Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Daratumumab (new therapeutic indication: multiple myeloma, at least 1 prior therapy, combination with Pomalidomide and Dexamethasone)

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

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

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

2. Key points of the resolution

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

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

Within the previously approved therapeutic indications, the sales volume of daratumumab with the statutory health insurance at pharmacy sales prices, including value-added tax

exceeded € 50 million. Evidence must therefore be provided for daratumumab in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 21 June 2021, daratumumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 20 July 2021, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient daratumumab with the new therapeutic indication ("[...] in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy").

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

The G-BA came to a resolution on whether an additional benefit of daratumumab compared 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

Darzalex is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy.

Therapeutic indication of the resolution (resolution of 3 February 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory

Appropriate comparator therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

b1) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

Appropriate comparator therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- pomalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomide and dexamethasone

or

- elotuzumab in combination with pomalidomide and dexamethasone

or

- carfilzomib in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomide and dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

b2) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression after the last therapy

Appropriate comparator therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomide and dexamethasone

or

- daratumumab in combination with bortezomib and 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 in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In addition to daratumumab, the following active ingredients are approved in the present therapeutic indication:

belantamab mafodotin, bortezomib, carfilzomib, carmustine, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, interferon alfa-2b, idecabtagen vicleucel, isatuximab, ixazomib, lenalidomide, melphalan, panobinostat, pomalidomide, prednisolone, prednisone, selinexor and vincristine.

The marketing authorisations are in part linked to (specified) concomitant active ingredients and to the type of the prior therapies.

on 2. It is assumed that high-dose chemotherapy with stem cell transplant is not an option for patients at the time of current therapy. Therefore, a non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication.

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

- Panobinostat – resolution of 17 March 2016
- Pomalidomide – resolutions of 17 March 2016 and 5 December 2019
- Elotuzumab – resolutions of 1 December 2016 and 16 December 2021
- Ixazomib – resolution of 6 July 2017
- Carfilzomib – resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolution of 15 February 2018
- Belantamab mafodotin – resolution of 4 March 2021
- Isatuximab – resolution of 4 November 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".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

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.

Based on the authorisation status and the available evidence on the relevant active ingredients or combinations of active ingredients, it is considered appropriate for the present treatment setting to determine the appropriate comparator therapy, differentiated according to the following patient groups:

a) Adults with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory

According to the authorisation status and underlying evidence, the treatment of individuals who have already received prior therapy is primarily based on the active ingredients bortezomib, carfilzomib, ixazomib, lenalidomide, elotuzumab and daratumumab.

In view of the fact that the present patient population is lenalidomide-refractory, lenalidomide and combination therapies containing lenalidomide cannot be considered as an appropriate comparator therapy.

Due to different toxicity profiles relevant to therapy, the dual combinations of bortezomib and dexamethasone and bortezomib + doxorubicin **(pegylated, liposomal)** will continue to be given appropriate importance, i.e. even after the introduction of new treatment options. In contrast, monotherapy with bortezomib is no longer recommended as a treatment option in relevant guidelines due to its proven inferiority in terms of overall survival and is therefore not considered an appropriate comparator therapy.

For the dual combination therapy of carfilzomib + dexamethasone, a hint for a considerable additional benefit compared to bortezomib + dexamethasone was identified by the resolution of 15 February 2018. In contrast, an additional benefit for carfilzomib in combination with daratumumab and dexamethasone compared with carfilzomib and dexamethasone is not proven (resolution of 15 July 2021), which is why this combination is not considered as an appropriate comparator therapy.

In the benefit assessment of the combination therapy of daratumumab + bortezomib + dexamethasone, the G-BA identified an indication for a considerable additional

benefit compared to bortezomib and dexamethasone by its resolution of 15 February 2018. The period of validity of the resolution is limited to 1 April 2022.

Pomalidomide is indicated in combination with bortezomib and dexamethasone in patients with at least one prior therapy, including lenalidomide. In the corresponding benefit assessment, no additional benefit could be identified for this combination in the designated patients compared with bortezomib in combination with dexamethasone by the resolution of 5 December 2019. Therefore, this combination is not considered as an appropriate comparator therapy.

For the combination therapy of isatuximab + carfilzomib + dexamethasone, it was identified by the resolution of 4 November 2021 that an additional benefit compared to the combination therapy of carfilzomib + dexamethasone is not proven, as no relevant differences in patient-relevant endpoints were shown. Isatuximab in combination with carfilzomib and dexamethasone is therefore not determined as an appropriate comparator therapy.

Pomalidomide in combination with dexamethasone, elotuzumab in combination with pomalidomide and dexamethasone, panobinostat in combination with bortezomib and dexamethasone, isatuximab in combination with pomalidomide and dexamethasone, the monotherapies with daratumumab, belantamab mafodotin and selinexor as well as the CAR-T cell therapy idecabtagen vicleucel are, according to their authorisation status and available evidence, only indicated after at least two or more prior therapies, which is a relevant difference regarding the treatment setting compared to subjects who have received at least one prior therapy. The above therapy options are therefore not considered as appropriate comparator therapy.

As recommended by guidelines and taking into account the respective authorisation status, the combinations of bortezomib with pegylated liposomal doxorubicin, bortezomib with dexamethasone, carfilzomib with dexamethasone or daratumumab with bortezomib and dexamethasone are equally appropriate therapy options for adults with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory.

b1) <u>Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy</u>

and

b2) <u>Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression after the last therapy</u>

In accordance with the authorisation status and the underlying evidence, the treatment of adults who have already received two prior therapies is primarily focused on the

agents bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, panobinostat and pomalidomide.

