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: Carfilzomib (New therapeutic indication: Multiple myeloma, at least 1 prior therapy, combination with daratumumab and dexamethasone)

of 15 July 2021

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 benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
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 carfilzomib was listed for the first time on 15 December 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 17 December 2020, carfilzomib 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 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 December 2008, p. 7).

Carfilzomib 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 carfilzomib with the statutory health insurance at pharmacy retail prices, including value-added tax exceeded € 50 million. Proof must therefore be provided for carfilzomib in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 13 January 2021, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company, on the approval of a new area of application, the pharmaceutical company has submitted a dossier 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 carfilzomib with the new therapeutic indication (combination with

daratumumab and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy).

The G-BA came to a resolution on whether an additional benefit of carfilzomib 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, and the statements submitted in the written statement and oral hearing procedure, and the addenda 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 carfilzomib.

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 carfilzomib (Kyprolis) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 15.07.2021):

Carfilzomib in combination with daratumumab and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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

– Bortezomib in combination with pegylated liposomal doxorubicin

or

– Bortezomib in combination with dexamethasone

or

– Lenalidomide in combination with dexamethasone

[1] AGeneral Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. Besides carfilzomib, medicinal products with the following active ingredients are approved for the present therapeutic indication:

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

on 2. A non-medicinal treatment option is not an appropriate comparator therapy for the therapeutic indication in question. For pretreated patients, a first or repeat autologous stem cell transplantation or an allogeneic stem cell transplantation may represent a treatment option in individual cases, but it cannot be considered as an appropriate comparator therapy 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 – resolution of 17 March 2016
- Elotuzumab – resolution of 1 December 2016
- Ixazomib – resolution of 6 July 2017
- Carfilzomib – resolution of 15 February 2018
- Daratumumab – resolution of 15 February 2018
- Pomalidomide – resolution of 5 December 2019
- Elotuzumab – resolution of 2 April 2020
- Belantamab mafodotin: Resolution of 4 March 2021

on 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies.

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.

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

Lenalidomide, bortezomib, and carfilzomib are used in combination with dexamethasone. Bortezomib can also be used in monotherapy or in combination with pegylated liposomal doxorubicin.

In addition, according to the marketing authorisation, carfilzomib as well as elotuzumab, ixazomib, and daratumumab are used together with the combination partners lenalidomide and dexamethasone in the second therapy line. Daratumumab can also be combined with bortezomib and dexamethasone in this therapy situation.

For carfilzomib, a resolution of 15 February 2018 found a hint for a considerable additional benefit both in combination with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone and for the dual combination with dexamethasone versus bortezomib plus dexamethasone.

In the benefit assessment of daratumumab, an indication of a considerable additional benefit was issued in each case for combination therapy with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone and for combination therapy with bortezomib and dexamethasone versus bortezomib plus dexamethasone in a resolution dated 15 February 2018; the resolution is limited to 1 October 2021.

A resolution of 1 December 2016 identified a hint for a minor additional benefit for elotuzumab in combination with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone.

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 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.

Pomalidomide is indicated in combination with bortezomib and dexamethasone in individuals with at least one prior therapy, including lenalidomide. In a resolution dated 5 December 2019, no additional benefit was identified for this combination therapy compared with bortezomib and dexamethasone. Therefore, this combination is not considered as an appropriate comparator therapy.

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 corresponding decision was limited to 1 August 2021, as the final analyses with data on overall survival and other patient-relevant endpoints that can be used for the benefit assessment are still pending. Therefore, this combination is also not considered as an appropriate comparator therapy.

Furthermore, the combination therapy of isatuximab, carfilzomib and dexamethasone is approved for the treatment situation after at least one previous therapy; these combination therapies are currently in the benefit assessment procedure by the G-BA. For this very new therapy option, the clinical significance cannot yet be conclusively assessed, so it is not considered 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 belantamab mafodotin and selinexor are, according to authorisation status and evidence, only indicated after at least two and four prior therapies, respectively, which is a relevant difference with regard to the treatment situation compared to persons who have received at least one prior therapy. The above combinations are not considered as appropriate comparator therapy.

In accordance with recommendations from guidelines and taking into account the respective authorisation status, for patients with multiple myeloma who have received at least one prior therapy, the following 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 or daratumumab with lenalidomide and dexamethasone or daratumumab with bortezomib and dexamethasone are suitable therapy options.

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 carfilzomib in combination with daratumumab and dexamethasone is assessed as follows:

An additional benefit is not proven for carfilzomib in combination with daratumumab and dexamethasone for the treatment of adults with multiple myeloma who have received at least one prior therapy.

