Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Pomalidomide (New Therapeutic Indication: Combination Therapy Multiple Myeloma)

of 5 December 2019

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1. Legal basis

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

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

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

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution 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 pomalidomide was listed for the first time on 1 September 2013 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

Pomalidomide 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 indication, the sales volume of pomalidomide with the statutory health insurance at pharmacy retail prices including value added tax exceeded € 50 million. Proof must therefore be provided for pomalidomide 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 May 2019, pomalidomide received marketing authorisation for a new therapeutic indication:

“Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide”.

The pharmaceutical company 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 pomalidomide on 7 June 2019 in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 September 2019 on the website of the G-BA (www.g-ba.de), 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 pomalidomide compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the 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 pomalidomide.

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

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

2.1.1 Approved therapeutic indication of pomalidomide (Imnovid®) in accordance with the product information

Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

2.1.2 Appropriate comparator therapy

Adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomid and dexamethasone

or

- carfilzomib in combination with lenalidomid and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomid and dexamethasone

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

or

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal 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. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

cyclophosphamide, melphalan, doxorubicin, doxorubicin (pegyliert liposomal), carmustine, vincristine, dexamethasone, prednisolone, prednisone, interferon alfa-2b, lenalidomide, bortezomib, carfilzomib, ixazomib, panobinostat, daratumumab, and elotuzumab.

On 2. A non-medicinal treatment option is not an appropriate comparator therapy for the therapeutic indication in question. In the case of previously treated patients, a first or renewed autologous stem cell transplantation or an allogeneic stem cell transplantation may be a treatment option in individual cases. However, this is not the rule.

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

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.

Accordingly, the treatment of multiple myeloma after at least one previous therapy is mainly based on the newer substances – including bortezomib, lenalidomide, daratumomab, elotuzumab, and carfilzomib.

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, 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 therapeutic situation.

For carfilzomib, a resolution of 15 February 2018 found a hint for a considerable additional benefit both in combination with lenalidomide and dexamethasone and for the dual combination with dexamethasone. In the benefit assessment for daratumumab, a resolution of 15 February 2018 for the combination therapies with lenalidomide and dexamethasone or bortezomib and dexamethasone give indication of a considerable additional benefit. For elotuzumab in combination with lenalidomide and dexamethasone, a resolution of 1 December 2016 identified a hint for a minor additional benefit. Because of potential therapy-relevant, different toxicity profiles, the dual combinations of bortezomib and lenalidomide continue to be given corresponding importance in the therapeutic indication. In view of the inferiority of bortezomib monotherapy demonstrated in randomised controlled trials, this therapeutic option is no longer recommended in the relevant guidelines and cannot be considered as an appropriate comparator therapy.

Ixazomib in combination with lenalidomide and dexamethasone represents a further treatment option after at least one prior therapy line. However, the evidence available for this combination, including the results of the benefit assessment, is currently considered less meaningful compared with the treatment options mentioned above.

According to the authorisation status and evidence, pomalidomide in combination with dexamethasone, elotuzumab in combination with pomalidomide and dexamethasone and for panobinostat in combination with bortezomib and dexamethasone are only indicated after at least two previous therapies. This means that there is a relevant difference in the treatment situation compared with patients who have received at least one previous therapy.

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

2.1.3 Extent and probability of the additional benefit

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

For pomalidomide in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen, including lenalidomide, an additional benefit is not proven.

Justification:

The pharmaceutical company has submitted data from the open, randomised, controlled Phase III MM-007 study for benefit assessment.

This study compares pomalidomide in combination with bortezomib and dexamethasone with bortezomib in combination with dexamethasone. At the start of study, 559 patients with multiple myeloma and one to three previous therapies, including lenalidomide for two or more consecutive cycles, were included in the study at baseline and randomised 1:1 to the two study arms. Stratification was performed by age (≤ 75 vs > 75 years), number of previous myeloma therapy regimens (1 vs > 1), and beta-2 microglobulin levels in screening (< 3.5 mg/l vs ≥ 3.5 to ≤ 5.5 mg/l vs > 5.5 mg/l).

The primary endpoint of the study was progression-free survival (PFS). Patient-relevant secondary endpoints were overall survival, morbidity, health-related quality of life, and adverse events.

