Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Daratumumab (reassessment due to new scientific knowledge: multiple myeloma, newly diagnosed, patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone)

of 18 March 2022

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

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

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

On 19 November 2019, daratumumab received the extension of the marketing authorisation for the indication of newly diagnosed multiple myeloma (patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone) which was classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, of 12.12.2008, p. 7). The G-BA conducted a benefit assessment for daratumumab in this indication in accordance with Section 35a SGB V and passed a resolution on 20 August 2020.

In its session on 19 August 2021, the G-BA decided to grant the pharmaceutical company, based on their request, a new benefit assessment according to Section 35a paragraph 5 SGB V.

The approval of the request was linked to the condition that the new benefit assessment is carried out on the basis of a data basis corresponding to the currently generally accepted state of medical-scientific knowledge, including the MAIA study.

By resolution of 19 August 2021, the pharmaceutical company was requested to submit the evidence required for the benefit assessment pursuant to Section 35a, paragraph 1, sentence 3 SGB V within three months of the notification of the decision under point I.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 4 VerfO on 30 September 2021. 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 3 January 2022, 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:

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

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

"Daratumumab is indicated in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisolone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant."

Therapeutic indication of the resolution (resolution of 18 March 2022):

Daratumumab is indicated 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.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for daratumumab in combination with lenalidomide and dexamethasone:

− 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

or

– bortezomib in combination with cyclophosphamide and dexamethasone [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive]

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant 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. In addition to daratumumab, the following active ingredients are approved in the present therapeutic indication:

bendamustine, carmustine, cyclophosphamide, doxorubicin, melphalan, vincristine, bortezomib, lenalidomide, thalidomide, daratumumab, interferon alfa-2b, dexamethasone, prednisolone and prednisone.

Some of the marketing authorisations are tied to (specific) concomitant active ingredients. In addition, the combination of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label.

on 2. According to the therapeutic indication, patients are ineligible for autologous stem cell transplant. A non-medicinal treatment option is not considered as a 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 20 August 2020
- Daratumumab – resolution of 22 March 2019

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

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

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

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into

account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The available evidence on the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant recommends combination therapies based on an immunomodulator and/or proteasome inhibitor. In this regard, the combination therapies bortezomib + melphalan + prednisone, thalidomide + melphalan + prednisone, lenalidomide + melphalan + prednisone, lenalidomide + dexamethasone and the combination therapy bortezomib + lenalidomide + dexamethasone can be considered according to the authorisation status. The evidence for combination therapy lenalidomide + melphalan + prednisone is worse overall. In contrast to bortezomib or thalidomide+ melphalan + prednisone, no advantage compared to melphalan + prednisone was shown with regard to survival. Lenalidomide + melphalan + prednisone is therefore not determined as an appropriate comparator therapy in the present therapeutic indication, in contrast to the other approved therapy options mentioned.

In addition, two combination therapies based on the CD38 antibody daratumumab are approved for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. In its resolution of 22 March 2019, the G-BA determined a considerable additional benefit of the combination therapy daratumumab + bortezomib + melphalan + prednisone, compared to a combination therapy according to doctor's instructions. In its resolution of 20 August 2020, the G-BA identified a hint for a minor additional benefit of the combination therapy daratumumab + lenalidomide + dexamethasone compared to lenalidomide + dexamethasone. Both combination therapies have found their way into current guidelines.

The subject of the present assessment is a reassessment of the combination therapy of daratumumab, lenalidomide and dexamethasone due to new scientific knowledge. Against this background, this combination cannot be considered as an appropriate comparator therapy.

Furthermore, the combination therapy of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy in the therapeutic indication of newly diagnosed multiple myeloma, irrespective of the eligibility for stem cell transplant. This combination is also recommended by guidelines.

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

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:

Compared to the original definition of the appropriate comparator therapy, this is supplemented by the combination therapy of bortezomib, cyclophosphamide and dexamethasone in the present resolution.

This takes into account the fact that the combination therapy of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy in the therapeutic indication of newly diagnosed multiple myeloma (resolution of 20 May 2021).

This does not affect the present assessment of the additional benefit of daratumumab.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of daratumumab in combination with lenalidomide and dexamethasone is assessed as follows:

There is a hint for a considerable additional benefit 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.