In the benefit assessment of pomalidomide in combination with dexamethasone, a hint for a considerable additional benefit was identified - by the resolution of 17 March 2016 - in the treatment of patients with relapsed and refractory multiple myeloma after at least two prior therapies, including lenalidomide and bortezomib, for whom dexamethasone (high-dose) represents the patient-individual therapy according to the doctor's instructions. For patients for whom dexamethasone (high-dose) does not represent the patient-individual therapy according to the doctor's instructions, an additional benefit is not proven.

For elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma after at least two prior therapies, including lenalidomide and a proteasome inhibitor, a hint for a considerable additional benefit over pomalidomide in combination with dexamethasone was identified by the resolution of 16 December 2021.

In addition, a hint for a minor additional benefit was identified for elotuzumab in combination with lenalidomide and dexamethasone compared with lenalidomide in combination with dexamethasone by the resolution of 1 December 2016.

For carfilzomib, a hint for a considerable additional benefit in the benefit assessments both in combination with lenalidomide and dexamethasone versus lenalidomide + dexamethasone and for the dual combination with dexamethasone versus bortezomib + dexamethasone was identified by the resolution of 15 February 2018.

In contrast, an additional benefit for carfilzomib in combination with daratumumab and dexamethasone compared with carfilzomib and dexamethasone is not proven (resolution of 15 July 2021). Therefore, this combination is not considered as an appropriate comparator therapy.

Also by resolution of 15 February 2018, an indication of a considerable additional benefit was determined for daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone compared with lenalidomide in combination with dexamethasone or bortezomib in combination with dexamethasone.

In the benefit assessment of ixazomib in combination with lenalidomide and dexamethasone, the resolution of 6 July 2017 concluded that there was an additional benefit for people with relapsed and refractory multiple myeloma after at least one prior therapy compared to lenalidomide and dexamethasone, but that this benefit was not quantifiable. The period of validity of the relevant resolution of 6 July 2017 was limited until 1 November 2021. For ixazomib in combination with lenalidomide and dexamethasone, a reassessment after the deadline will be carried out in parallel to the present benefit assessment procedure. Therefore, this combination is also not considered as an appropriate comparator therapy.

For the combination therapy of isatuximab + carfilzomib + dexamethasone, it was identified by the resolution of 4 November 2021 that an additional benefit compared to the combination therapy of carfilzomib + dexamethasone is not proven, as no relevant differences in patient-relevant endpoints were shown. Isatuximab in combination with carfilzomib and dexamethasone is therefore not determined as an appropriate comparator therapy. For the combination therapy isatuximab + pomalidomide + dexamethasone, the G-BA identified a hint for a minor additional benefit compared to pomalidomide + dexamethasone in its resolution of 4 November 2021. This combination therapy is not currently considered an appropriate comparator therapy as isatuximab + pomalidomide + dexamethasone is a fairly new treatment option whose therapeutic significance cannot yet be conclusively assessed.

Also, in adults who have received two prior therapies, the dual combinations of bortezomib and doxorubicin (pegylated, liposomal), bortezomib and dexamethasone, lenalidomide and dexamethasone, carfilzomib and dexamethasone, and pomalidomide and dexamethasone are given appropriate priority due to different toxicity profiles that may be relevant to therapy. For this reason, these options are considered to be the appropriate comparator therapy.

Elotuzumab in combination with lenalidomide and dexamethasone, carfilzomib in combination with dexamethasone or lenalidomide and dexamethasone, and daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone are already approved for the treatment of patients with only one prior line of therapy. However, the benefit assessments were based on studies in which patients with at least two previous therapies had been included to a considerable extent. Accordingly, study evidence is also available for the present indication. Thus, these treatment options are considered to be the appropriate comparator therapy for the present patient group.

The monotherapies with daratumumab, belantamab mafodotin, and selinexor as well as the CAR-T cell therapy idecabtagen vicleucel are only indicated after at least three or four prior therapies, according to their authorisation status and the available evidence, which means that there is a relevant difference with regard to the treatment setting compared to subjects who have received at least two prior therapies. The above therapy options are therefore not considered as appropriate comparator therapy.

The marketing authorisation of pomalidomide + dexamethasone and elotuzumab + pomalidomide + dexamethasone is restricted to subjects with disease progression on their last therapy. Taking into account the authorisation status of the combination therapies, the G-BA therefore considers it appropriate to differentiate the patient population according to the criterion of "disease progression on the last therapy" and "disease progression after the last therapy". For the group of patients with disease progression after the last therapy, bortezomib in combination with pegylated liposomal doxorubicin, bortezomib in combination with dexamethasone, lenalidomide

in combination with dexamethasone, elotuzumab in combination with lenalidomide and dexamethasone, carfilzomib in combination with lenalidomide and dexamethasone, carfilzomib in combination with dexamethasone, daratumumab in combination with lenalidomide and dexamethasone or daratumumab in combination with bortezomib and dexamethasone represent equally appropriate therapy options. For the patient group with disease progression on the last therapy, pomalidomide in combination with dexamethasone and elotuzumab in combination with pomalidomide and dexamethasone represent further equally appropriate comparator therapies.

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

2.1.3 Extent and probability of the additional benefit

a) Adults with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory

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

An additional benefit is not proven.

Justification:

For the benefit assessment of patient population a), the pharmaceutical company presents in the dossier the results of the intervention arm of the phase III APOLLO study for adults who received one prior therapy and the results of the MM-014 cohort study.

For the description of the APOLLO study, please refer to the explanations below on patient population b1). Adults who received one prior therapy were required to have progressed (lenalidomide-refractory) during or within 60 days of completing the lenalidomide-containing treatment regimen for enrolment in the APOLLO study.

