arms, treatment was given until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study.

The MAIA study is still ongoing. There are two data cut-offs. The data cut-off of 24 September 2018 is a pre-specified interim analysis for the primary endpoint progression-free survival. The

2nd data cut-off of 10 June 2019 was requested by the EMA. Because of the longer observation period, this is used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

With regards to overall survival, no statistically significant difference was established between the two treatment arms. Under daratumumab + lenalidomide + dexamethasone, this event occurred in 85 patients (23.1%). Under lenalidomide + dexamethasone, it occurred in 103 patients (27.9%).

With regard to the overall survival endpoint, an additional benefit for daratumumab in combination with lenalidomide + dexamethasone is not proven.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the MAIA study. It is operationalised as the time from randomisation to the onset of disease progression in accordance with the criteria of the IMWG or death. There is a statistically significant difference between the two study arms. Under daratumumab + lenalidomide + dexamethasone, 120 patients (32.6%) had experienced an event at the time of the 2nd data cut-off compared with 171 patients (46.3%) under lenalidomide + dexamethasone.

The PFS endpoint is a combined endpoint composed of endpoints of the “mortality” and “morbidity” categories. The endpoint component “mortality” is already surveyed via the endpoint “overall survival” as an independent endpoint. The morbidity component “disease progression” is surveyed according to IMWG criteria and thus not in a symptom-related manner but rather by means of laboratory parametric, imaging, and haematological procedures. Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on additional benefit remains unaffected.

Symptomatology

The disease symptomatology was operationalised as time to deterioration by ≥ 10 points using the cancer-specific EORTC QLQ-C30 questionnaire. The survey was conducted up to 16 weeks after the onset of disease progression.

There were statistically significant benefits under daratumumab + lenalidomide + dexamethasone in terms of the two symptom scales “pain” and “dyspnoea”. For the symptom scale “pain”, the median time to deterioration was 35.0 months in the test arm compared with 18.0 months in the control arm. With regard to the symptom scale “dyspnoea”, the median time to deterioration was 27.2 months in the test arm compared with 15.7 months in the control arm.

In the symptom scales “fatigue”, “nausea and vomiting”, “insomnia”, “loss of appetite”, “constipation” and “diarrhoea”, there was no statistically significant difference between the two study arms.

Within the written statement procedure, the pharmaceutical company subsequently submitted data on the use of opioids in the MAIA study. These show that 51% of the patients had already been treated with opioids at the start of study; this increased to 70% in the course of the study. Against the background of these explanations, the advantage with regard to the symptom pain is considered a relevant advantage.

Overall, there is thus an advantage under the daratumumab triple combination in terms of symptomatology.

Health status according to EQ-5D VAS

In the MAIA study, health status is measured with the help of the visual analogue scale (VAS) of EQ-5D. The survey was conducted up to 16 weeks after the onset of disease progression. The pharmaceutical company presented responder analyses operationalised as time to deterioration by 7 or 10 points.

In the dossier assessment of the IQWiG, the analyses of mean differences were used. The responder analyses were also presented in the annex to the dossier assessment. There are no comments on the decision-making process regarding the inclusion of continuous analyses or responder analyses.

In the recent past, the IQWiG has not used the responder analyses because the study on which the derivation of the minimal important difference MID is based (Pickard et al., 2007) is no longer considered suitable by the IQWiG to prove the validity of the MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID.

Instead of responder analyses, the IQWiG used analyses of mean differences.

The standardised mean differences show a statistically significant difference in favour of the triple combination. However, the 95% confidence interval of the Hedges' g is not completely outside the irrelevance range of −0.2 to 0.2. Consequently, it cannot be derived with sufficient certainty that the effects are clinically relevant for the standardised mean differences.

Because responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and because the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status.

In the responder analyses, there was no statistically significant difference between the two treatment arms.

There is therefore no advantage or disadvantage in terms of health status.

Quality of life

Health-related quality of life

The health-related quality of life was operationalised as time to deterioration by ≥ 10 points using the functional scales of the cancer-specific EORTC QLQ-C30 questionnaire. The survey was conducted up to 16 weeks after the onset of disease progression.

There were statistically significant benefits under daratumumab + lenalidomide + dexamethasone in terms of the two functional scales "physical function" and "social function".

There was no statistically significant difference in the functional scales "global health status", "role function", "emotional function", and "cognitive function".

In the health-related quality of life category, there is thus an overall advantage for the daratumumab combination therapy in the area of the "physical function" and "social function".

Side effects

Adverse events (AE) in total

The results for the "combined adverse events" endpoint are presented additionally.

In both study arms, almost every patient suffered an adverse event (daratumumab + lenalidomide + dexamethasone: 100%; lenalidomide + dexamethasone: 99.2%).

