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 after the deadline (multiple myeloma, after at least 1 prior therapy, combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone))

of 15 September 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.

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient daratumumab (Darzalex) on 15 August 2017. For the resolution of 15 February 2018 passed by the G-BA in this procedure, a limitation was announced for patient population a (adult patients with multiple myeloma who have received at least one prior therapy) until 1 October 2021. At the pharmaceutical company's request, this limitation was extended until 1 April 2022 by the resolution of the G-BA of 17 June 2021.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Darzalex recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 31 March 2022.

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

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

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

2.1.1 Approved therapeutic indication of Daratumumab (Darzalex) according to product information

Darzalex is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Therapeutic indication of the resolution (resolution of 15.09.2022):

see the approved therapeutic indication

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with multiple myeloma who have received at least one prior therapy

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

− 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

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 patient-relevant benefit has already been determined by the (G-BA 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. Besides daratumumab, medicinal products with the following active ingredients are approved for the present therapeutic indication:

Belantamab mafodotin, bortezomib, carfilzomib, carmustine, cyclophosphamide, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, idecabtagen vicleucel, ciltacabtagene autoleucel[2], interferon alfa-2b, isatuximab, ixazomib, lenalidomide, melphalan, melphalan flufenamide[2], panobinostat, pomalidomide, prednisolone, prednisone, selinexor[2] 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 in the present 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
- Carfilzomib – resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolutions of 15 February 2018 and 3 February 2022
- Belantamab mafodotin – resolution of 4 March 2021
- Isatuximab – resolution of 4 November 2021
- Ixazomib – resolution of 21 April 2022
- Idecabtagen vicleucel – resolution of 16 June 2022

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

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.

a) <u>Adults with multiple myeloma who have received at least one prior therapy</u>

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.

Due to different toxicity profiles relevant to therapy, the dual combinations of bortezomib and lenalidomide will continue to be given appropriate importance, i.e., even after introducing 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 carfilzomib, the resolution of 15 February 2018 found a hint for a considerable additional benefit in the G-BA's benefit assessments both in combination with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone and for the

[2] Currently not sold in Germany.

dual combination with dexamethasone versus bortezomib plus dexamethasone. 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.

By resolution of 1 December 2016, a hint for a minor additional benefit was identified for elotuzumab in combination with lenalidomide and dexamethasone compared with lenalidomide in combination with dexamethasone for patients after at least one prior therapy.

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

By resolution of 4 November 2021, it was determined that an additional benefit of the combination therapy isatuximab + carfilzomib + dexamethasone, compared to the combination therapy carfilzomib + dexamethasone was 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.

By resolution of 21 April 2022, the G-BA identified in the benefit assessment a hint for a non-quantifiable additional benefit of ixazomib in combination with lenalidomide and dexamethasone versus lenalidomide in combination with dexamethasone for patients after at least one prior therapy. The scientific data basis did not allow for quantification. This combination therapy is currently not considered as an appropriate comparator therapy.

The combination therapy of daratumumab in combination with pomalidomide and dexamethasone was approved in June 2021 for adults after one prior therapy as well as after at least two prior therapies and with disease progression during or after the last therapy. By resolution of 3 February 2022, the G-BA did not identify any additional benefit for patients after prior therapy compared to the appropriate comparator therapy. This combination therapy is currently not considered 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, as well as the monotherapies with daratumumab, belantamab mafodotin, selinexor, idecabtagen vicleucel and ciltacabtagene autoleucel[2] are, according to authorisation status and available evidence, only indicated after at least two and more prior therapies, which is marked by a relevant difference regarding the treatment setting compared to subjects who have received at least one prior therapy. The above treatment options are therefore not considered as appropriate comparator therapy.

By resolution of 15 February 2018, the G-BA declared an indication of considerable additional benefit in the benefit assessment for the combination therapies daratumumab with bortezomib and dexamethasone and with lenalidomide and dexamethasone, respectively, compared to bortezomib and lenalidomide each in

combination with dexamethasone. The period of validity of the resolution was limited until 1 April 2022, and the corresponding benefit reassessment after the deadline is the subject of the present assessment.