Patients who received one as well as two prior therapies were enrolled in the MM-014 cohort study. The prior therapy had to include a lenalidomide-containing regimen with at least two consecutive cycles. For the MM-014 study, the pharmaceutical company presents the results of the cohort in which adults received treatment with daratumumab + pomalidomide + dexamethasone (D-Pd). Of these, a total of 63% had one prior therapy.

In both studies, D-Pd was compared to pomalidomide + dexamethasone (Pd). Pd is not approved for the present patient population and accordingly does not represent an appropriate comparator therapy.

As the pharmaceutical company does not present suitable data for the assessment of the additional benefit of patient population a) compared to the appropriate comparator therapy, an additional benefit for D-Pd is not proven.

b1) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

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

Hint for a minor additional benefit

Justification:

For the benefit assessment of patient population b1), the pharmaceutical company uses the results of the randomised, open-label, phase III APOLLO study in the dossier. The study compared daratumumab + pomalidomide + dexamethasone (D-Pd) versus pomalidomide + dexamethasone (Pd).

The study was conducted in adults who have received one prior therapy containing lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy. Here, refractory multiple myeloma was defined as non-response to therapy or the occurrence of disease progression within 60 days of the end of therapy. In contrast, relapsed multiple myeloma was defined as the occurrence of disease progression after prior therapy that requires renewed therapy without meeting the definition of refractory multiple myeloma.

The adults in the study were on average 66 years old. Of the adults enrolled in the study, 84% received two to three prior therapies and 78% or 79% were refractory to the last therapy.

A total of 304 patients were randomised in a 1:1 ratio to the two study arms (N = 151 D-Pd, N = 151 Pd). Randomisation was stratified by number of prior therapies and the International Staging System (ISS) stage.

In the dossier for the benefit assessment, the pharmaceutical company submits the sub-population of the APOLLO study which received two prior therapies containing lenalidomide and a proteasome inhibitor, and demonstrated disease progression on or after the last therapy. The comparator therapy Pd used in the study is not approved for adults with disease progression after the last therapy. For the present benefit assessment of patient population b1), the results of the sub-population of the APOLLO study are therefore relevant, which received two prior therapies containing lenalidomide and a proteasome inhibitor, and demonstrated disease progression on the last therapy.

The adjustment of the appropriate comparator therapy according to the final approved therapeutic indication could only take place after the European Medicines Agency (EMA) granted the positive opinion and thus, shortly before submission of the dossier, so that the pharmaceutical company was not able to adequately consider the sub-population relevant to the assessment in its dossier. With its written statement, the pharmaceutical company submits the results of the APOLLO study for the sub-population of adults with disease progression on the last therapy that is relevant for the assessment. These evaluations are used for this benefit assessment.

Treatment in the APOLLO study was given in 28-day cycles in both study arms until disease progression, unacceptable toxicity or withdrawal of consent. After discontinuation of daratumumab or of pomalidomide + dexamethasone, treatment could be continued with the remaining components of the combination therapy.

Data on subsequent therapies are only available for the total population of the APOLLO study and at the active ingredient level. The percentage of patients with at least one subsequent therapy directed against multiple myeloma is lower in the intervention arm than in the comparator arm (36.2% versus 56%). The greatest differences were seen with regard to subsequent therapy with daratumumab (2.1% versus 33.3%).

The ongoing study is being conducted at 40 study sites across Europe. The primary endpoint of the study is progression-free survival (PFS). Secondary endpoints were overall survival, morbidity and quality of life, as well as adverse events.

Two data cut-offs are available for the benefit assessment. The data cut-off of 21.07.2020 is a pre-specified analysis planned after 188 events occurred in the primary PFS endpoint and conducted upon occurrence of 190 PFS events. Results for all patient-relevant endpoints are available for this data cut-off. Another non-pre-specified interim analysis was conducted for adverse events due to the 120-day safety update required by the US Food and Drug Administration (FDA) (data cut-off of 15.11.2020). The final analysis of overall survival is still pending and is planned after the occurrence of 166 deaths or 5 years after randomisation of the last patient.

With its written statement, the pharmaceutical company submits a further non-pre-specified data cut-off of 19.08.2021, which was carried out on the basis of a presentation of results for the congress of the "American Society of Haematology". The exploratory, non-prespecified data cut-off of 19.08.2021 is not used for the benefit assessment since suitable pre-specified data cut-offs or those requested by regulatory authorities are available for the assessment of additional benefit in the present case.

The results of the data cut-off of 21.07.2020 are used for the endpoint categories of mortality, morbidity and health-related quality of life. The assessment of the endpoints of side effects is based on the data cut-off of 15.11.2020.

Extent and probability of the additional benefit

Mortality

The endpoint of overall survival is operationalised in the APOLLO study as the time between randomisation and death from any cause.

There are no signs of statistically significant differences between the treatment arms. The median survival time was not reached in the D-Pd arm.

Morbidity

Progression-free survival (PFS)

PFS was the primary endpoint of the APOLLO study and was operationalised as the time from randomisation to the date of disease progression or death from any cause. Disease progression was determined using the International Myeloma Working Group (IMWG) criteria, based on laboratory parameters and haematological and imaging procedures.

For the PFS endpoint, there is a statistically significant advantage in favour of D-Pd.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The “mortality” endpoint component is already assessed via the “overall survival” endpoint as an independent endpoint. The morbidity component "disease progression" was 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.