Serious adverse events (SAE)

There is no statistically significant difference in severe adverse events between the two study arms.

Severe adverse events (CTCAE grade ≥ 3)

There is a statistically significant difference to the disadvantage of the daratumumab triple combination. 336 patients (92.3%) in the test arm and 315 patients (86.3%) in the reference arm suffered a severe AE (CTCAE grade ≥ 3).

Discontinuation because of AE

With regard to the endpoint discontinuation because of AE, the pharmaceutical company presented additional evaluations on the endpoint discontinuation because of AE within the framework of the written statement procedure. For the present benefit assessment, the operationalisation as discontinuation of at least one active ingredient component is used.

In this respect, there is no statistically significant difference between the two treatment arms.

Specific adverse events

Specific AE were selected by the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.

In detail, for the specific AE “chills (PT, AE)”, “respiratory, thoracic, and mediastinal disorders (SOC, AE)”, “infections and infestations (SOC, SAE)”, and “neutropenia (PT, CTCAE grade ≥ 3)”, there is a statistically significant difference to the detriment of daratumumab combination therapy. With respect to the specific AE “skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)” and “anaemia (PT, CTCAE grade ≥ 3)”, there is a statistically significant difference in favour of daratumumab + lenalidomide + dexamethasone.

In the overall view of the side effects category, there is a disadvantage of the daratumumab triple combination compared with the dual combination lenalidomide + dexamethasone with regard to severe AE (CTCAE grade ≥ 3).

Overall assessment/conclusion

To assess the additional benefit of daratumumab in combination with lenalidomide + dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, data from the MAIA study are available in the mortality, morbidity, health-related quality of life, and side effects categories.

In terms of mortality, there is neither an advantage nor a disadvantage for the daratumumab triple combination.

In the area of morbidity, there is an advantage of therapy with daratumumab + lenalidomide + dexamethasone with respect to the endpoints pain and dyspnoea. In particular, the advantage in terms of the pain endpoint is considered a clinically relevant advantage. With respect to health status surveyed using the EQ-5D VAS, no clinically relevant difference between the two treatment arms can be deduced with sufficient certainty.

In the quality of life category, there are advantages in terms of physical function and social function.

In terms of adverse events, one disadvantage of the daratumumab triple combination is the occurrence of severe adverse events (CTCAE grade ≥ 3). There are no statistically significant differences with regard to serious AE and discontinuations because of AE (discontinuation ≥ 1 component).

Overall, advantages in symptomatology and quality of life are offset by disadvantages in severe adverse events (CTCAE grade ≥ 3). The disadvantages with regard to severe AE (CTCAE grade ≥ 3) are seen as moderate. The adverse effects in this case do not call into question the positive, relevant effects, especially in the symptom pain.

Therefore, for daratumumab in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, a minor additional benefit was found.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled Phase III MAIA study.

There are relevant uncertainties, in particular with regard to the patient population included. The study also includes patients who, based on current recommendations, would receive an autologous stem cell transplant. Because the magnitude of the effects in the patient-relevant endpoints is quite similar in the comparison between the total population and the sub-population “ASCT ineligibility” defined post hoc, the benefit assessment is based on the results for the total population.

At the study level, the risk of bias is classified as low. For the endpoints in the area of symptomatology, health status, and health-related quality of life, the risk of bias because of the lack of blinding is considered high. Another contributing factor for the endpoints on symptomatology and health-related quality of life is that the measurements are incomplete for a relevant proportion of patients.

The aforementioned uncertainties lead to the derivation of a hint.

2.1.4 Summary of the assessment

This assessment refers to 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 lenalidomide 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 appropriate comparator therapy was determined by the G-BA as follows:

– Daratumumab in combination with bortezomib, melphalan, and prednisone

or

– Bortezomib in combination with melphalan and prednisone

or

– Bortezomib in combination with lenalidomide and dexamethasone

or

– Thalidomide in combination with melphalan and prednisone

or

– Lenalidomide in combination with dexamethasone

The pharmaceutical company presented results of the open, randomised, controlled MAIA study, in which daratumumab + lenalidomide + dexamethasone is compared with lenalidomide + dexamethasone.

There is no advantage or disadvantage in terms of overall survival. With regard to the disease symptomatology, there is a particular advantage with regard to the symptoms pain and dyspnoea. The benefit is considered to be clinically relevant primarily in relation to the pain endpoint. There are also benefits in terms of health-related quality of life (physical function and social function). In terms of side effects, there is a disadvantage to the detriment of the daratumumab triple combination.

Because of the lack of blinding and partly incomplete measurements, the bias is classified as high except for the endpoints mortality and severe AE (CTCAE grade ≥ 3) Relevant uncertainties regarding the probability arise in particular from the fact that the total population contains patients who are ineligible for ASCT according to current criteria.