Justification:

For the proof of the additional benefit of carfilzomib in combination with daratumumab and dexamethasone, the pharmaceutical company presented the results of the CANDOR study.

CANDOR is a multicenter, open-label, randomised controlled study comparing carfilzomib in combination with daratumumab and dexamethasone to carfilzomib in combination with dexamethasone. The relative treatment effects reflect the addition of daratumumab to therapy with carfilzomib in combination with dexamethasone. The currently ongoing study, which started in June 2017, enrolled adult patients with multiple myeloma that had relapsed or progressed after their last treatment and who had received 1 to 3 previous therapies. Under certain conditions, the inclusion of patients with relapse after previous therapy with carfilzomib or daratumumab was allowed. Similarly, the inclusion of patients with refractarity to prior therapy with lenalidomide or a proteasome inhibitor (excluding carfilzomib) was allowed.

Furthermore, patients should have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 to 2 for inclusion.

The 466 included patients were randomised 2:1 to the intervention arm (carfilzomib + daratumumab + dexamethasone; N = 312) and to the comparator arm (carfilzomib + dexamethasone; N = 154) stratified according to disease stage (International Staging System (ISS)-stage 1 or 2 vs 3), by prior therapy with a proteasome inhibitor (yes vs no), by the number of prior lines of therapy (1 vs ≥ 2), and by prior therapy with an anti-CD38 antibody (yes vs no).

Treatment with the study medication should be given up to a maximum of 2 years, until disease progression or discontinuation for other reasons, e.g. due to adverse events or patient choice.

CANDOR is conducted in 102 study centres in Asia, Australia, Europe and North America.

The 1st and 2nd data cut-off from the 14 July 2019 and 15 June 2020 were submitted for the benefit assessment. The 1st data cut-off corresponds to the analysis planned after approximately 188 PFS events; the 2nd data cut-off corresponds to the analysis of overall survival planned approximately 36 months after the inclusion of the last patient. For the present benefit assessment, the results of the 2nd data cut-off from 15 June 2020 are used.

Further analysis of overall survival is planned approximately 48 months after the inclusion of the last patient. The final data cut-off is planned after approximately 230 deaths or 58 months after the inclusion of the last patient.

Extent and probability of the additional benefit

Mortality

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

For the endpoint overall survival, there is no statistically significant difference between carfilzomib in combination with daratumumab and dexamethasone and carfilzomib in combination with dexamethasone. In the CANDOR study, a small number of events were registered for the endpoint overall survival; final analyses are pending.

The pharmaceutical company submitted a meta-analysis of the CANDOR and CASTOR studies in the benefit assessment dossier for the endpoint overall survival. The CASTOR study compared treatment with daratumumab in combination with bortezomib and dexamethasone to treatment with bortezomib and dexamethasone. In view of the fact that the relevant intervention was not investigated in the CASTOR study, the meta-analysis presented in the dossier is assessed as not relevant to the assessment in IQWiG's dossier evaluation. Following this assessment, the G-BA does not use the corresponding meta-analysis for the present assessment.

The pharmaceutical company submitted a further meta-analysis on the endpoint overall survival of the studies CANDOR and ASPIRE within the written statement procedure on the present benefit assessment. In the ASPIRE study, treatment with carfilzomib in combination with lenalidomide and dexamethasone was compared to treatment with lenalidomide and dexamethasone. With regard to the meta-analysis of the CANDOR and ASPIRE studies, it should be noted that the ASPIRE study has a weighting of approximately 85% in the meta-analysis and thus strongly outweighs the CANDOR study in terms of weighting. In addition, it is clear from the assessments of clinical experts presented in the written statement procedure that the CANDOR and ASPIRE studies examined different study populations. In this regard, according to clinical experts, it is particularly relevant that at the time of the implementation of the ASPIRE study, the patients had received different therapies in the context of the previous first-line therapy than at the time of the implementation of the CANDOR study. Therefore, the meta-analysis presented in the context of the written statement procedure is not used for the present assessment.

No additional benefit is identified for the endpoint overall survival.

Morbidity

Progression-free survival (PFS)

The PFS represents the primary endpoint of the CANDOR study. It is operationalised as time from randomisation to disease progression according to IMWG or death from any cause. PFS is statistically significantly prolonged with carfilzomib in combination with daratumumab and dexamethasone compared to carfilzomib in combination with dexamethasone.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component "disease progression" is assessed according to IMWG criteria and thus not in a symptom-related manner but rather by means of laboratory parametric, imaging, and haematological procedures.

Considering the aspects mentioned above, there are different views within the G-BA regarding the patient relevance of the endpoint PFS.