Justification:

For the present indication, the G-BA has already conducted a benefit assessment for daratumumab in combination with lenalidomide and dexamethasone by resolution of 20 August 2020. The present benefit assessment procedure represents a reassessment of daratumumab in combination with lenalidomide and dexamethasone due to new scientific knowledge at the request of the pharmaceutical company.

The benefit assessment is based on the results of the open-label, randomised controlled MAIA study. The study compares daratumumab in combination with lenalidomide and dexamethasone versus the dual combination consisting of lenalidomide and dexamethasone.

A total of 737 patients were randomised into the two treatment arms (test arm: N = 368, control arm: N = 369). Stratification was by International Staging System (ISS stage) (I vs II vs III), region (North America vs other), and age (< 75 years vs ≥ 75 years).

Adults with newly diagnosed multiple myeloma with a general condition corresponding to an ECOG-PS (Eastern Cooperative Oncology Group-Performance Status) of 0 to 2, who were not eligible for high-dose chemotherapy followed by autologous stem cell transplant (ASCT) at the time of enrolment, were enrolled in the study. To be appropriately classified as ineligible, patients had to be at least 65 years of age; if younger than 65, they should have relevant comorbidities.

This operationalisation was appropriate at the time of study design to reflect ineligibility for ASCT. However, the criteria for assessing ineligibility for an ASCT have changed ever since. Compared to the chronological age, biological age has gained in importance. Accordingly, the eligibility for ASCT is assessed patient-individually, taking into account the general condition, existing comorbidities and organ functions. Against this background, sub-populations were formed post hoc within the marketing authorisation procedure to assess ASCT (in)eligibility based on age, comorbidities and ECOG-PS.

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) accounted 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" was also very similar in each case for the now newly available 3rd data cut-off. In view of this, the total population is used for the present benefit assessment - as was already the case in the initial assessment based on the 2nd data cut-off. This is analogous to the EMA's procedure which had also recommended marketing authorisation on the basis of the total population.

Patient characteristics were balanced between the two study arms. Treatment was given in both study arms until disease progression, unacceptable toxicity, withdrawal of consent, or end of study.

The MAIA study was launched in March 2015 and is currently ongoing. Currently, three data cut-offs are available. The data cut-off from 24 September 2018 is a pre-specified interim analysis for the primary endpoint of progression-free survival. The 2nd data cut-off from 10 June 2019 was requested by the EMA and formed the basis of the first benefit assessment procedure of the G-BA. The third data cut-off from 19 February 2021 is a pre-specified interim analysis after occurrence of 273 events of the endpoint of overall survival. The third data cut-off is used for the present reassessment due to new scientific knowledge.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the MAIA study as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of daratumumab in combination with lenalidomide and dexamethasone. This prolongation of survival time by treatment with daratumumab in combination with lenalidomide and dexamethasone compared to treatment with lenalidomide in combination with dexamethasone is assessed as a significant improvement.

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 according to IMWG criteria or death.

PFS was statistically significantly prolonged with daratumumab in combination with lenalidomide and dexamethasone compared to lenalidomide in combination with dexamethasone.

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.

Symptomatology

Disease symptomatology was assessed in the MAIA study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30. The assessment is conducted up to 16 weeks after the onset of disease progression.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint of both the time to first deterioration and the time to first improvement by ≥ 10 points each.

In this regard, the G-BA basically follows the estimate in IQWiG's benefit assessment that an evaluation of the time to deterioration is primarily relevant due to the expected disease progression in the present therapeutic indication and taking into account, in particular, the distribution of the absolute values of the scales at the start of the study.

As death due to progression was also defined as a deterioration in the responder analyses in the pharmaceutical company's dossier, the pharmaceutical company submitted analyses of the time to first deterioration without including death due to disease progression as part of the written statement procedure. In addition, the pharmaceutical company submitted responder analyses of the time until "permanent" - referred to by the pharmaceutical company - as well as "confirmed permanent deterioration" as part of the written statement procedure.

According to IQWiG's comments in the addendum to the benefit assessment, there were no divergent results at the endpoint level in the present data situation between the responder analyses of time to first deterioration with or without inclusion of death due to disease progression. Against this background, according to IQWiG, the corresponding analyses including death due to disease progression are significant.