In accordance with recommendations from guidelines and taking into account the respective authorisation status, the combinations of bortezomib with pegylated liposomal doxorubicin or bortezomib with dexamethasone or lenalidomide with dexamethasone or elotuzumab with lenalidomide and dexamethasone or carfilzomib with lenalidomide and dexamethasone or carfilzomib with dexamethasone are suitable treatment options for patients with multiple myeloma who have received at least one prior therapy.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with multiple myeloma who have received at least one prior therapy

Proof of a considerable additional benefit

Justification:

By resolution of 15 February 2018, the G-BA has already conducted a benefit assessment for daratumumab in combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone. The corresponding resolution on the benefit assessment was limited by the G-BA with regard to patient population a). The present benefit assessment procedure is a new benefit assessment after the expiry of this limitation.

The pharmaceutical company submitted the results of the CASTOR and POLLUX studies for the evidence of an additional benefit of daratumumab in combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone. IQWiG's dossier assessment also identified the LEPUS study as a further study relevant to the present benefit assessment.

CASTOR study

The randomised, open-label, controlled phase III CASTOR study compared treatment with daratumumab in combination with bortezomib and dexamethasone (DVd) versus combination therapy of bortezomib and dexamethasone (Vd). The study enrolled patients who had received at least one prior therapy and had documented disease progression after the last therapy.

The patients enrolled in the study were on average 64 years old. Of the patients enrolled, 55% and 59% were male and approximately 61% were pretreated with an autologous stem cell

transplant. The majority of patients (76% and 79% respectively) had ISS stage I or II multiple myeloma. About half of the patients were pretreated with two or more therapies.

A total of 498 patients were randomised in a 1:1 ratio into the two treatment arms of the study (N = 251 DVd; N = 247 Vd). Randomisation was stratified by ISS stage at screening (I, II or III), number of previous lines of therapy (1 vs 2 or 3 vs > 3) and previous bortezomib treatment (no vs yes). Of these, 480 patients received the study medication (N = 243 DVd, N = 237 Vd).

The study, which is still ongoing, is being conducted at 117 study sites in 16 countries in Europe, the Americas and Asia. Enrolment of the patients was between September 2014 and September 2015.

There are 3 data cut-offs from the CASTOR study. The previous initial assessment by the G-BA was carried out on the basis of the first and second data cut-off (11 January 2016 and 30 June 2016). The final data cut-off of 28.06.2021 which was conducted by default when 320 events were reached in the endpoint of overall survival is relevant for this new benefit assessment.

POLLUX study

The randomised, open-label, controlled phase III POLLUX study compared daratumumab in combination with lenalidomide and dexamethasone (DRd) versus lenalidomide in combination with dexamethasone (Rd). The study enrolled patients who had received at least one prior therapy and had documented disease progression after the last therapy.

The patients enrolled in the study were on average 64 years old. About 60% of the patients were male and about 63% had received an autologous stem cell transplant as prior therapy. The majority of the patients enrolled (approx. 80%) had ISS (International Staging System) stage I or II multiple myeloma. About half of the patients were pretreated with two or more therapies.

A total of 569 patients were randomised in a 1:1 ratio to the two study arms (N = 286 DRd; N= 283 Rd). Randomisation was stratified by ISS stage at screening (I, II or III), number of previous lines of therapy (1 vs 2 or 3 vs > 3) and previous lenalidomide treatment (no vs yes). Of these, 564 patients received the study medication (N = 283 DRd; N = 281 Rd). Treatment was given in 28-day cycles until disease progression or the occurrence of unacceptable toxicity.

The study, which is still ongoing, is being conducted at 136 study sites in 18 countries in Europe, the Americas and Asia. The patients were enrolled between June 2014 and July 2015.