The treatment of the patients was terminated, among other things, at the onset of disease progression or unacceptable toxicity. A follow-up treatment of multiple myeloma was only initiated after the onset of progression; a change from the control arm to the intervention arm was not planned as a study measure.

In the MM-007 study, it was possible to continue therapy with bortezomib in combination with dexamethasone in the control arm beyond eight cycles. In accordance with the product information of bortezomib, previously treated patients who respond or stabilise after four cycles of treatment with bortezomib in combination with dexamethasone can receive this combination for a maximum of four further treatment cycles.

In addition, in the control arm of the MM-007 study dexamethasone was administered to patients over 75 years of age at a dose of 10 mg per day instead of the 20 mg per day dose as indicated in the product information of bortezomib.

In the dossier, the pharmaceutical company presents the results of the ongoing MM-007 study for the first a priori planned data cut-off of 26 October 2017 and for a second data cut-off of 15 September 2018 prepared at the request of the European Medicines Agency (EMA). The present benefit assessment is based on the results of the second data cut-off for the endpoints overall survival and progression-free survival and the endpoints of the side effects category and on the results of the first data cut-off for the remaining endpoints morbidity and health-related quality of life.

The final analysis of the MM-007 study will be carried out after the occurrence of 379 deaths.

Extent and probability of the additional benefit

Mortality

In the MM-007 study, overall survival is defined as the time from randomisation to death of any cause.

As of 15 September 2018, a total of 242 patients had died, 116 in the intervention arm and 126 in the comparator arm. The median survival time was 40.5 months in the intervention arm and 30.5 months in the comparator arm. The event time analysis does not show any statistically significant difference (hazard ratio (HR): 0.91; [95% confidence interval (CI): 0.70; 1.18]; p value 0.476).

An additional benefit of pomalidomide in combination with bortezomib and dexamethasone is therefore not proven in the mortality category.

Morbidity

Progression-free survival (PFS)

Progression-free survival is the primary endpoint of the MM-007 study. It is operationalised as time from randomisation to first documented disease progression or death during study treatment or in the PFS follow-up phase. In the intervention arm, there was a statistically significant increase in median PFS of 4.83 months compared with the control arm (median of 11.70 vs 6.87 months; HR: 0.58; [95% CI: 0.47; 0.71]; $p < 0.001$).

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

consideration the aforementioned aspects, there are different views within the G-BA regarding the patient relevance of the endpoint PFS.

The study results on disease-specific symptomatology and health-related quality of life are used to interpret the PFS results. These data are relevant to evaluate effects on morbidity and/or quality of life of patients associated with the event of a laboratory parametric, imaging, or haematological disease progression.

The study results on disease-specific symptomatology and on health-related quality of life show no relevant changes in this respect. However, the corresponding endpoints in the study were only surveyed up to progression and therefore allow statements to be made only up to the time of progression. In order to be able to assess the possible effects of a laboratory-parametric, imaging, or haematologically determined progression on the disease-specific symptomatology and quality of life, reliable analyses of data before and after the time of the progression event are required.

In addition, the data available do not suggest that the statistically significant prolongation of PFS (disease progression according to IMWG criteria) under pomalidomide in combination with bortezomib and dexamethasone is associated with an improvement in morbidity or health-related quality of life.

The extent to which the prolonged PFS under pomalidomide in combination with bortezomib and dexamethasone translates into prolonged survival cannot yet be conclusively assessed – the final analysis on the overall survival endpoint is still pending.

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

Symptomatology

In the MM-007 study, the symptomatology of the patients is determined by the eight symptom scales of the EORTC-QLQ-C30 questionnaire and the two symptom scales of the EORTC-QLQ-MY20 questionnaire. For the time until the first clinically relevant deterioration by at least 10 points compared with baseline, the responder analysis shows a statistically significant difference between the treatment arms only for the symptom constipation. This difference shows a disadvantage of pomalidomide in combination with bortezomib and dexamethasone. In view of the present disease and the difference in the extent of the effect, this result is not considered sufficient for the overall statement on the symptomatology in order to infer any damage.

An additional benefit of pomalidomide in combination with bortezomib and dexamethasone is therefore not proven in the morbidity category.