The available data on morbidity and health-related quality of life are used to interpret the results on PFS. These data are relevant in the present case because disease progression determined by laboratory parametric, imaging, and haematologic methods may affect morbidity and/or quality of life.

The prolonged PFS with carfilzomib in combination with daratumumab and dexamethasone was not associated with a relevant benefit in terms of morbidity or quality of life in the CANDOR study, as there was a positive effect of carfilzomib in combination with daratumumab and dexamethasone in only one scale in each of the two categories.

The observation period of the corresponding endpoints in the CANDOR study comprises the treatment period with the study medication (plus 30 days). However, robust analyses of data before and after the time of progression as determined by laboratory parametric, imaging and haematological methods are required to assess any impact of progression on quality of life and morbidity.

However, the available data do not allow a sufficient assessment of the extent to which the progression determined in the CANDOR study by laboratory parametric, imaging and haematological methods is associated with a change in morbidity and/or quality of life.

The extent to which the present prolonged PFS under carfilzomib in combination with daratumumab and dexamethasone also translates into prolonged survival cannot be conclusively assessed at present.

The results on the progression-free survival endpoint are not therefore used in this assessment.

Symptomatology

Symptomatology will be assessed in the CANDOR study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the disease-specific additional module for multiple myeloma EORTC QLQ-MY20.

For EORTC QLQ-C30 and -MY20, the pharmaceutical company submitted responder analyses for the time to deterioration (defined as an increase in the score by at least 10 points compared to the baseline value) as well as continuous evaluations (analyses of mean differences) in the dossier for the benefit assessment.

IQWIG's dossier assessment uses analysis of mean differences. In addition, the responder analysis were presented in the addendum of the dossier assessment.

Within the written statement procedure framework on the present benefit assessment, the pharmaceutical company submitted additional responder analysis on EORTC QLQ-C30 and EORTC QLQ-MY20 using a response threshold of 15% of the scale range.

In the present assessment, the G-BA uses the responder analyses presented in the dossier for the time until deterioration by at least 10 points to assess the effects on symptomatology.

Based on these analyses, there was no statistically significant difference between the study arms for any of the endpoints. Thus, with regard to symptomatology, neither positive nor negative effects of carfilzomib in combination with daratumumab and dexamethasone are available.

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

The general health status is assessed by means of the EQ-5D visual analogue scale.

For the benefit assessment, the pharmaceutical company submitted a responder analysis for the time to deterioration by ≥ 7 or 10 points of the VAS score compared to baseline and continuous evaluations (analysis of mean differences).

IQWIG's dossier assessment uses analysis of mean differences. In addition, the responder analysis was presented in the addendum of the dossier assessment. The mean difference between the treatment groups was not statistically significant.

Within the written statement procedure on the present benefit assessment framework, additional responder analysis were submitted by the pharmaceutical company using a response threshold of ≥ 15 points.

The study on which the derivation of the minimal important difference (MID) for the responder analysis is based (Pickard et al., 2007) is not considered by IQWiG to be appropriate for demonstrating the validity of the MID. This is justified on the one hand because the work mentioned earlier does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion to derive a valid MID. Furthermore, the anchors ECOG-PS and FACT-G sum score used in the study are also considered by IQWiG to be inappropriate for deriving a MID.
In view of the fact that responder analysis based on a MID for a clinical assessment of effects generally have advantages over an analysis of standardised mean differences, and taking into account that the validation study in question has already been used in previous evaluations,

the G-BA uses the responder analysis for the evaluation of the effects on symptomatology in the present evaluation.

There was no statistically significant difference between the study arms for the response criterion of ≥ 7 points. For response criteria of ≥ 10 and ≥ 15 points, respectively, there is an effect in favour of carfilzomib in combination with daratumumab and dexamethasone. In this respect, for the result on the response criterion of ≥ 10 points, uncertainties have to be taken into account in view of wide interval limits of the 95 % confidence interval of the effect estimator.

Conclusion regarding symptomatology and health status

When interpreting the results on symptomatology and health status, relevant uncertainties must be taken into account, which results from the fact that due to the lack of blinding, the high proportion of persons not included in the analysis, and the strongly decreasing response rates in the course of the study (> 10 %), which differ between the study arms, a high risk of bias of the patient-reported outcomes must be assumed in the CANDOR study. In addition, a positive effect is shown for only one endpoint, whereby uncertainties must also be taken into account for one of the response criteria in view of the broad limits of the confidence interval of the effect estimator. Against this background, no relevant difference was found in the overall results for symptomatology or health status.

Quality of life

Health-related quality of life is assessed in the CANDOR study using the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the disease-specific additional module for multiple myeloma EORTC QLQ-MY20.