Time to disease progression accompanied by symptoms

In addition, the pharmaceutical company submits the endpoint time to disease progression accompanied by symptoms in the dossier. The endpoint was defined post hoc as the time from randomisation to the occurrence of death or disease progression occurring relatively closely to at least one symptom, defined by the pharmaceutical company as patient-relevant. The symptoms selected by the pharmaceutical company included both specific adverse events (AEs) and severe AEs (CTCAE grade ≥ 3) as well as deterioration of symptomatology by ≥ 10 points assessed via individual items of the EORTC QLQ-C30 and QLQ-MY20 questionnaires. Disease progression was recorded using the IMWG criteria as described above. A period of 30 days before and after the occurrence of the progression event was defined as the time relatively close to a disease progression.

Basically, disease progression associated with symptomatology is assessed as patient-relevant. However, the operationalisation of the endpoint presented by the pharmaceutical company is considered inappropriate to adequately record symptomatic disease progression. On the one hand, the pharmaceutical company did not sufficiently justify the methodology for selecting the symptoms defined as patient-relevant and there were also no pre-specified criteria for the selection. On the other, relatively close occurrence is not sufficient proof for a connection between disease progression and symptom onset, especially since disease progression and symptom onset could occur within a relatively large period of 60 days in the present case.

As part of the written statement, the pharmaceutical company refers to the information stored in the Statistical Analysis Report (SAR). However, these as well as the further explanations of the pharmaceutical company as part of the written statement procedure are

inappropriate to remedy the above-mentioned points of criticism regarding the underlying operationalisation and the insufficient justification for the selection of the symptoms.

Due to the described aspects, the endpoint of time to disease progression accompanied by symptoms is not used for the benefit assessment.

Symptomatology

Disease symptomatology was assessed in the APOLLO study using the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20. In the dossier, the pharmaceutical company submits evaluations for the time to first improvement and for the time to first deterioration by ≥ 10 points as well as by ≥ 15% of the scale range.

The improvement of disease-specific symptomatology may represent a separate therapeutic goal in the present indication. However, taking into account the analyses presented, it can be stated that in the overall assessment of the baseline at the start of study and the available responder analyses, the percentage of patients with deterioration exceeds the percentage of subjects with an improvement in symptomatology to a relevant extent. Against this background and taking into account the expected progressive course of the disease, the evaluations on deterioration are used for the present benefit assessment.

With its written statement, the pharmaceutical company also submits evaluations for the time to (confirmed) permanent deterioration by ≥ 10 points as well as by ≥ 15% of the scale range for the sub-population of patients with disease progression on the last therapy. In the benefit assessment of the active ingredient isatuximab in the indication for multiple myeloma, it was determined that a higher relevance is attributed to prolonged deterioration due to its permanent nature for patients than the time to first deterioration (benefit assessment of 16 August 2021 and resolution of the G-BA of 4 November 2021). The benefit assessment procedure for daratumumab started on 1 August 2021. Due to the simultaneous publication of the benefit assessment and the resolution on the active ingredient isatuximab, the pharmaceutical company was not able to take into account the higher relevance of the evaluation in the present therapeutic indication of the time to (confirmed) permanent deterioration in the dossier. Therefore, in view of the present special case constellation, the evaluations submitted subsequently during the written statement procedure on the time to (confirmed) permanent deterioration are included for the present benefit assessment.

The time to (confirmed) permanent deterioration is defined as a deterioration by the respective response criterion compared to the start of study, at which the response criterion is considered to be fulfilled in all subsequent observations until the end of the observation. For the benefit assessment, the time to confirmed permanent deterioration, in which patients who have reported one-off deterioration at the last survey time point are evaluated as non-responders, represents the appropriate operationalisation.

Even though both the operationalisation at the time to first deterioration and at the time to confirmed permanent deterioration are considered relevant for patients, the latter is taken as a basis for the present benefit assessment due to the higher relevance for patients described above. Thus, the evaluation at time to confirmed permanent deterioration is used with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 and the additional module QLQ-MY20.

There is a statistically significant difference in favour of D-Pd for the symptom scale of fatigue.

Health status (EQ-5D VAS)

Health status was assessed in the APOLLO study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company submits responder analyses for the time to first deterioration including response criteria ≥ 7 points, ≥ 10 points and 15% of the scale range (0-100).

With its written statement, the pharmaceutical company also submits evaluations for the time to (confirmed) permanent deterioration for the sub-population of patients with disease progression on the last therapy. Reference is made to the above explanations on symptomatology.

When looking at the time to confirmed permanent deterioration, there is no statistically significant difference between the treatment arms for any of the response criteria.

Quality of life

In the APOLLO study, health-related quality of life was assessed using the functional scales and the global health status scale of the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20. In the dossier, the pharmaceutical company submits evaluations for the time to first improvement and for the time to first deterioration by ≥ 10 points as well as by ≥ 15% of the scale range.

Taking into account the explanations on symptomatology, the evaluations for the time to confirmed permanent deterioration in quality of life with the previously accepted response threshold of 10 points are used for the present benefit assessment.

There are statistically significant differences in favour of D-Pd for the emotional functioning scale of the EORTC QLQ-C30 and the future prospects scale of the EORTC QLQ-MY20.

In subgroup analyses, there is proof of an effect modification for the age characteristic for the social functioning scale of the QLQ-C30. For patients aged ≥ 65 years, there is a statistically significant difference in favour of D-Pd. For patients aged < 65 years, there were no statistically significant effects between the treatment arms. In addition, there is proof of an effect modification for the body image scale of the QLQ-MY20 for the gender characteristic. For female patients, there is a statistically significant difference in favour of D-Pd, whereas for male patients there is no statistically significant difference. As these effect modifications do

not show up in further endpoints, the significance of the available subgroup results for the assessment of the overall additional benefit is considered insufficient.