There are 3 data cut-offs from the POLLUX study. The previous initial assessment by the G-BA was carried out on the basis of the first and second data cut-off (7 March 2016 and 30 June 2016). The final data cut-off of 30.09.2021 which was conducted by default when 330 events were reached in the endpoint of overall survival is relevant for this new benefit assessment.

LEPUS study

The randomised, open-label, controlled phase III LEPUS study compared treatment with daratumumab in combination with bortezomib and dexamethasone (DVd) versus combination therapy of bortezomib and dexamethasone (Vd). The study enrolled patients who had received at least one prior therapy and had documented disease progression after the last therapy.

A total of 211 patients were randomised in a 2:1 ratio into the two treatment arms of the study (N = 141 DVd; N = 70 Vd). Randomisation was stratified by ISS stage at screening (I, II or III), number of previous lines of therapy (1 vs 2 or 3 vs > 3) and previous bortezomib treatment (no vs yes).

The study, which has been ongoing since December 2017, is being conducted at 27 study sites exclusively in China and Taiwan.

2 data cut-offs (1st and 2nd interim analysis, respectively, dated 7 October 2019 and 30 July 2021, respectively) are available from the LEPUS study. The final data cut-off is planned after 140 deaths or 3 years after randomisation of the last patient and is not yet available.

On the relevance of the LEPUS study

In the dossier for the benefit assessment, the LEPUS study was not included by the pharmaceutical company on the grounds that final results were not yet available for the study. The results from the 1st data cut-off are not relevant due to the low number of events in the endpoint of overall survival, while the results of the 2nd data cut-offs were available just before the dossier was submitted. Thus, no processed data from the LEPUS study were presented in the dossier.

In contrast, the LEPUS study was considered relevant for the benefit assessment in IQWiG's dossier assessment. According to IQWiG, the LEPUS study fulfilled the inclusion criteria for the present benefit assessment and was to be used as a relevant study in the therapeutic indication. In addition, the study report on the 2nd data cut-off dates back to 11 February 2022, so that, according to IQWiG's assessment, it would have been possible to consider the results available so far in the dossier.

In view of the fact that the study report only contains data on overall survival for the 2nd data cut-off and that data on side effects usable for the 1st data cut-off are also missing, the LEPUS study was not used in IQWiG's benefit assessment to derive the additional benefit; however, available results were presented additionally. In view of the low number of patients in the LEPUS study and the similarity of the results for the endpoint of overall survival to those of the CASTOR and POLLUX studies, it was assumed in IQWiG's benefit assessment that the results from the LEPUS study did not call the overall weighing into question.

Within the framework of the written statement procedure on the present benefit assessment, the pharmaceutical company presented the results of the 2nd data cut-off of the LEPUS study.

In view of the fact that the results on overall survival from the LEPUS study are similar to those of the CASTOR and POLLUX studies and that no conflicting results are apparent, the G-BA follows IQWiG's assessment to the effect that the LEPUS study does not call the overall weighting into question. However, in the present benefit assessment, the LEPUS study is not used due to medical aspects. The medical aspects are reflected in the different baseline characteristics of the Asian study population, particularly with regard to prior therapies, which were also pointed out by the clinical experts within the framework of the written statement procedure on the present benefit assessment. In the LEPUS study, for example, the patients were more heavily pretreated compared to the CASTOR and POLLUX studies. In the LEPUS study, about 72% had received two or more prior therapies compared to about 50% each in the CASTOR and POLLUX studies. Furthermore, fewer patients in the LEPUS study had received an autologous stem cell transplant as prior therapy (about 20% vs 61 and 63%, respectively). In addition, far more patients in the LEPUS study were treated with thalidomide in the prior therapy (about 80% vs about 50% and 44%, respectively). In this regard, according to the assessments of the clinical experts presented within the framework of the written statement procedure for the present benefit assessment, a high relevance of an early and high-dose use of thalidomide for the ongoing prognosis can be assumed.