Quality of life

The health-related quality of life is reported by the patients in the MM-007 study and assessed using the six functional scales of the EORTC-QLQ-C30 questionnaire and the two functional scales of the EORTC-QLQ-MY20 questionnaire. Based on the total population in the responder analyses, no statistically significant differences between the treatment groups were found for the time until the first clinically relevant deterioration of at least 10 points compared with the baseline value. For the endpoint global health status of EORTC-QLQ-C30, there is an effect modification by the feature International Staging System (ISS) stage ($p = 0.007$). For the sub-group of patients in ISS stage III, there is a statistically significant advantage for pomalidomide in combination with bortezomib and dexamethasone.

There is also an effect modification for the endpoint social function of the EORTC-QLQ-C30 by the characteristic number of previous myeloma therapy regimes ($p = 0.012$). For patients with a previous myeloma therapy regimen, there is a statistically significant difference to the disadvantage of pomalidomide in combination with bortezomib and dexamethasone.

In summary, no additional benefit of pomalidomide in combination with bortezomib and dexamethasone has been demonstrated in the quality of life category.

Side effects

Adverse events (AE) in total

In both the intervention arm and the control arm, almost every patient suffered an adverse event. The results for the endpoint “Total adverse events” are only presented as a supplement.

Serious AE

In the MM-007 study, approximately 61% of patients in the intervention arm and approximately 43% of patients in the comparator arm experienced a serious adverse event (SAE) at the time of the second data cut-off. In the comparator arm, SAE occurred 12.8 months (median) later than in the intervention arm. The event time analysis shows a statistically significant difference to the disadvantage of pomalidomide in combination with bortezomib and dexamethasone.

Severe AE (CTCAE grade ≥ 3)

In the MM-007 study, approximately 93% of patients in the intervention arm and approximately 72% of patients in the comparator arm experienced a severe adverse event (CTCAE grade ≥ 3) at the time of the second data cut-off. In the comparator arm, a severe AE occurred 0.9 months (median) later than in the intervention arm. The event time analysis shows a statistically significant difference to the disadvantage of pomalidomide in combination with bortezomib and dexamethasone.

The subgroup analyses for the endpoint severe AE result in an effect modification by the characteristic ISS stage ($p = 0.016$). For the sub-group of patients in ISS stage I, there is a statistically significant difference to the disadvantage of pomalidomide in combination with bortezomib and dexamethasone. However, for the aggregated sub-group of patients in ISS stages II and III, there is no statistically significant difference between the treatment groups.

Against the background that the effect direction is identical in both sub-groups (ISS stage I vs ISS stages II and III) and that this effect modification is not reflected in any further endpoints of the category side effects, the G-BA considers it justified to evaluate the endpoint severe AE without a sub-division according to ISS stage.

Therapy discontinuation because of AE

In the case of therapy discontinuation because of AE, no statistically significant difference between the treatment groups was found in the event time analysis.

Specific AE

In the area of specific adverse events, there are statistically significant disadvantages for pomalidomide in combination with bortezomib and dexamethasone with regard to venous thromboembolic events (SMQ, AE), neutropoenia (PT, severe AE), cataracts (PT, AE), constipation (PT, AE), stomatitis (PT, AE), peripheral oedema (PT, AE), fever (PT, AE), muscle weakness (PT, AE), tremor (PT, AE), pulmonary embolism (PT, AE), rash (PT, AE), blood and lymphatic system disorders (SOC, severe AE), and infections and infestations (SOC, SAE), there are statistically significant disadvantages for pomalidomide in combination with bortezomib and dexamethasone.

In the overall view, numerous statistically significant differences to the detriment of pomalidomide in combination with bortezomib and dexamethasone can be seen in the side effects. These are clearly pronounced in terms of their extent of effect.

For example, in the MM-007 study at the time of the second data cut-off, the risk of patients in the intervention arm experiencing SAE was 28% higher than in the comparator arm. It the intervention arm, an SAE occurred 12.8 months (mean) earlier than in the comparator arm.

With respect to the occurrence of severe AEs (CTCAE grade ≥ 3), the risk in the intervention arm was 56% higher. In the median, a severe AE occurred 0.9 months earlier. In detail, there are numerous, sometimes serious disadvantages in the area of specific AE. Particular importance is attached to venous thromboembolic events (approx. 12% of patients in the intervention arm vs approx. 3% of patients in the comparator arm) and neutropenia (approx. 45% of patients in the intervention arm vs approx. 9% of patients in the comparator arm). This is because in spite of the accompanying measures to prevent venous thromboembolic events and neutropenia or the respective subsequent complications (pulmonary embolism, infections, febrile episodes), which were permitted or partly prescribed in the MM-007 study and which were carried out in accordance with the product information, these events occurred very frequently in the intervention arm.