In the overall view, there is a hint for a minor additional benefit.

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 will be based on the patient numbers from the dossier of the pharmaceutical company. In addition to the patients who are ineligible for ASCT, the pharmaceutical company also calculates those who are eligible for ASCT and compares these data with the number of initial transplants in the German stem cell register. Because these are of a similar order of magnitude, it can be assumed that the number of patients who are ineligible for ASCT is also of a plausible order of magnitude, even if the derivation of the target population is subject to uncertainty.

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: 7 May 2020):
https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_de.pdf

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient identification card. Training materials for healthcare professionals and blood banks include instructions on how to deal with the risks of interference with blood grouping caused by daratumumab (indirect anti-human globulin test or Coombs test). Daratumumab-induced interference with blood grouping may persist for up to six months after the last infusion of the medicinal product; healthcare professionals should therefore advise patients to carry their patient ID card for up to six months after the end of treatment.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2020).

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”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[2].

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

Treatment duration:

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	28 day cycle: Week 1 – 8: every 7 days, Week 9 – 24: every 14 days; from Week 25: every 28 days	13	1–4	23

[2] German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Lenalidomide	Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone [3]	Day 1, 8, 15, and 22 of a 28-day cycle (as pre-medication on the days of daratumumab administration	13	0–3	29
Appropriate comparator therapy				
Daratumumab in combination with bortezomib, melphalan, and prednisone				
Daratumumab	42 day cycle: Weeks 1–6: 1 × every 7 days, from Week 7 - 54: 1 × every 21 days; from Week 55, every 28 days	8.7	2–6	21.4
Bortezomib	2 × within 7 days in Weeks 1, 2, 4, and 5 of the first 42-day cycle; then per cycle: 1 × every 7 days in Weeks 1, 2, 4, and 5	8.7	Cycle 1: 8 Afterwards: 4	38.8
Melphalan	Day 1–4 of the 42-day cycles	8.7	4	34.8

[3] On the days of the DARZALEX infusion, the dose of dexamethasone was given as pre-medication before the infusion.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Prednisone	Day 2–4 of the 42-day cycles	8.7	3	26.1
Bortezomib in combination with melphalan and prednisone				
Bortezomib	42 day cycle: Cycles 1–4, each 8 applications; cycles 5–9, each 4 applications	8.7	4–8	50.8
Melphalan	Day 1–4 of the 42-day cycles	8.7	4	34.8
Prednisone	Day 1–4 of the 42-day cycles	8.7	4	34.8
Bortezomib in combination with lenalidomide and dexamethasone				
Induction				
Bortezomib	On Days 1, 4, 8, and 11 of a 21-day cycle	8	4	32
Lenalidomide	Day 1–14 of a 21-day cycle	8	14	112
Dexamethasone	On Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle	8	8	64
Follow-up treatment				
Lenalidomide	Day 1–21 of a 28-day cycle	7	21	147
Dexamethasone	On Days 1, 8, 15, and 22 of a 28-day cycle	7	4	28
Thalidomide in combination with melphalan and prednisone				

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Thalidomide	Day 1–42 of a 42-day cycle	8.7	42	365
Melphalan	Day 1–4 of a 42-day cycle	8.7	4	34.8
Prednisone	Day 1–4 of a 42-day cycle	8.7	4	34.8
Lenalidomide in combination with dexamethasone				
Lenalidomide	Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone	Days 1, 8, 15, and 22 of a 28-day cycle	13	4	52