In summary, the LEPUS study is not used due to the medical aspects mentioned, and the present benefit assessment focuses on the CASTOR and POLLUX studies.

On the meta-analytic summary of the CASTOR and POLLUX studies

The studies were very similar in terms of design, with the exception of the respective concomitant or control therapy, and the reported effects were clearly homogeneous for almost all endpoints considered. Accordingly, there were no effects of the respective concomitant active ingredients bortezomib and dexamethasone or lenalidomide and dexamethasone. Therefore, IQWiG prepared a meta-analytic summary of the results of the POLLUX and CASTOR studies by using a model with fixed effects. As in the previous initial assessment of the G-BA, this meta-analytic summary of the results of the two studies is used for the present assessment, as far as possible.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the CASTOR and POLLUX studies in each case as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, the meta-analysis of the CASTOR and POLLUX studies showed a statistically significant difference in favour of daratumumab combination therapy compared to lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone. This prolongation of survival time due to treatment with daratumumab combination therapy is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

PFS was the primary endpoint of the CASTOR and POLLUX studies and was operationalised as the time from randomisation to the first documented evidence of disease progression according to International Myeloma Working Group (IMWG) criteria or death from any cause.

In both studies, prolongation of PFS was statistically significant in the intervention arm compared to the control arm.

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 CASTOR and POLLUX studies using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30.

For this endpoint, the pharmaceutical company submitted time-to-event analyses of the time to first improvement, confirmed permanent improvement, first deterioration and confirmed permanent deterioration by ≥ 10 points each in the dossier for the benefit assessment.

The analyses of time to first deterioration are used for the present benefit assessment.

In the meta-analysis of the CASTOR and POLLUX studies, there was no difference between daratumumab combination therapy and treatment with lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone.

With regard to symptomatology, there are therefore neither positive nor negative effects of daratumumab combination therapy.

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

Health status was assessed in the CASTOR and POLLUX studies using the visual analogue scale (VAS) of the EQ-5D questionnaire.

For this endpoint, the pharmaceutical company submitted time-to-event analyses of the time to first improvement, confirmed permanent improvement, first deterioration and confirmed permanent deterioration by ≥ 15 points each in the dossier for the benefit assessment.

The analyses of time to first deterioration are used for the present benefit assessment.

In the meta-analysis of the CASTOR and POLLUX studies, there was no difference between daratumumab combination therapy and treatment with lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone.

Also with regard to health status, there are therefore neither positive nor negative effects of the daratumumab combination therapy.

Quality of life

Health-related quality of life was assessed in the CASTOR and POLLUX studies using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

For this endpoint, the pharmaceutical company submitted time-to-event analyses of the time to first improvement, confirmed permanent improvement, first deterioration and confirmed permanent deterioration by ≥ 10 points each in the dossier for the benefit assessment.

The analyses of time to first deterioration are used for the present benefit assessment.

In the meta-analysis of the CASTOR and POLLUX studies, there was no difference between daratumumab combination therapy and treatment with lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone.

With regard to health-related quality of life, there are therefore neither positive nor negative effects of daratumumab combination therapy.

Side effects

Adverse events (AEs)

In the CASTOR and POLLUX studies, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAE)

For serious adverse events, the meta-analysis of the CASTOR and POLLUX studies showed no statistically significant difference between the treatment groups.

Severe AE (CTCAE grade ≥ 3)

For serious adverse events with CTCAE grade ≥ 3, there was a statistically significant difference to the disadvantage of daratumumab combination therapy in the meta-analysis of the CASTOR and POLLUX studies.

There was effect modification by the ISS (International Staging System) stage characteristic for severe AEs. Accordingly, there was a statistically significant effect to the disadvantage of daratumumab combination therapy for ISS stage I patients. However, there was no significant difference between the treatment groups for ISS stage II and III patients.

When interpreting this result, the following relevant uncertainties come into play.