In the time-to-event analyses up to the so-called "permanent deterioration", all patients who showed a deterioration by at least the threshold value at the time of the last assessment were included as responders, whereas patients who showed a deterioration by at least the threshold value at the time of the last assessment alone were censored in the event time analyses for "confirmed permanent deterioration".

The assessment of patient-reported endpoints was discontinued 16 weeks after the onset of disease progression. Against this background, IQWiG states on the one hand that it is not considered appropriate to speak of a "permanent deterioration" in this situation, as it is rather a deterioration confirmed over the shortened observation period. Furthermore, based on the information in the dossier on the median treatment durations and on the observation periods, it can be assumed that the observation period in the intervention arm is about twice as long as in the comparator arm. As a result, sustained deterioration is potentially harder to achieve in the intervention arm observed for a longer period than in the comparator arm observed for a shorter period. Against this background, IQWiG uses the time-to-event analysis up to the "first deterioration", which is considered reasonable for interpretation.

Following IQWiG's estimates, the G-BA uses the analyses of the time to first deterioration. These were also used in the initial assessment of daratumumab in combination with lenalidomide and dexamethasone in the present therapeutic indication.

There were statistically significant advantages of daratumumab in combination with lenalidomide and dexamethasone with regard to the endpoints "pain" and "dyspnoea". For all other endpoints, no statistically significant difference was detected between the study arms.

Overall, there is an advantage of daratumumab in combination with lenalidomide and dexamethasone with regard to symptomatology.

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

General health status is assessed in the MAIA study using the EQ-5D visual analogue scale (VAS). The assessment is conducted up to 16 weeks after the onset of disease progression.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint of both the time to first deterioration and the time to first improvement by ≥ 7, ≥ 10 and ≥ 15 points each.

Also, for the health status, the pharmaceutical company submitted analyses of the time to first deterioration, without including death due to disease progression (by ≥ 15 points) as part of the written statement procedure. In addition, the pharmaceutical company submitted responder analyses of the time to permanent as well as confirmed permanent deterioration (by ≥ 15 points) as part of the written statement procedure.

For the endpoint of health status, the analyses of the time to first deterioration are also used in accordance with the above comments on symptomatology.

There was no statistically significant difference between the study arms for any of the three response thresholds. Thus, there are neither positive nor negative effects of daratumumab in combination with Lenalidomide and dexamethasone with regard to the health status.

Quality of life

Health-related quality of life is assessed in the MAIA study using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30 questionnaire. The assessment is conducted up to 16 weeks after the onset of disease progression.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for this endpoint of both the time to first deterioration and the time to first improvement by ≥ 10 points each.

Also, for health-related quality of life, the pharmaceutical company submitted analyses of the time to first deterioration, without including death due to disease progression as part of the written statement procedure. In addition, the pharmaceutical company submitted responder analyses of the time to permanent as well as confirmed permanent deterioration as part of the written statement procedure.

For the endpoint of health-related quality of life, the analyses of the time to first deterioration are also used in accordance with the above comments on symptomatology.

There were statistically significant advantages of daratumumab in combination with lenalidomide and dexamethasone with regard to the endpoints "physical functioning" and "social functioning". For all other endpoints, no statistically significant difference was detected between the study arms.

Overall, there is an advantage of daratumumab in combination with lenalidomide and dexamethasone with regard to health-related quality of life.

Side effects

Adverse events (AEs)

All endpoints of the AE category will be assessed until 30 days after the last dose of study medication, until withdrawal of consent, or until the start of subsequent myeloma therapy, whichever is earlier.

Serious adverse events (SAE)

For the endpoint serious adverse events, no statistically significant difference was detected between the treatment arms.

Severe AE (CTCAE grade ≥ 3)

For the serious adverse events with CTCAE grade ≥ 3, there is a significant difference to the disadvantage of daratumumab in combination with lenalidomide and dexamethasone.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, no statistically significant difference is detected between the study arms.

Specific AEs

In detail, for the specific AE "chills (PT, AE)", "respiratory, thoracic and mediastinal disorders (SOC, AE)", "infections and infestations (SOC, SAE)" as well as "neutropenia (PT, CTCAE grade ≥ 3)", there was a statistically significant difference to the disadvantage of daratumumab combination therapy. With regard to the specific AEs "skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)" and "anaemia (PT, CTCAE grade ≥ 3)", there is a statistically significant difference to the advantage of daratumumab + lenalidomide + dexamethasone.