Side effects

Adverse events (AEs) in total

Almost all study participants experienced AEs. The results were only presented additionally.

Serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs (≥ 1 active ingredient component)

For the endpoints of serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs (≥ 1 active ingredient component), there is no statistically significant difference between the treatment arms.

Specific AEs (CTCAE grade ≥ 3)

For the specific preferred terms (PT) of lymphopenia and febrile neutropenia, there is a statistically significant difference to the disadvantage of D-Pd.

Conclusion on the side effects

In the overall assessment of the results on side effects, there are no relevant differences for the benefit assessment between the treatment arms. In detail, the specific AEs of lymphopenia and febrile neutropenia show disadvantages for D-Pd.

Overall assessment

For the assessment of the additional benefit of daratumumab in combination with pomalidomide and dexamethasone (D-Pd), results from the open-label, randomised, phase III APOLLO study are available for the endpoint categories of mortality, morbidity, quality of life, and side effects. In the APOLLO study, D-Pd is compared to pomalidomide + dexamethasone (Pd). Pd is only approved for subjects with disease progression on the last therapy. Therefore, the assessment-relevant sub-population of the APOLLO study refers to adults who have received at least two prior therapies containing lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on the last therapy.

For overall survival, there is no statistically significant difference between the study arms.

For the patient-reported endpoints, the evaluation for the time to deterioration is considered, taking into account the baseline at the start of study, the available responder analyses and the expected disease progression. Since prolonged deterioration is considered to be more relevant for patients than first-time deterioration due to its permanent nature, the present assessment is based on the analyses of the time to confirmed permanent deterioration.

In the endpoint category of morbidity, the symptom scale of fatigue of the EORTC-QLQ-C30 shows an advantage for D-Pd over Pd. There were no statistically significant differences in health status as recorded by the EQ-5D VAS.

With regard to health-related quality of life, there is an advantage of D-Pd over Pd for the scales of emotional functioning and future prospects.

For the endpoint category of side effects, there are no relevant differences for the benefit assessment between the treatment arms. In detail, the specific AEs of lymphopenia and febrile neutropenia show disadvantages for D-Pd.

Overall, D-Pd thus shows advantages in individual scales of the questionnaires on patient-reported morbidity and health-related quality of life. In the overall assessment, the G-BA concludes that daratumumab in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma in adults who have received at least two prior therapies containing lenalidomide and a proteasome inhibitor, and who demonstrated disease progression on the last therapy, has a minor additional benefit compared with pomalidomide in combination with dexamethasone.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing, open-label, randomised phase III APOLLO study.

The risk of bias at the study level is rated as low.

Since the benefit assessment is based on the results of only one study, only indications of an additional benefit can be derived with regard to the reliability of data of the results.

At the endpoint level, the risk of bias for the endpoint of overall survival is rated as low. Uncertainties remain because relatively few events occurred in the endpoint of overall survival at the time of the data cut-off available for the benefit assessment.

Due to the open-label study design and the resulting lack of blinding in the subjective endpoint assessment, the endpoints of morbidity and health-related quality of life are classified as highly biased. In addition, there are decreasing and highly differential return rates for the patient-reported endpoints of morbidity and health-related quality of life.

As a result of the lack of blinding in the subjective endpoint assessment, the endpoint of therapy discontinuation due to adverse events (≥ 1 active ingredient component) is also classified as highly biased.

In summary, due to the uncertainty described at the endpoint level with regard to the reliability of data (probability of additional benefit), a hint for an additional benefit identified is derived.

b2) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression after the last therapy

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

An additional benefit is not proven.

Justification:
For the benefit assessment of patient population b2), the pharmaceutical company uses the results of the randomised, open-label, phase III APOLLO study in the dossier. The study compared daratumumab + pomalidomide + dexamethasone (D-Pd) versus pomalidomide + dexamethasone (Pd).

For the description of the APOLLO study, please refer to the explanations on patient population b1). A relapsed multiple myeloma (disease progression after the last therapy) was defined as the occurrence of disease progression after a prior therapy that requires renewed therapy, without meeting the definition of refractory multiple myeloma.

The marketing authorisation of Pd refers exclusively to adults with disease progression on the last therapy. Therefore, Pd was not determined as an appropriate comparator therapy for adults with disease progression after the last therapy.

As the pharmaceutical company does not present suitable data for the assessment of the additional benefit of patient population b2) compared to the appropriate comparator therapy, an additional benefit for D-Pd is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient daratumumab. Daratumumab was approved as an orphan drug.

The therapeutic indication assessed here is as follows: […] for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy.

In the therapeutic indication to be considered, three patient groups were distinguished:

a) Adults with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory

The appropriate comparator therapy is:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

For this patient population, the pharmaceutical company does not submit suitable data compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

b1) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

The appropriate comparator therapy is:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- pomalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomide and dexamethasone

or

- elotuzumab in combination with pomalidomide and dexamethasone

or

- carfilzomib in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomide and dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

For these patient groups, data are available from the phase III APOLLO study comparing daratumumab + pomalidomide + dexamethasone (D-Pd) with pomalidomide + dexamethasone (Pd). The assessment-relevant sub-population of the APOLLO study refers to adults who have received at least two prior therapies containing lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on the last therapy.

There is no statistically significant difference for the overall survival.

For the time to confirmed permanent deterioration, there is an advantage for D-Pd in the symptom scale of fatigue in the endpoint category of morbidity. With regard to health-related

quality of life, there is an advantage for D-Pd for the scales emotional functioning and future prospects.