For EORTC QLQ-C30 and -MY20, the pharmaceutical company submitted responder analyses for the time to deterioration (defined as a decrease in the score by at least 10 points compared to the baseline value) as well as continuous evaluations (analyses of mean differences) in the dossier for the benefit assessment.

IQWIG's dossier assessment uses analysis of mean differences. In addition, the responder analysis were presented in the addendum of the dossier assessment.

Within the written statement procedure framework on the present benefit assessment, the pharmaceutical company submitted additional responder analysis on EORTC QLQ-C30 and EORTC QLQ-MY20 using a response threshold of 15% of the scale range.

In the present assessment, the G-BA uses the responder analyses presented in the dossier for the time until deterioration by at least 10 points to assess the effects on symptomatology.

On the basis of these analyses, there were no statistically significant differences between the study arms for the endpoints assessed, with only one exception. For the endpoint "social function", there is a statistically significant effect in favour of carfilzomib in combination with daratumumab and dexamethasone.

When interpreting the results, relevant uncertainties have to be taken into account, which results from the fact that due to the lack of blinding, the high proportion of persons not included in the analysis, as well as the strongly decreasing response rates in the course of the study and the different response rates between the study arms (> 10 %) in the CANDOR study, a high risk of bias of the patient-reported outcomes has to be assumed. In addition, only one endpoint showed a positive effect. Against this background, no relevant difference was found in the overall results for health-related quality of life.

Side effects

Adverse events (AEs)

All endpoints in the AE category are collected up to 30 days after the last study medication.

Serious adverse events (SAEs)

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

Severe AE (CTCAE grade ≥ 3)
For serious adverse events with CTCAE grade ≥ 3, there was no statistically significant difference between treatment arms.

Discontinuation due to AE

For the endpoint discontinuation due to AEs, the pharmaceutical company submitted evaluations of the odds ratio, the relative risk (RR) and the absolute risk reduction in the benefit assessment dossier, but no evaluations of the hazard ratio (HR). In IQWiG's dossier assessment, the analyses presented are not used because of the different observation durations between the treatment arms.
Within the written statement procedure framework on the present benefit assessment, the pharmaceutical company submitted additional evaluations on the hazard ratio. Based on these analyses, there was no statistically significant difference between the study arms for the endpoint discontinuation due to AEs (in terms of discontinuation of at least one component).

Specific AE

There is a statistically significant disadvantage for carfilzomib in combination with daratumumab and dexamethasone compared to carfilzomib in combination with dexamethasone with regard to the specific AE diarrhoea (PT) as well as the specific severe AE (CTCAE grade ≥ 3) thrombocytopenia (PT). For the specific severe AE (CTCAE grade ≥ 3) Renal and urinary disorders (SOC), carfilzomib has a statistically significant advantage in combination with daratumumab and dexamethasone.

The pharmaceutical company submits different operationalisations in the dossier for the benefit assessment for specific AE infusion-related reactions. However, precise information on operationalisation is missing for all analyses presented for the endpoint infusion-related reactions. In addition, there were significant differences between the individual operationalisations with regard to event rates. The pharmaceutical company could also not adequately clarify the uncertainties in the written statement procedure on the present benefit assessment. Therefore, no usable data are available for any of the operationalisations presented for the endpoint infusion-related reactions.
Against this background, it should be noted with regard to the specific adverse events that, on the basis of the available data, no statements can be made regarding the endpoint infusion-related reactions.

A further limitation in the interpretation of the results on side effects arises with regard to the cardiotoxicity occurring in the CANDOR study. In this regard, CANDOR shows high rates in both study arms. As is also evident from the assessments of clinical experts presented in the present written statement procedure, it can be assumed that these are due to the cardiotoxicity associated with carfilzomib. Given the comparison of carfilzomib in combination with daratumumab and dexamethasone versus carfilzomib in combination with dexamethasone examined in the CANDOR study, no comparative conclusions can be made in comparison to a carfilzomib-free treatment option. Although the addition of daratumumab to carfilzomib and

dexamethasone is not expected to increase cardiotoxicity compared to carfilzomib in combination with dexamethasone, the cardiotoxicity associated with carfilzomib is, according to clinical experts, also to be classified as relevant in the triple combination with daratumumab and dexamethasone, particularly with regard to the choice of alternative therapy options.
The interpretability of the available data on cardiotoxicity occurring under carfilzomib in combination with daratumumab and dexamethasone is thus limited in view of the limitations described.