The side effects observed are significant for the patients and serious. However, it is uncertain to what extent they can be directly transferred to the German healthcare context. In the statements of clinical experts it was explained in detail that in Germany, a particularly attentive side effect management is to be assumed. This is based on extensive knowledge about the active ingredient lenalidomide (same class of active ingredients) as well as the application of the active ingredient pomalidomide in its therapeutic indication of the 'third line' of relapsed or refractory multiple myeloma.

With regard to venous thromboembolic events, which are among the serious side effects, the study protocol provided for thrombosis prophylaxis in patients with an increased risk, the determination of which was at the discretion of the investigator. According to the pharmaceutical company, 70% of patients received prophylaxis with acetylsalicylic acid (ASA). In view of the increased rate of venous thromboembolic events and pulmonary embolisms occurring in the intervention arm compared with the comparator arm in the MM-007 study, it appears uncertain whether a thrombosis prophylaxis adapted to the individual thrombosis risk and in line with the guidelines was applied in all cases. In this context, the commentators stressed that the adverse study results – especially in the area of thromboembolic but also neutropoenic side effects against the background of the standard established in Germany to prevent such side effects by means of prophylactic or concomitant medications – could only be transferred to the local health care context to a limited extent.

According to the assessment presented by clinical experts in the written statement procedure, the risk for the occurrence of the observed side effects of pomalidomide in combination with bortezomib and dexamethasone can be reduced by appropriate prophylactic measures. This also corresponds to the assessment of the European Medicines Agency (EMA) in EPAR.

The present assessment also takes into account that there are no differences in treatment discontinuations because of adverse events.

All this justifies the assessment of the G-BA that, despite the clear negative effects in the endpoint category side effects according to the study results, the finding of a "lower benefit" in the overall assessment cannot be made with the necessary certainty.

Overall assessment

For the benefit assessment of pomalidomide in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regiment, including lenalidomide, results from the MM-007 study on overall survival, morbidity, health-related quality of life, and adverse events are available.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups. With regard to overall survival, the additional benefit of pomalidomide in combination with bortezomib and dexamethasone is not proven.

In the area of morbidity (symptomatology measured using EORTC-QLQ-C30 and EORTC-QLQ-MY20), there is a statistically significant difference with regard to the symptom constipation to the detriment of pomalidomide in combination with bortezomib and dexamethasone. However, this does not change the overall statement on the symptomatology in view of the present disease and the difference in the extent of the effect. With regard to morbidity, no additional benefit of pomalidomide in combination with bortezomib and dexamethasone has been proven.

For the health-related quality of life, based on the total population, there are neither positive nor negative effects of a treatment with pomalidomide in combination with bortezomib and dexamethasone.

With regard to the side effects, numerous statistically significant disadvantages of pomalidomide in combination with bortezomib and dexamethasone, which are also clearly pronounced in terms of the extent of their effects, can be observed with regard to the endpoints serious AE, severe AE as well as in the area of specific AE.

The side effects observed are significant for the patients and serious. However, it is uncertain to what extent they can be directly transferred to the German healthcare context. In the opinions of clinical experts it was explained in detail that in Germany a particularly attentive management of side effects is to be assumed in the treatment with pomalidomide. It was stressed that the adverse study results – especially in the area of thromboembolic but also neutropenic side effects against the background of the standard established in Germany to prevent such side effects by means of prophylactic or concomitant medications – could only be transferred to the local health care context to a limited extent.

The G-BA comes to the conclusion that, despite the clear negative effects in the endpoint category side effects according to the study results, the finding of a “lower benefit” in the overall assessment cannot be made with the necessary certainty.

In the overall assessment, the G-BA concludes that there is no proof of an additional benefit of pomalidomide in combination with bortezomib and dexamethasone compared with bortezomib in combination with dexamethasone.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for pomalidomide.

The therapeutic indication assessed here is as follows: “Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide”.

Pomalidomide has received marketing authorisation as an orphan drug.