For the endpoint category of side effects, there are no relevant differences for the benefit assessment. In detail, the specific AEs of lymphopenia and febrile neutropenia show disadvantages for D-Pd.

Overall, the G-BA found a hint for a minor additional benefit for D-Pd compared to Pd.

b2) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression after the last therapy

The appropriate comparator therapy is:

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with lenalidomide and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomide and dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

For this patient population, the pharmaceutical company does not submit suitable data compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

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

a) Adults with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory

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

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

However, the pharmaceutical company's approach to determining the patient numbers is not fully comprehensible methodologically and is viewed critically. The pharmaceutical company determines the patient numbers by starting from a patient population (population A: adults who have received at least 1 prior therapy containing lenalidomide) another population (population B: adults who have received at least 2 prior therapies containing lenalidomide and a proteasome inhibitor, and who have demonstrated disease progression on the last therapy). Uncertainties arise in particular because the population B used by the pharmaceutical company does not represent all adults who have received at least two prior therapies. Thus, the prior therapy of the population B used must have contained both lenalidomide and a proteasome inhibitor. This means that the calculated difference to population A may also include adults who received one prior therapy with lenalidomide but without a proteasome inhibitor and more than one prior therapy with lenalidomide but without a proteasome inhibitor. In addition, both population A and population B are not restricted to patients who are lenalidomide-refractory. Overall, the identified patient population is therefore considered to be overestimated.

However, at the same time, population A is based on the patient numbers, which were determined in the benefit assessment procedure of pomalidomide + bortezomib + dexamethasone (resolution of 05.12.2019) and were assessed as being associated with uncertainties and potentially underestimated. It is unclear to what extent the counteracting effects offset the level of patient numbers.

The patient numbers determined in the present procedure are therefore subject to relevant uncertainties.

b1) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

and

b2) Adult patients with multiple myeloma who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression after the last therapy

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

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

The patient numbers presented are based on the patient numbers determined in the benefit assessment procedure for elotuzumab + pomalidomide + dexamethasone (resolution of 02.04.2020). These were considered to be plausible in terms of magnitude. The transferability to the present patient population is fraught with uncertainties as the criterion of disease progression after the last therapy is not represented in the underlying patient population from the elotuzumab procedure. However, it is uncertain whether it is mathematically possible to

demarcate the number of patients with disease progression on the last therapy and disease progression after the last therapy.

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: 29 November 2021):

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

Treatment with daratumumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in treating 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: 15 January 2022).

The costs for the first year of treatment are shown for the cost representation in the resolution.

Treatment period:

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

For bortezomib in combination with pegylated liposomal doxorubicin, a treatment duration of 8 cycles is assumed, even if the actual treatment duration may differ from patient to patient.

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 Pomalidomide and Dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: every 14 days From week 25: every 28 days	1st year: 23 Subsequent year: 13	1	1st year: 23
Pomalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	1st year: 0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	1st year: 29[2]
Appropriate comparator therapy				
Patient population a)				
Bortezomib in combination with pegylated liposomal Doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Doxorubicin (pegylated, liposomal)	Day 4 21-day cycle	8 cycles	1	8
Bortezomib in combination with Dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	4 - 8 cycles	4	16 - 32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21-day cycle	4 - 8 cycles	8	32 - 64

[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
Carfilzomib in combination with Dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13 cycles	6	78
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-day cycle	13 cycles	8	104
Daratumumab in combination with Bortezomib and Dexamethasone				
Daratumumab	Week 1 - 9: 1 x every 7 days Week 10 - 24: every 21 days From week 25: every 28 days	1st year: 21 Subsequent year: 13	1	1st year: 21
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8 cycles	6 (cycle 1 - 3) 7 (cycle 4 - 8)	1st year: 53[2]
Patient populations b1) and b2)				
Carfilzomib in combination with Lenalidomide and Dexamethasone				
Carfilzomib	1st -12th cycle Day 1, 2, 8, 9, 15, 16 From 13th cycle Day 1, 2, 15, 16 28-day cycle	13 cycles	1st -12th cycle 6	1st year 76
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52
Carfilzomib in combination with Dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13 cycles	6	78

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-day cycle	13 cycles	8	104
Bortezomib in combination with Dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	4 - 8 cycles	4	16 - 32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21-day cycle	4 - 8 cycles	8	32 - 64
Bortezomib in combination with pegylated liposomal Doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Doxorubicin (pegylated, liposomal)	Day 4 21-day cycle	8 cycles	1	8
Lenalidomide in combination with Dexamethasone				
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	1st - 4th cycle Day 1- 4, 9 - 12, 17 - 20 From 5th cycle Day 1 - 4 28-day cycle	13 cycles	1st - 4th cycle 12	1st year 84
Elotuzumab in combination with Lenalidomide and Dexamethasone				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1, 15 28-day cycle	13 cycles	1st - 2nd cycle 4 From 3rd cycle 2	1st year 30
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Elotuzumab in combination with Pomalidomide and Dexamethasone (only for patient population b1)				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1 28-day cycle	13 cycles	1st - 2nd cycle 4 From 3rd cycle 1	1st year 19
Pomalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52
Pomalidomide in combination with Dexamethasone (only for patient population b1)				
Pomalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52
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	1st year: 23 Subsequent year: 13	1	1st year: 23
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	1st year: 0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	1st year: 29[2]

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Daratumumab in combination with Bortezomib and Dexamethasone				
Daratumumab	Week 1 - 9: 1 x every 7 days Week 10 - 24: every 21 days From week 25: every 28 days	<u>1st year:</u> 21 <u>Subsequent year:</u> 13	1	<u>1st year:</u> 21
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8 cycles	6 (cycle 1 - 3) 7 (cycle 4 - 8)	<u>1st year:</u> 53[2]

<u>Consumption:</u>

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[3].