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

Overall assessment

This assessment is a reassessment of daratumumab in combination with lenalidomide and dexamethasone due to new scientific knowledge for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. Compared to treatment with lenalidomide in combination with dexamethasone, results from the MAIA study are available from the new 3rd data cut-off on mortality, morbidity, health-related quality of life and side effects.

For the endpoint of overall survival, the present results show a statistically significant prolongation of survival time by treatment with daratumumab in combination with lenalidomide and dexamethasone compared to a treatment with lenalidomide in combination with dexamethasone, which is assessed as a significant improvement.

With regard to symptomatology (assessed using the EORTC QLQ-C30), there were advantages for therapy with daratumumab in combination with lenalidomide and dexamethasone in the endpoints of pain and dyspnoea. With regard to health status (assessed by EQ-5D VAS), there was no statistically significant difference between the study arms.

With regard to health-related quality of life (assessed by EORTC QLQ-C30), there are advantages for daratumumab in combination with lenalidomide and dexamethasone with regard to the endpoints of physical functioning and social functioning.

With regard to adverse events, there is a disadvantage of the daratumumab triple combination in terms of the occurrence of severe adverse events (CTCAE grade ≥ 3). There are no statistically significant differences with regard to serious AEs and discontinuations due to AEs.

Overall, a significant improvement in terms of prolonged survival time and advantages in symptomatology and quality of life are offset by a disadvantage in serious adverse events (CTCAE grade ≥ 3). The disadvantage is rated as moderate.

In the overall assessment, the G-BA concludes that there is considerable additional benefit 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 compared to lenalidomide in combination with dexamethasone.

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.

Relevant uncertainties exist in particular with regard to the enrolled patient population. The study also enrolled patients who would receive an autologous stem cell transplant on the basis of current recommendations. Since the magnitude of the effects in the patient-relevant endpoints are very similar in the comparison between the total population and the sub-population defined post hoc "ASCT ineligibility" even for the now newly available 3rd data cut-off, the benefit assessment is carried out on the basis of the results for the total population.

At the study level, the risk of bias is considered low. For the endpoints in the areas of symptomatology, health status and health-related quality of life, the risk of bias is classified as high due to the lack of blinding. Furthermore, for the endpoints of symptomatology and health-related quality of life, the measurements are incomplete for a relevant percentage of patients.

The uncertainties mentioned lead to a hint being derived overall.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient daratumumab based on an application due to new scientific knowledge according to Section 14 VerfO.

The therapeutic indication reassessed here is as follows: Daratumumab is indicated 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.

Daratumumab has received marketing authorisation as an orphan drug.

The G-BA determined the following as 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

or

− lenalidomide in combination with dexamethasone

or

– bortezomib in combination with cyclophosphamide and dexamethasone [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive]

For the reassessment, the pharmaceutical company submits the results of the new 3rd data cut-off of the open-label RCT MAIA, in which daratumumab + lenalidomide + dexamethasone is compared with lenalidomide + dexamethasone.

For the endpoint of overall survival, there is a statistically significant effect to the advantage of daratumumab + lenalidomide + dexamethasone that was assessed as a significant improvement.

For symptomatology, there are advantages for daratumumab + lenalidomide + dexamethasone with regard to pain and dyspnoea. There is no statistically significant difference with regard to health status.

For health-related quality of life, there are advantages for daratumumab + lenalidomide + dexamethasone (physical functioning and social functioning).

In the area of side effects, there is a disadvantage of the daratumumab triple combination.

Due to the lack of blinding and partly incomplete measurements, the risk of bias is classified as high apart from the endpoints of mortality and severe AEs (CTCAE grade ≥ 3). Relevant uncertainties with regard to the probability result in particular from the fact that the total population contains patients who are eligible for an ASCT according to current criteria.

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

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

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

In the dossier for the benefit assessment, the pharmaceutical company derived the number of patients by deducting the percentage of all patients with smoldering multiple myeloma (SMM) at initial diagnosis. This approach is not considered appropriate since only the deduction of the percentage of patients with non-progressive SMM is appropriate.