Overall, there was no statistically significant difference in side effects between the study arms with respect to the endpoints serious AEs, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to AEs. In detail, the specific AEs show two negative and one positive effect of carfilzomib in combination with daratumumab and dexamethasone compared to carfilzomib in combination with dexamethasone. As a limitation, it has to be taken into account that no statements can be made on the endpoint infusion-related reactions based on the available data. Furthermore, the interpretability of the available data on cardiotoxicity occurring under carfilzomib in combination with daratumumab and dexamethasone is limited.

Overall assessment

For the assessment of the additional benefit of carfilzomib in combination with daratumumab and dexamethasone, results are available from the open-label, randomised controlled CANDOR study in comparison to carfilzomib in combination with dexamethasone on mortality (overall survival), morbidity (symptomatology and health status), quality of life and side effects.

The present results show no statistically significant difference for the endpoint overall survival in the endpoint category mortality. Final analysis from the CANDOR study on the endpoint overall survival is pending. No additional benefit is determind for the endpoint overall survival.

For the endpoints of the category morbidity, there were no relevant differences between treatment with carfilzomib in combination with daratumumab and dexamethasone and treatment with carfilzomib in combination with dexamethasone in the overall analysis of the results with regard to symptomatology (assessed by EORTC QLQ-C30 and EORTC QLQ-MY20) and general health status (assessed by EQ-5D VAS).

There were also no relevant differences in the overall results for health-related quality of life (assessed using the EORTC QLQ-C30 and EORTC QLQ-MY20).

There were no statistically significant differences in side effects between the study arms with regard to the endpoints serious AEs, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to AEs. In detail, the specific AEs show two negative and one positive effect of carfilzomib in combination with daratumumab and dexamethasone compared to carfilzomib in combination with dexamethasone. As a limitation, it has to be taken into account that on the basis of the available data, no statements can be made on the endpoint infusion-related reactions and the interpretability of the available data on cardiotoxicity occurring with carfilzomib in combination with daratumumab and dexamethasone is limited.

Overall, the G-BA concludes that there is no proof of an additional benefit of carfilzomib in combination with daratumumab and dexamethasone compared with carfilzomib in combination with dexamethasone.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient carfilzomib.

"Carfilzomib in combination with daratumumab and dexamethasone [...] is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."

The appropriate comparator therapy was determined by the G-BA as follows:

- 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

The pharmaceutical company presents results from the open-label, randomised controlled CANDOR study comparing carfilzomib plus daratumumab and dexamethasone with carfilzomib plus dexamethasone.

In the category mortality, there was no statistically significant difference. The final analysis for the endpoint overall survival is pending.

In the category morbidity (symptomatology and general health status), there are no relevant differences in the overall analysis.

No relevant differences were found in the overall analysis for health-related quality of life.

Regarding the side effects, two negative and one positive effect are shown in detail for the specific AE. Statements on the endpoint infusion-related reactions cannot be made. The interpretability of the cardiotoxicity data is limited.

Overall, the G-BA concludes that there is no proof of an additional benefit of carfilzomib in combination with daratumumab and dexamethasone compared with carfilzomib in combination with dexamethasone.

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 initial resolutions on carfilzomib (15 February 2018, 19 January 2017, and 2 June 2016) and additional decisions on multiple myeloma after at least one therapy (ixazomib (6 July 2017) and elotuzumab (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 Kyprolis (active ingredient: carfilzomib) at the following publicly accessible link (last access: 24 March 2021):

https://www.ema.europa.eu/documents/product-information/kyprolis-epar-product-information_de.pdf

Treatment with carfilzomib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in treating patients with multiple myeloma.

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 June 2021).

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

Treatment duration:

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 eight cycles is assumed, even if the actual treatment duration may differ from patient to patient.

For the cost calculation, in the combination therapies with daratumumab and dexamethasone, it is assumed on the days of the intravenous daratumumab infusion that the dexamethasone dose is given i.v. as premedication before the infusion and on the other days the dexamethasone can be given orally.

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Carfilzomib in combination with daratumumab and dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13 cycles	6	78
Daratumumab	Zyklus1 - 2: Day 1, 8, 15, 22[2] cycle: 36 once every 14 days; From cycle 7 onwards: once every 28 days	1st year: 13 Subsequent year: 13	1st year: Cycle 1-2: 4 cycle: 36 2 From cycle 7 onwards: 1 Subsequent year: 1	1st year: 23 Subsequent year: 13
Dexamethasone	on day 1, 2, 8, 9, 15, 16, 22 28-day cycle	13 cycles	1st year: Cycle 1-2: 3 cycle: 36 5 From cycle 7 onwards: 6 Subsequent year: 6	1st year: 68 Subsequent year: 78
Appropriate comparator therapy				
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 from 13th cycle 4	1st year 76 Subsequent year 52
Lenalidomide	Day 1 - 21 28 days cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28 days cycle	13 cycles	4	52
Carfilzomib in combination with dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28 days cycle	13 cycles	6	78