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Daratumumab in combination with Pomalidomide and Dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1,800 mg	<u>1st year:</u> 23	<u>1st year:</u> 23 x 1,800 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	<u>1st year:</u> 29	<u>1st year</u> 29 x 40 mg

[3] Federal Health Reporting. Average body measurements of the population (2017, both genders), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Appropriate comparator therapy					
Patient population a)					
Bortezomib in combination with pegylated liposomal Doxorubicin					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32	32 x 2.5 mg +
Doxorubicin (pegylated, liposomal)	30 mg/m²	57 mg	1 x 50 mg 1 x 20 mg	8	8 x 50 mg + 8 x 20 mg
Bortezomib in combination with Dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	16 - 32	16 - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32 - 64	32 - 64 x 20 mg
Carfilzomib in combination with Dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 56 mg/m²	1st cycle day 1, 2 38 mg Thereafter 106.4 mg	1st cycle Day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78	1st year 154 x 10 mg + 78 x 30 mg + 76 x 60 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	104	104 x 20 mg
Daratumumab in combination with Bortezomib and Dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 21	1st year: 21 x 1,800 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32	32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	53	53 x 20 mg
Patient populations b1) and b2)					
Carfilzomib in combination with Lenalidomide and Dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 27 mg/m²	1st cycle day 1, 2 38 mg Thereafter 51.3 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 1 x 60 mg	1st year 76	1st year 2 x 10 mg + 2 x 30 mg + 74 x 60 mg
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	Annual average consumption by potency
Carfilzomib in combination with Dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 56 mg/m²	1st cycle day 1, 2 38 mg Thereafter 106.4 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78	1st year 154 x 10 mg + 78 x 30 mg + 76 x 60 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	104	104 x 20 mg
Bortezomib in combination with pegylated liposomal Doxorubicin					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32	32 x 2.5 mg +
Doxorubicin (pegylated, liposomal)	30 mg/m²	57 mg	1 x 50 mg 1 x 20 mg	8	8 x 50 mg + 8 x 20 mg
Bortezomib in combination with Dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	16 - 32	16 - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32 - 64	32 – 64 x 20 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	1st year: 84	1st year 84 x 40 mg
Elotuzumab in combination with Lenalidomide and Dexamethasone					
Elotuzumab	10 mg/kg	770 mg	2 x 400 mg	1st year 30	1st year 60 x 400 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8, 22 40 mg	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8.22 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52	1st year 30 x 8 mg + 30 x 20 mg + 22 x 40 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
Elotuzumab in combination with Pomalidomide and Dexamethasone (only for patient population b1)					
Elotuzumab	1st -2nd cycle 10 mg/kg From 3rd cycle 20 mg/kg = 1,540 mg	1st -2nd cycle 770 mg From 3rd cycle 1,540 mg	1st -2nd cycle 2 x 400 mg From 3rd cycle 4 x 400 mg	1st year 8 11	1st year 16 x 400 mg + 44 x 400 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273	273 x 4 mg
Dexamethasone	28 mg - 40 mg	28 mg 40 mg	1 x 20 mg + 1 x 8 mg 1 x 40 mg	19 33	19 x 20 mg + 19 x 8 mg + 33 x 40 mg
Pomalidomide in combination with Dexamethasone (only for patient population b1)					
Pomalidomide	4 mg	4 mg	1 x 4 mg	273	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52	52 x 40 mg
Daratumumab in combination with Lenalidomide and Dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 23	1st year: 23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 29	1st year 29 x 40 mg
Daratumumab in combination with Bortezomib and Dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 21	1st year: 21 x 1,800 mg
Bortezomib	1.3 mg/m^2	2.47 mg	1 x 2.5 mg	32	32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	53	53 x 20 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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Daratumumab 1,800 mg	1 SFI	€ 5,809.83	€ 1.77	€ 0.00	€ 5,808.06
Pomalidomide 4 mg	21 HC	€ 9,061.45	€ 1.77	€ 516.91	€ 8,542.77
Dexamethasone 40 mg[4]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 1,039.63	€ 1.77	€ 48.80	€ 989.06
Carfilzomib 10 mg	1 PSI	€ 222.32	€ 1.77	€ 11.68	€ 208.87
Carfilzomib 30 mg	1 PSI	€ 644.36	€ 1.77	€ 35.05	€ 607.54
Carfilzomib 60 mg	1 PSI	€ 1,277.44	€ 1.77	€ 70.10	€ 1,205.57
Daratumumab 1,800 mg	1 SFI	€ 5,809.83	€ 1.77	€ 0.00	€ 5,808.06
Dexamethasone 8 mg[3]	100 TAB	€ 123.37	€ 1.77	€ 8.88	€ 112.72
Dexamethasone 20 mg[3]	10 TAB	€ 32.38	€ 1.77	€ 0.00	€ 30.61
Dexamethasone 20 mg[3]	20 TAB	€ 54.05	€ 1.77	€ 0.00	€ 52.28
Dexamethasone 20 mg[3]	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08
Dexamethasone 40 mg[3]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 776.63	€ 1.77	€ 96.86	€ 678.00
Pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,912.60	€ 1.77	€ 242.14	€ 1,668.69
Elotuzumab 400 mg	1 PIC	€ 1,557.88	€ 1.77	€ 85.68	€ 1,470.43
Lenalidomide 25 mg	21 HC	€ 8,331.13	€ 1.77	€ 475.20	€ 7,854.16
Pomalidomide 4 mg	21 HC	€ 9,061.45	€ 1.77	€ 516.91	€ 8,542.77
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate; 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 differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