When determining the patient numbers, the G-BA therefore refers to the derivation of the target population used as a basis in the corresponding initial resolution on the benefit assessment of daratumumab (resolution of 20 August 2020), as the corresponding patient percentages were deducted appropriately here and thus, a better estimate can be assumed.

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: 4 January 2022):
https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf

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

In accordance with the 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 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: every 14 days From week 25: every 28 days	23	1	23
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	29[2]
Appropriate comparator therapy				
Daratumumab in combination with bortezomib, melphalan and prednisolone				
Daratumumab	42-day cycle: Week 1 - 6: 1 x every 7 days Week 7 - 54: every 21 days From week 55: every 28 days	8.7	2 - 6	21.3
Bortezomib	2 x within 7 days in weeks 1, 2, 4, 5 of the first 42-day cycle Subsequently, for each cycle: 1 x every 7	8.7	4 - 8	38.7

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

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	days in weeks 1, 2, 4, 5			
Melphalan	Day 1 - 4 of the 42-day cycles	8.7	4	34.8
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, 8 applications each; cycles 5 - 9, 4 applications each	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

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone	On days 1, 8, 15 and 22 of a 28-day cycle	7	4	28
Thalidomide in combination with melphalan and prednisone				
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	13.0	21	273
Dexamethasone	Days 1, 8, 15 and 22 of a 28-day cycle	13.0	4	52
Bortezomib in combination with cyclophosphamide and dexamethasone[3]				
Bortezomib	Day 1, 4, 8, 11 of a 21-day cycle	17.4	4	69.6
Cyclophosphamide	Day 1 of a 21-day cycle	17.4	1	17.4
Dexamethasone	Day 1, 2, 4, 5, 8, 9,11, 12 of a 21-day cycle	17.4	1st year: 8	1st year: 139.2

[3] cf. Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use):

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average 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)[4]

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23	23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	40 mg	29	29 x 40 mg
Appropriate comparator therapy					
Daratumumab in combination with bortezomib, melphalan and prednisolone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	21.3	21.3 x 1,800 mg
Bortezomib	1.3 mg/m2 = 2.5 mg	2.5 mg	1 x 2.5 mg	38.7	38.7 x 2.5 mg
Melphalan	9 mg/m² = 17.1 mg	17.1 mg	9 x 2 mg	34.8	313.2 x 2 mg
Prednisone	60 mg/m2 = 114 mg	114 mg	2 x 50 mg + 1 x 20 mg	26.1	52.2 x 50 mg + 26.1 x 20 mg
Bortezomib in combination with melphalan and prednisone					
Bortezomib	1.3 mg/m2 = 2.5 mg	2.5 mg	1 x 2.5 mg	50.8	50.8 x 2.5 mg

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/ (last access: 24.01.2022).

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Melphalan	9 mg/m^2 = 17.1 mg	17.1 mg	9 x 2 mg	34.8	313.2 x 2 mg
Prednisone	60 mg/m2 = 114 mg	114 mg	2 x 50 mg + 1 x 20 mg	34.8	69.6 x 50 mg + 34.8 x 20 mg
Bortezomib in combination with lenalidomide and dexamethasone					
Induction					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	32	32 x 2.5 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	112	112 x 25 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	64	64 x 20 mg
Follow-up treatment					
Lenalidomide	25 mg	25 mg	1 x 25 mg	147	147 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	28	28 x 40 mg
Thalidomide in combination with melphalan and prednisone					
Thalidomide	200 mg	200 mg	4 x 50 mg	365	1,460 x 50 mg
Melphalan	0.25 mg/kg = 19.25 mg	19.25 mg	10 x 2 mg	34.8	348 x 2 mg
Prednisone	2 mg/kg = 154.00 mg	154 mg	3 x 50 mg	34.8	104.4 x 50 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52	52 x 40 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Bortezomib in combination with cyclophosphamide and dexamethasone					
Bortezomib	1.30 mg/m² = 2.47 mg	2.47 mg	1 x 2.5 mg	69.6	69.6 x 2.5 mg
Cyclophosphamide	900 mg/m² = 1,710 mg	1,710 mg	1 x 2,000 mg[5]	17.4	17.4 x 2,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	139.2	139.2 x 40 mg²

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Daratumumab 1,800 mg	1 SFI	€ 5,809.83	€ 1.77	€ 0.00	€ 5,808.06
Lenalidomide 25 mg	21 HC	€ 4,103.36	€ 1.77	€ 528.13	€ 3,573.46
Dexamethasone 40 mg[6]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 1,022.73	€ 1.77	€ 48.00	€ 972.96

[5] The administration form must be intravenous according to Annex VI of the Pharmaceuticals Directive.