On the one hand, the assessments by clinical experts presented in this written statement procedure show that the increased occurrence of severe side effects in patients in the less severe stage of the disease does not correspond to the clinically plausible expectations. According to clinical experts, no other medicinal product study in the present indication with comparable subgroup effects is known.

On the other, it should be taken into account that there was no effect modification by the characteristic ISS stage for any of the other endpoints of the studies and especially not for the endpoint of overall survival. The interpretation of the present effect modification also takes into account that there are no opposing effects in the results of the different ISS stages.

Against the background of the uncertainties described above, the existing data basis on the observed effect modification by the characteristic ISS stage for the endpoint of severe AE (CTCAE grade ≥ 3) are not considered sufficient to derive corresponding separate statements on the additional benefit in the overall assessment with the necessary certainty.

Discontinuation due to AEs
For the endpoint of discontinuation due to AEs, no statistically significant difference was detected between the treatment groups in the meta-analysis of the CASTOR and POLLUX studies.

Specific AEs

For the specific AEs of vomiting (PT, AE), blood and lymphatic system disorders (SOC, severe AE), respiratory, thoracic and mediastinal disorders (SOC, severe AE), diarrhoea (PT, severe AE) and hypertension (PT, severe AE), the meta-analysis of the CASTOR and POLLUX studies showed a statistically significant difference to the disadvantage of daratumumab combination therapy in each case.

For the endpoint of peripheral neuropathy (not recorded elsewhere (NRE); HLT, severe AE), there was no statistically significant difference between the study arms in the CASTOR study. This endpoint is of particular interest as a specific AE of bortezomib only for patients treated with bortezomib.

In summary, a disadvantage of daratumumab combination therapy can be identified in the side effects due to the negative effects in the severe AEs (CTCAE grade ≥ 3) as well as, in detail, in the specific AEs.

Overall assessment

The present assessment is a new benefit assessment after the expiry of the limitation of the G-BA's initial resolution of 15 February 2018 for daratumumab in combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone for the treatment of adults with multiple myeloma who have received at least one prior therapy (patient population a). In comparison to treatment with lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone, results of the CASTOR and POLLUX studies are available from the respective final data cut-offs 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 the treatment with daratumumab combination therapy compared to a treatment with lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone which is assessed as a significant improvement.

There was no statistically significant difference between the treatment groups for symptomatology (assessed by EORTC QLQ-C30) and health status (assessed by EQ-5D VAS).

There was also no statistically significant difference between the treatment groups in health-related quality of life (assessed by EORTC QLQ-C30).

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

In summary, a significant improvement in terms of prolongation of survival time is offset by a disadvantage in terms of serious adverse events (CTCAE grade ≥ 3) and, in detail, in the specific AEs.

In the overall assessment, the G-BA concludes that there is considerable additional benefit for daratumumab in combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy compared to lenalidomide in combination with dexamethasone, or bortezomib in combination with dexamethasone.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is carried out with the meta-analytic evaluation of the CASTOR and POLLUX studies on the basis of two randomised, direct comparator, open-label, long-term phase III studies. The risk of bias at the study level is rated as low.

The risk of bias for the results for the endpoint of overall survival is also classified as low in the studies.

Due to the open-label study design and the resulting lack of blinding in the subjective endpoint assessment, as well as due to clear differences in the questionnaire response between the study arms of the two studies, the risk of bias for the endpoints of health status, symptomatology and health-related quality of life is classified as high.

In the initial assessment of daratumumab in the present therapeutic indication, the reliability of data was classified in the "indication" category primarily due to the low number of events and the associated low significance of the data on overall survival.
In contrast, significant data for the endpoint of overall survival are available for the present new benefit assessment, taking into account the final data cut-offs of the CASTOR and POLLUX studies, which are based on long follow-up durations of approx. 6 years.