[2] In cycle 1, the dose is divided into 8 mg/kg on each of days 1 and 2. (Product information on Kyprolis®, last revised: April 2021)

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28 days cycle	13 cycles	8	104
Bortezomib in combination with dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21 days cycle	4 - 8 cycles	4	16 - 32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21 days cycle	4 - 8 cycles	8	32 - 64
Bortezomib in combination with pegylated, liposomal doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21 days cycle	8 cycles	4	32
Doxorubicin (pegylated, liposomal)	Day 4 21 days cycle	8 cycles	1	8
Lenalidomide in combination with dexamethasone				
Lenalidomide	Day 1 - 21 28 days cycle	13 cycles	21	273
Dexamethasone	1st - 4th cycle Day 1- 4, 9 - 12, 17 - 20 From 5th cycle Day 1 - 4 28 days cycle	13 cycles	1st – 4th cycle 12 From 5th cycle 4	1st year 84 Subsequent year 52
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1, 15 28 days cycle	13 cycles	1st - 2nd cycle 4 From 3rd cycle 2	1st year 30 Subsequent year 26
Lenalidomide	Day 1 - 21 28 days cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28 days 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 Subsequent year: 13
Lenalidomide	Day 1 - 21	13 cycles	21	273

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
	28 days cycle			
Dexamethasone	Day 1, 8, 15, 22 28 - days cycle	13 cycles	1st year: 0 (cycle 1 – 2) 2 (cycle 3 – 6) 3 (from cycle 7) Subsequent year: 3	1st year: 29 Subsequent year: 39
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1 - 9: Once every 7 days Week 10 - 24: every 21 days From week 25: once every 28 days	1st year: 21 Subsequent year: 13	1	1st year: 21 Subsequent year: 13
Bortezomib	Day 1, 4, 8, 11 21 days 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

Consumption:

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 used as a basis (average height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[3].

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Carfilzomib in combination with daratumumab and dexamethasone					

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

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Carfilzomib	Cycle 1: 20 mg/m² on day 1 and 2 after that 56 mg/m²	38 mg - 106.4 mg	1 x 30 mg + 1 x 10 mg 1 x 60 mg + 1 x 30 mg + 2 x 10 mg	78	1st year 76 x 60 mg + 78 x 30 mg + 154 x 10 mg Subsequent year 78 x 60 mg + 78 x 30 mg + 156 x 10 mg
Daratumumab	16 mg/kg = 1,232 mg	1,232 mg	3 x 400 mg + 1 x 100 mg	1st year 23 Subsequent year 13	1st year 69 x 400 mg + 23 x 100 mg Subsequent year 39 x 400 mg + 13 x 100 mg
Dexamethasone	on day 1, 2, 8, 9, 15, 16: 20 mg on day 22: 40 mg	 20 mg – 40 mg	 1 x 20 mg – 1 x 40 mg	1st year 68 Subsequent year 78	1st year 57 x 20 mg + 11 x 40 mg Subsequent year 65 x 20 mg + 13 x 40 mg
Appropriate comparator therapy					
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	1st cycle Day 1, 2 20 mg/m² after that 27 mg/m²	1st cycle Day 1, 2 38 mg after that 51.3 mg	1st cycle Day 1, 2 1 x 10 mg + 1 x 30 mg after that 1 x 60 mg	1st year 76 Subsequent year 52	1st year 2 x 10 mg + 2 x 30 mg + 74 x 60 mg Subsequent year 52 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 after that 56 mg/m²	1st cycle Day 1, 2 38 mg after that 106.4 mg	1st cycle Day 1, 2 1 x 10 mg + 1 x 30 mg after that 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 Subsequent year 156 x 10 mg + 78 x 30 mg + 78 x 60 mg

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
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/m^2	2.47 mg	1 x 2.5 mg	32	32 x 2.5 mg +
Doxorubicin (pegylated, liposomal)	30 mg/m^2	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/m^2	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 Subsequent year: 52	1st year 84 x 40 mg Subsequent year 52 x 40 mg
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	10mg/kg	770 mg	2 x 400 mg	1st year 30 Subsequent year 26	1st year 60 x 400 mg Subsequent year 52 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 respectively 1 x 40 mg	52	1st year 30 x 8 mg + 30 x 20 mg + 22 x 40 mg Subsequent year 26 x 8 mg + 26 x 20 mg + 26 x 40 mg
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	16mg/kg	1,232 mg	3 x 400 mg + 1 x 100 mg	1st year: 23 Subsequent year:	1st year: 69 x 400 mg + 23 x 100 mg Subsequent year: 39 x 400 mg +