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

[4] Fixed reimbursement rate

expenditure in the course of the treatment are not shown.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[5]	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed: ***Daratumumab*** *in combination with Pomalidomide and Dexamethasone*					
Premedication[6]					
Dexamethasone 40 mg, oral	€ 188.00[3] 50 x 40 mg	€ 186.23 [€ 1.77; € 0.00]	€ 3.72	1st year 23	1st year € 85.67
Paracetamol[7] 500 - 1,000 mg, oral	€ 1.50 20 x 500 mg € 1.06 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 23	1st year € 1.56 - € 2.23
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 23	1st year € 139.75
Appropriate comparator therapy					
Patient population a)					
Daratumumab *in combination with Bortezomib and Dexamethasone*					
Premedication[6]					
Dexamethasone 20 mg, oral	€ 118.85[3] 50 x 20 mg	€ 117.08 [€ 1.77; € 0.00]	€ 2.34	1st year 21	1st year € 49.17
Paracetamol[6] 500 – 1,000 mg, oral	€ 1.50 20 x 500 mg € 1.06 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 21	1st year € 1.43 - € 2.04
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 21	1st year € 127.60

5 Proportionate share of cost per pack for consumption per treatment day. Rounded interim result.

6 According to the product information for Darzalex (last revised: July 2021)

7 Fixed reimbursement rate. Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Section 12, paragraph 7, of the AM-RL (information as concomitant medication in the product information of the prescription medicinal product) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003:

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[8]	Treatment days/ year	Costs/ patient/ year
Patient populations b1) and b2)					
***Elotuzumab** in combination with Lenalidomide and Dexamethasone*					
***Premedication**[9]*					
Dexamethasone 8 mg, IV	€ 20.35[3] 10 x 8 mg	€ 17.86 [€ 1.77; € 0.72]	€ 1.78	1st year 30	1st year € 53.58
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 30	1st year € 182.28
Famotidine 20 mg, oral	€ 20.15[3] 100 x 20 mg	€ 17.66 [€ 1.77; € 0.72]	€ 0.18	1st year 30	1st year € 5.30
Paracetamol[6] 500 – 1,000 mg, oral	€ 1.50 20 x 500 mg € 1.06 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 30	1st year € 2.04 - € 2.91 -
***Elotuzumab** in combination with Pomalidomide and Dexamethasone (only for patient population b1)*					
***Premedication**[9]*					
Dexamethasone 8 mg, IV	€ 20.35[3] 10 x 8 mg	€ 17.86 [€ 1.77; € 0.72]	€ 1.78	1st year 19	1st year € 33.93
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 19	1st year € 115.44
Famotidine 20 mg, oral	€ 20.15[3] 100 x 20 mg	€ 17.66 [€ 1.77; € 0.72]	€ 0.18	1st year 19	1st year € 3.36
Paracetamol[6] 500 – 1,000 mg, oral	€ 1.50 20 x 500 mg € 1.06 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 19	1st year € 1.29 - € 1.84 -

[8] Proportionate share of cost per pack for consumption per treatment day. Rounded interim result.
[9] According to the product information for Empliciti (last revised: December 2020)

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[10]	Treatment days/ year	Costs/ patient/ year
Daratumumab *in combination with Lenalidomide and Dexamethasone*					
Premedication[6]					
Dexamethasone 40 mg, oral	€ 188.00[3] 50 x 40 mg	€ 186.23 [€ 1.77; € 0.00]	€ 3.72	1st year 23	1st year € 85.67
Paracetamol[6] 500 – 1,000 mg, oral	€ 1.50 20 x 500 mg € 1.06 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 23	1st year € 1.56 - € 2.23
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 23	1st year € 139.75
Daratumumab *in combination with Bortezomib and Dexamethasone*					
Premedication[6]					
Dexamethasone 20 mg, oral	€ 118.85[3] 50 x 20 mg	€ 117.08 [€ 1.77; € 0.00]	€ 2.34	1st year 21	1st year € 49.17
Paracetamol[6] 500 – 1,000 mg, oral	€ 1.50[7] 20 x 500 mg € 1.06[7] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 21	1st year € 1.43 - € 2.04
Dimetindene 1 mg/10 kg BW, IV	€ 18.86 5 x 4 mg	€ 15.19 [€ 1.77; € 1.90]	€ 6.08	1st year 21	1st year € 127.60

Patients receiving therapy with carfilzomib, 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[11]. 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.

[10] Proportionate share of cost per pack for consumption per treatment day. Rounded interim result.

[11] 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

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 - patient population a), b1) and b2)				
Carfilzomib 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 the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 22 September 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 6 July 2021.

On 20 July 2021, the pharmaceutical company submitted a dossier for the benefit assessment of daratumumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 27 July 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient daratumumab.

Another review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 August 2021.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2021. The deadline for submitting written statements was 22 November 2021.

The oral hearing was held on 06 December 2021.

By letter dated 21 December 2021, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 21 January 2022.

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 25 January 2022, and the proposed resolution was approved.

At its session on 3 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	22 September 2020	Implementation of the appropriate comparator therapy
Subcommittee Medicinal product	6 July 2021 10 August 2021	New implementation of the appropriate comparator therapy
Working group Section 35a	1 December 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	6 December 2021	Conduct of the oral hearing
Working group Section 35a	15 December 2021 5 January 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	25 January 2022	Concluding discussion of the draft resolution
Plenum	3 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 February 2022

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

Prof. Hecken