Thus, on the basis of the meta-analytic evaluation of the CASTOR and POLLUX studies, the reliability of data for the additional benefit identified is classified in the "proof" category.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient daratumumab due to the expiry of the limitation of the resolution of 15 February 2018. The assessment relates exclusively to the use of daratumumab in combination with lenalidomide and dexamethasone (DRd), or bortezomib and dexamethasone (DVd) in the following patient population:

a) Adults with multiple myeloma who have received at least one prior therapy.

The appropriate comparator therapy was determined to be:

- 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

The pharmaceutical company presents the final results of the randomised, open-label, controlled CASTOR and POLLUX studies comparing DVd and DRd, respectively, with treatment with bortezomib and lenalidomide in combination with dexamethasone (Vd and Rd, respectively). A meta-analytic summary of the two studies is used for the present assessment.

For the endpoint of overall survival, there is a statistically significant effect to the advantage of DRd and DVd, respectively that is assessed as a significant improvement.

There is no statistically significant difference for symptomatology and health status as well as for the health-related quality of life.

For the side effects, there is a disadvantage of DRd and DVd, respectively in the endpoint of severe adverse events (CTCAE grade ≥ 3) and, in detail, in the specific AEs.

In conclusion, the G-BA found a proof of a considerable additional benefit for daratumumab in combination with Rd and Vd, respectively, compared to Vd and Rd, respectively, on the basis of the meta-analytic evaluation of the CASTOR and POLLUX studies.

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

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

The resolution is based on the number of patients from the last resolution on multiple myeloma after at least one prior therapy (ixazomib (21 April 2022)).

The figures were already used as a basis for other resolutions on multiple myeloma after at least one prior therapy (resolutions on carfilzomib dated 15 July 2021, 15 February 2018; initial resolution on daratumumab dated 15 February 2018 and resolution on elotuzumab dated 1 December 2016).

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: 1 June 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: 15 August 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 the maximum treatment duration, if specified in the product information.

For bortezomib in combination with pegylated liposomal doxorubicin, a treatment duration of eight 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 lenalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	1st year: 23	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[3]
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1 - 9: 1 x every 7 days Week 10 - 24: 1 x every 21 days From week 25 1 x every 28 days	1st year 21	1	1st year 21
Bortezomib	Day 1, 4, 8 and 11 21-day cycle	8 cycles	4	32

[3] 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
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8 cycles	6 (cycle 1 - 3) 7 (cycle 4 - 8)	53[3]
Appropriate comparator therapy				
a) Adults with multiple myeloma who have received at least one prior therapy				
Bortezomib in combination with pegylated liposomal doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Doxorubicin (pegylated, lysosomal)	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
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 From 5th cycle 4	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
Carfilzomib in combination with lenalidomide and dexamethasone				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-day cycle	13 cycles	8	104

Consumption:

For dosages depending on body weight or body surface area, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). 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 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					

[4] 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	Average annual consumption by potency
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
Appropriate comparator therapy					
a) Adults with multiple myeloma who have received at least one prior therapy					
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, lysosomal)	30 mg/m²	57 mg	1 x 20 mg 1 x 50 mg	8	8 x 20 mg 8 x 50 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	Average annual consumption by potency
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
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

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	€ 104.84	€ 1.77	€ 4.44	€ 98.63
Bortezomib 2.5 mg	1 PSI	€ 914.11	€ 1.77	€ 42.85	€ 869.49