[6] Fixed reimbursement rate

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
Cyclophosphamide 1,000 mg	1 PSIl	€ 70.34	€ 1.77	€ 2.80	€ 65.77
Daratumumab 1,800 mg	1 SFI	€ 5,809.83	€ 1.77	€ 0.00	€ 5,808.06
Dexamethasone 40 mg[6]	10 TAB	€ 46.26	€ 1.77	€ 0.00	€ 44.49
Dexamethasone 40 mg[6]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Dexamethasone 20 mg[6]	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08
Dexamethasone 20 mg[6]	20 TAB	€ 54.05	€ 1.77	€ 0.00	€ 52.28
Lenalidomide 25 mg	21 HC	€ 4,103.36	€ 1.77	€ 528.13	€ 3,573.46
Melphalan 2 mg	50 FCT	€ 54.18	€ 1.77	€ 2.38	€ 50.03
Prednison 20 mg[6]	100 TAB	€ 29.25	€ 1.77	€ 1.42	€ 26.06
Prednison 50 mg[6]	50 TAB	€ 68.02	€ 1.77	€ 4.49	€ 61.76
Thalidomide 50 mg	28 HC	€ 516.34	€ 1.77	€ 28.89	€ 485.68
Abbreviations: FCT = film-coated tablets; HC = hard capsules; SFI = solution for injection; PSI = powder for solution for injection; PSIl = powder for solution for injection or infusion; TAB = tablets					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular costs in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

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	Cost/ performance	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed: Daratumumab (in combination with lenalidomide and dexamethasone)								
Dexamethasone 40 mg[6]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23	€ 3.72	23	€ 85.67
Paracetamol 500 – 1,000 mg[6]	20 TAB (500 mg)	€ 1.50	€ 0.08	€ 0.06	€ 1.36	€ 0.07	23	€ 1.56
	10 TAB (1,000 mg)	€ 1.06	€ 0.05	€ 0.04	€ 0.97	€ 0.10		€ 2.23
Dimetindene IV 1 mg/10 kg	5 SFI (4 mg)	€ 18.86	€ 1.77	€ 1.90	€ 15.19	€ 6.08	23	€ 139.75
Appropriate comparator therapy								
Daratumumab (in combination with bortezomib, melphalan and prednisone)								
Dexamethasone 20 mg[6]	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	€ 2.34	22	€ 51.52
Paracetamol 500 – 1,000 mg[6]	20 TAB (500 mg)	€ 1.50	€ 0.08	€ 0.06	€ 1.36	€ 0.07	22	€ 1.50
	10 TAB (1,000 mg)	€ 1.06	€ 0.05	€ 0.04	€ 0.97	€ 0.10		€ 2.13
Dimetindene IV 1 mg/10 kg	5 SFI (4 mg)	€ 18.86	€ 1.77	€ 1.90	€ 15.19	€ 6.08	22	€ 133.67
Abbreviations: SFI = solution for injection; TAB = tablets								

Patients receiving therapy with daratumumab and lenalidomide should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of

suspected chronic hepatitis B, sensibly coordinated steps are required[7]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

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

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

Other SHI services:

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

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

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

the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

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

On 30 September 2021, the pharmaceutical company submitted a dossier for the benefit assessment of daratumumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 4 VerfO.

By letter dated 30 September 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient daratumumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 22 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 January 2022. The deadline for submitting written statements was 24 January 2022.

The oral hearing was held on 7 February 2022.

By letter dated 8 February 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 24 February 2022.

On 16 February 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 16 February 2022 replaces version 1.0 of the dossier assessment dated 22 December 2021. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 March 2022, and the proposed resolution was approved.

At its session on 18 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	25 June 2019	Determination of the appropriate comparator therapy
Working group Section 35a	2 February 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	7 February 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 February 2022 2 March 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 March 2022	Concluding discussion of the draft resolution
Plenum	18 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 18 March 2022

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

Prof. Hecken