Designation of the therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
				13	13 x 100 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 Subsequent year: 39	1st year 29 x 40 mg Subsequent year 39 x 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	16mg/kg	1,232 mg	3 x 400 mg + 1 x 100 mg	1st year: 21 Subsequent year: 13	1st year: 63 x 400 mg + 21 x 100 mg Subsequent year: 39 x 400 mg + 13 x 100 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 based on the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. I To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on 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 § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Carfilzomib 10 mg	1 PIE	€ 222.08	€ 1.77	€ 11.68	€ 208.63
Carfilzomib 30 mg	1 PIE	€ 644.12	€ 1.77	€ 35.05	€ 607.30
Carfilzomib 60 mg	1 PIE	€ 1,277.20	€ 1.77	€ 70.10	€ 1,205.33

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Daratumumab 100 mg	1 CIS	€ 467.46	€ 1.77	€ 0.00	€ 465.69
Daratumumab 400 mg	1 CIS	€ 1,827.29	€ 1.77	€ 0.00	€ 1,825.52
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84
Dexamethasone 40 mg[4]	50 TAB	€ 187.76	€ 1.77	€ 0.00	€ 185.99
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PIE	€ 1,039.39	€ 1.77	€ 48.80	€ 988.82
Carfilzomib 10 mg	1 PIE	€ 222.08	€ 1.77	€ 11.68	€ 208.63
Carfilzomib 30 mg	1 PIE	€ 644.12	€ 1.77	€ 35.05	€ 607.30
Carfilzomib 60 mg	1 PIE	€ 1,277.20	€ 1.77	€ 70.10	€ 1,205.33
Daratumumab 100 mg	1 CIS	€ 467.46	€ 1.77	€ 0.00	€ 465.69
Daratumumab 400 mg	1 CIS	€ 1,827.29	€ 1.77	€ 0.00	€ 1,825.52
Dexamethasone 8 mg[4]	100 TAB	€ 123.13	€ 1.77	€ 8.87	€ 112.49
Dexamethasone 20 mg[4]	10 TAB	€ 32.14	€ 1.77	€ 0.00	€ 30.37
Dexamethasone 20 mg[4]	20 TAB	€ 53.81	€ 1.77	€ 0.00	€ 52.04
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84
Dexamethasone 40 mg[4]	50 TAB	€ 187.76	€ 1.77	€ 0.00	€ 185.99
pegylated liposomal doxorubicin 20 mg	1 CIS	€ 772.58	€ 1.77	€ 42.16	€ 728.65
pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,903.13	€ 1.77	€ 105.41	€ 1 795.95
Elotuzumab 400 mg	1 PIC	€ 1 557.64	€ 1.77	€ 85.68	€ 1,470.19
Lenalidomide 25 mg	21 HC	€ 8,289.49	€ 1.77	€ 472.83	€ 7,814.89
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; PIE = powder for concentrate for solution for infusion, PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets					

LAUER-TAXE® last revised: 15 June 2021

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.

[4] Fixed reimbursement rate

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

Type of service	Unit cost	Costs after deduction of statutory rebate	Costs per services[5]	Treatment days per year	Costs / patient / year
Medicinal product to be assessed: *Carfilzomib in combination with **daratumumab** and dexamethasone*					
Premedication[6]					
Dexamethasone 20 mg, i.v.	€ 16.65[4] 10 x 4 mg	€ 14.44 [€ 1.77; € 0.44]	€ 7.22	1st year 21 Subsequent year 13	1st year € 151.62 Subsequent year € 93.86
Dexamethasone 40 mg, i.v.	€ 16.65[4] 10 x 4 mg	€ 14.44 [€ 1.77; € 0.44]	€ 14.44	1st year 2 Subsequent year 0	1st year € 28.88
Paracetamol[9] 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 23 Subsequent year 13	1st year € 1.56 - € 2.23 Subsequent year € 0.88 - € 1.26
Dimetindene 1 mg/10 kg bw, i.v.	€ 18.62 5 x 4 mg	€ 14.93 (€ 1.77; € 1.92)	€ 5.97	1st year 23 Subsequent year 13	1st year € 137.36 Subsequent year € 77.64
Appropriate comparator therapy					
***Elotuzumab** in combination with lenalidomide and dexamethasone*					
Premedication[8]					
Dexamethasone 8 mg, i.v.	€ 20.11[4] 10 x 8 mg	€ 17.62 (€ 1.77; € 0.72)	€ 1.76	1st year 30 Subsequent year 26	1st year € 52.86 Subsequent year € 45.81