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Daratumumab	16 mg/kg = 1,232 mg	1,232 mg	1 × 1,800 mg	23	23 × 1,800 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	40 mg	29	29 × 40 mg
Appropriate comparator therapy					
Daratumumab in combination with bortezomib, melphalan, and prednisone					
Daratumumab	16 mg/kg	1,232 mg	1 × 1,800 mg	22	22 × 1,800 mg
Bortezomib	1.3 mg/m^2	2.5 mg	1 × 2.5 mg	38.8	38.8 × 2.5 mg
Melphalan	9 mg/m^2	17.1 mg	9 × 2 mg	34.8	313.2 × 2 mg
Prednisone	60 mg/m^2	114 mg	2 × 50 mg + 1 × 20 mg	26.1	52.2 × 50 mg + 26.1 × 20 mg
Bortezomib in combination with melphalan and prednisone					
Bortezomib	1.3 mg/m^2	2.5mg	1 × 2.5 mg	50.8	50.8 × 2.5 mg
Melphalan	9 mg/m^2	17.1 mg	9 × 2 mg	34.8	313.2 × 2 mg
Prednisone	60 mg/m^2	114 mg	2 × 50 mg + 1 × 20 mg	34.8	69.6 × 50 mg + 34.8 × 20 mg
Bortezomib in combination with lenalidomide and dexamethasone					
Induction					
Bortezomib	1.3 mg/m^2	2.5 mg	1 × 2.5 mg	32	32 × 2.5 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	112	112 × 25 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	64	64 × 20 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Follow-up treatment					
Lenalidomide	25 mg	25 mg	1 × 25 mg	147	147 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	28	28 × 40 mg
Thalidomide in combination with melphalan and prednisone					
Thalidomide	200mg	200mg	4 × 50 mg	365	1,460 × 50 mg
Melphalan	0.25 mg/kg	19.25 mg	10 × 2 mg	34.8	348 × 2 mg
Prednisone	2 mg/kg	154mg	3 × 50 mg	34.8	104.4 × 50 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	52	52 × 40 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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	€ 6,145.56	€ 1.77	€ 356.77	€ 5,787.02
Lenalidomide 25 mg	21 HC	€ 8,080.51	€ 1.77	€ 472.83	€ 7,605.91
Dexamethasone 40 mg[4]	50 TAB	€ 183.02	€ 1.77	€ 0.00	€ 181.25

[4] Fixed reimbursement rate

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Appropriate comparator therapy					
Bortezomib	1 PIJ	€ 1,116.94	€ 1.77	€ 53.85	€ 1061.32
Daratumumab 1,800 mg	1 SFI	€ 6,145.56	€ 1.77	€ 356.77	€ 5,787.02
Dexamethasone 40 mg[4]	50 TAB	€ 183.02	€ 1.77	€ 0.00	€ 181.25
Dexamethasone 20 mg[4]	50 TAB	€ 115.62	€ 1.77	€ 0.00	€ 113.85
Lenalidomide 25 mg	21 HC	€ 8,080.51	€ 1.77	€ 472.83	€ 7,605.91
Melphalan 2 mg	50 FCT	€ 158.65	€ 1.77	€ 72.45	€ 84.43
Prednisone 20 mg[4]	100 TAB	€ 28.28	€ 1.77	€ 1.42	€ 25.09
Prednisone 50 mg[4]	50 TAB	€ 66.07	€ 1.77	€ 4.49	€ 59.81
Thalidomide 50 mg	28 HC	€ 500.64	€ 1.77	€ 28.75	€ 470.12
Abbreviations: FCT = film-coated tablets; HC = hard capsules; SFI = solution for injection; PIJ = powder for the preparation of an injection solution; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2020

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 assessed 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.

Non-prescription medicinal products that are reimbursable by the statutory health insurance in accordance with Annex I of the Pharmaceuticals Directive (OTC exemption list) are not subject to the current medicinal product price regulation. Instead, in accordance with Section 129, paragraph 5a SGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Medicinal product to be assessed: daratumumab (in combination with lenalidomide and dexamethasone)							
Dexamethasone 40 mg i.v.[4]	1 × 40 mg SFI	€ 27.27	€ 1.77	€ 1.34	€ 24.16	23	€ 555.68
Paracetamol 500 – 1,000 mg[4]	20 × 500 mg TAB	€ 1.46	€ 0.07	€ 0.06	€ 1.33	23	€ 1.53 – 3.10
Dimetindene i.v. 1 mg/10 kg	5 × 4 mg SFI	€ 18.15	€ 1.77	€ 1.92	€ 14.46	23	€ 133.03
Appropriate comparator therapy							
Daratumumab (in combination with bortezomib, melphalan, and prednisone)							
Dexamethasone 20 mg i.v.[4]	5 × 4 mg SFI	€ 13.63	€ 1.77	€ 0.23	€ 11.63	22	€ 255.86
Paracetamol 500 – 1,000 mg[4]	20 × 500 mg TAB	€ 1.46	€ 0.07	€ 0.06	€ 1.33	22	€ 1.46 – 2.93
Dimetindene i.v. 1 mg/10 kg	5 × 4 mg SFI	€ 18.15	€ 1.77	€ 1.92	€ 14.46	22	€ 127.25
Abbreviations: SFI = solution for injection; TAB = tablets							

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of 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

At its session on 25 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 February 2020, 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 2, number 2 VerfO.

By letter dated 17 February 2020 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 13 May 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 May 2020. The deadline for submitting written statements was 5 June 2020.

The oral hearing was held on 22 June 2020.

By letter dated 23 June 2020, 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 16 July 2020.

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 28 July 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	25 June 2019	Determination of the appropriate comparator therapy

Working group Section 35a	17 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 June 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 June 2020; 14 July 2020; 21 July 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 July 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

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

Prof. Hecken