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
Dexamethasone 40 mg[5]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Dexamethasone 20 mg[5]	10 TAB	€ 32.38	€ 1.77	€ 0.00	€ 30.61
Dexamethasone 20 mg[5]	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08
Appropriate comparator therapy					
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 801.89	€ 1.77	€ 44.90	€ 755.22
Pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,973.82	€ 1.77	€ 112.24	€ 1,859.81
Bortezomib 2.5 mg	1 PSI	€ 914.11	€ 1.77	€ 42.85	€ 869.49
Dexamethasone 8 mg[5]	100 TAB	€ 123.37	€ 1.77	€ 8.87	€ 112.73
Dexamethasone 20 mg[5]	20 TAB	€ 54.05	€ 1.77	€ 0.00	€ 52.28
Dexamethasone 20 mg[5]	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08
Dexamethasone 40 mg[5]	50 TAB	€ 188.00	€ 1.77	€ 0.00	€ 186.23
Lenalidomide 25 mg	21 HC	€ 104.84	€ 1.77	€ 4.44	€ 98.63
Elotuzumab 400 mg	1 PIC	€ 1,557.88	€ 1.77	€ 85.68	€ 1,470.43
Carfilzomib 10 mg	1 PIS	€ 201.30	€ 1.77	€ 10.52	€ 189.01
Carfilzomib 30 mg	1 PIS	€ 581.36	€ 1.77	€ 31.56	€ 548.03
Carfilzomib 60 mg	1 PIS	€ 1,151.46	€ 1.77	€ 63.13	€ 1,086.56
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 PIS = powder for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 August 2022

Costs for additionally required SHI services:

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

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

[5] Fixed reimbursement rate

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[6]	Treatment days per year	Costs/ patient/ year
Medicinal product to be assessed: ***Daratumumab*** *in combination with lenalidomide and dexamethasone*					
Premedication[7]					
Dexamethasone 40 mg, oral	€ 188.00[5] 50 x 40 mg	€ 186.23 [€ 1.77; € 0.00]	€ 3.72	1st year 23	1st year € 85.67
Paracetamol[8] 500 x 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	€ 23.67 5 x 4 mg	€ 16.32 [€ 1.77; € 5.58]	€ 6.53	1st year 23	1st year € 150.14
Medicinal product to be assessed: ***Daratumumab*** *in combination with bortezomib and dexamethasone*					
Premedication[7]					
Dexamethasone 20 mg, oral	€ 118.85[5] 50 x 40 mg	€ 117.08 [€ 1.77; € 0.00]	€ 2.34	1st year 21	1st year € 49.17
Paracetamol[8] 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	€ 23.67 5 x 4 mg	€ 16.32 [€ 1.77; € 5.58]	€ 6.53	1st year 21	1st year € 137.09

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

[7] According to the product information for Darzalex (last revised: January 2022)

[8] 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[9]	Treatment days per year	Costs/ patient/ year
Appropriate comparator therapy					
a) Adults with multiple myeloma who have received at least one prior therapy					
Elotuzumab *in combination with lenalidomide and dexamethasone*					
Premedication[10]					
Dexamethasone 8 mg, IV	€ 20.35[5] 10 x 8 mg	€ 17.86 [€ 1.77; € 0.72]	€ 1.78	1st year 30	1. year € 53.58
Dimetindene 1 mg/10 kg bw, IV	€ 23.67 5 x 4 mg	€ 16.32 [€ 1.77; € 5.58]	€ 6.53	1st year 30	1st year € 195.84
Famotidine 20 mg, oral	€ 20.15[5] 100 x 20 mg	€ 17.66 [€ 1.77; € 0.72]	€ 0.18	1st year 30	1st year € 5.30
Paracetamol[8] 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 -

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.

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

[10] According to the product information for Empliciti (last revised: February 2022)

[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	Cost per unit	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				
a) Adults with multiple myeloma who have received at least one prior therapy				
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 25 July 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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 10 April 2018.

On 31 March 2022, 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 5 VerfO.

By letter dated 1 April 2022 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 29 June 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2022. The deadline for submitting written statements was 22 July 2022.

The oral hearing was held on 8 August 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 6 September 2022, and the proposed resolution was approved.

At its session on 15 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 July 2017	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	10 April 2018	New determination of the appropriate comparator therapy
Working group Section 35a	2 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing
Working group Section 35a	16 August 2022 30 August 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 September 2022	Concluding discussion of the draft resolution
Plenum	15 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 September 2022

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

Prof. Hecken