[5] Proportionate share of cost per pack for consumption per treatment day. rounded interm result

[6] According to the product information for Darzalex (last revised: July 2020)

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

[8] According to the product information for Empliciti® (last revised: December 2020)

Type of service	Unit cost	Costs after deduction of statutory rebate	Costs per services[5]	Treatment days per year	Costs / patient / year
Dimetindene 1 mg/10 kg bw, i.v.	€ 18.62 5 x 4 mg	€ 14.93 (€ 1.77; € 1.92)	€ 5.97	1st year 30 Subsequent year 26	1st year € 179.16 Subsequent year € 155.27
Famotidine 20 mg, oral	€ 19.91[4] 100 x 20 mg	€ 17.44 (€ 1.77; € 0.70)	€ 0.17	1st year 30 Subsequent year 26	1st year € 5.23 Subsequent year € 4.53
Paracetamol[9] 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 30 Subsequent year 26	1st year € 2.04 - € 2.91 - Subsequent year € 1.77 - € 2.52
Daratumumab *in combination with lenalidomide and dexamethasone*					
Premedication[6]					
Dexamethasone 40 mg, i.v.	€ 16.65[4] 10 x 4 mg	€ 14.44 [€ 1.77; € 0.44]	€ 14.44	1st year 23 Subsequent year 13	1st year € 332.12 Subsequent year € 187.72
Paracetamol[9] 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 23 Subsequent year 13	1st year € 1.56 - € 2.23 Subsequent year € 0.88 - € 1.26
Dimetindene 1 mg/10 kg bw, i.v.	€ 18.62 5 x 4 mg	€ 14.93 (€ 1.77; € 1.92)	€ 5.97	1st year 23 Subsequent year 13	1st year € 137.36 Subsequent year € 77.64
Daratumumab *in combination with bortezomib and dexamethasone*					
Premedication[6]					
Dexamethasone 20 mg, i.v.	€ 16.65[4] 10 x 4 mg	€ 14.44 [€ 1.77; € 0.44]	€ 7.22	1st year 21 Subsequent year 13	1st year € 151.62 Subsequent year € 93.86

[9] The dosage of 650 mg paracetamol in premedication stated in the product information cannot be achieved by tablets. Because of this, a dosage of 500 - 1,000 mg is used.

Type of service	Unit cost	Costs after deduction of statutory rebate	Costs per services[5]	Treatment days per year	Costs / patient / year
Paracetamol[9] 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 Subsequent year 13 1st year 21 Subsequent year 13	1st year € 1.43 - € 2.04 Subsequent year € 0.88 - € 1.26 -
Dimetindene 1 mg/10 kg bw, i.v.	€ 18.62 5 x 4 mg	€ 14.93 (€ 1.77; € 1.92)	€ 5.97	1st year 21 Subsequent year 13	1st year € 125.41 Subsequent year € 77.64

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[10]. 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 necessary SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the drug to be evaluated and the appropriate comparative therapy and are consequently considered as additionally required SHI services in the resolution.

Designation of the therapy	Designation of the service	Number/	Unit cost	Costs / patient Year
Medicinal product to be assessed				
Carfilzomib Daratumumab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[11]	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[12]	1	€ 89.50	€ 89.50

10 "Update of the S3 guideline on prophylaxis, 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

11 Only if HBs antigen negative and anti-HBc antibody positive.

12 Invoicing for GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

Designation of the therapy	Designation of the service	Number/	Unit cost	Costs / patient Year
Appropriate comparator therapy				
Carfilzomib Daratumumab Lenalidomide	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[11]	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[10]	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (contract on price formation for substances and preparation of substances) from 1.10.2009 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 retail 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 sales 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 8 October 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 January 2021 the pharmaceutical company submitted a dossier for the benefit assessment of carfilzomib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 15 January 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 carfilzomib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 April 2021. The deadline for submitting written statements was 6 May 2021.

The oral hearing was held on 25 May 2021.

In a letter dated 25 May 2021, IQWiG was commissioned to perform a supplementary assessment (here only if aspects actually submitted in SN were reassessed: of data submitted in the written statement procedure). The addenda prepared by IQWiG was submitted to the G-BA on 22 June 2021.

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 the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 July 2021, and the proposed resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 October 2019	Determination of the appropriate comparator therapy
Working group Section 35a	18 May 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	25 May 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 June 2021 29 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 July 2021	Concluding discussion of the draft resolution
Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof. Hecken