The G-BA determined the appropriate comparator therapy

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- bortezomib in combination with dexamethasone

or

- lenalidomide in combination with dexamethasone

or

- elotuzumab in combination with lenalidomid and dexamethasone

or

- carfilzomib in combination with lenalidomid and dexamethasone

or

- carfilzomib in combination with dexamethasone

or

- daratumumab in combination with lenalidomid and dexamethasone

or

- daratumumab in combination with bortezomib and dexamethasone

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For the benefit assessment, the pharmaceutical company presents the results of the randomized, open, controlled MM-007 study in which pomalidomide in combination with bortezomib and dexamtehasone is compared with bortezomib in combination with dexamethasone.

In the endpoint category mortality, there is no statistically significant difference for overall survival between the study arms. An additional benefit of pomalidomide in combination with bortezomib and dexamethasone is therefore not proven in the mortality category.

In the endpoint categories of morbidity and quality of life, there are neither advantages nor disadvantages of treatment with pomalidomide in combination with bortezomib and dexamethasone based on the total population.

In the endpoint category side effects, for serious adverse events (SAE), severe adverse events (CTCAE grade ≥ 3), and the specific side effects venous thromboembolic events (SMQ, AE), neutropoenia (PT, severe AE), cataracts (PT, AE), constipation (PT, AE), stomatitis (PT, AE), peripheral oedema (PT, AE), fever (PT, AE), muscle weakness (PT, AE), tremor (PT, AE), pulmonary embolism (PT, AE), rash (PT, AE), blood and lymphatic system disorders (SOC, severe AE), and infections and infestations (SOC, SAE), there are statistically significant disadvantages for pomalidomide in combination with bortezomib and dexamethasone.

The observed side effects are significant for the patients and in particular also serious. However, considering the comments made by clinical experts, it is uncertain to what extent they can be directly applied to the German health care context. The G-BA comes to the conclusion that, despite the clear negative effects in the endpoint category side effects according to the study results, the finding of a “lower benefit” in the overall assessment cannot be made with the necessary certainty.

Overall, the G-BA concludes that there is no proof of an additional benefit of pomalidomide in combination with bortezomib and dexamethasone compared with bortezomib 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 information from the dossier of the pharmaceutical company regarding the number of patients. The procedure of the pharmaceutical company is mathematically comprehensible. Overall, however, it is assumed that the number of patients indicated is an underestimate. This is due, in particular, to the secondary data analysis used by the pharmaceutical company to derive the proportion of patients with multiple myeloma with at least one previous therapy, including lenalidomide. In this analysis, some of the assumptions made (e.g. a different rounding of the number of prescriptions for identifying patients with multiple myeloma and those previously treated with lenalidomide) lead to a tendency to underestimate the target population. The proportional value for patients with multiple myeloma with at least one previous therapy, including lenalidomide, used by the pharmaceutical company in the result of the secondary data analysis appears to be very low. This also corresponds to the assessment made by clinical experts in the written statement procedure.

In addition, the assumptions and criteria made in the context of the secondary data analysis are in some cases not comprehensible or assessable. The figures given are thus associated with further uncertainties.

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 Imnovid (active ingredient: pomalidomide at the following publicly accessible link (last access: 16 October 2019):

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

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

Pomalidomide should not be taken during pregnancy.

The prescribing doctor must inform the patient about the expected teratogenic risk and the strict contraceptive measures as described in the contraceptive programme and provide the patient with the appropriate patient information brochure, a patient card (therapy passport), and/or similar materials in accordance with the nationally implemented patient card system. The training material for medical professionals includes instructions on prophylaxis and the handling of the side effects potentially caused by pomalidomide, in particular thromboembolic events, cytopoenia, and infections.

Treatment with pomalidomide should be discontinued if the disease progresses.

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 November 2019).

The costs for the first year of treatment are shown for the cost presentation 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 period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

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				
Pomalidomide in combination with bortezomib and dexamethasone				
Pomalidomide	Day 1–14 21-day cycle	17 cycles	14	238
Bortezomib	1st –8th cycle: Day 1, 4, 8, 11 From 9th cycle: Day 1, 8 21-day cycle	17 cycles	1st –8th cycle: 4 From 9th cycle: 2	1st year 50 Following year 34
Dexamethasone	1st –8th cycle: day 1, 2, 4, 5, 8, 9, 11, 12 From 9th cycle: Day 1, 2, 8, 9 21-day cycle	17 cycles	1st –8th cycle: 8 From 9th cycle:4	1st year 100 Following year 68
Appropriate comparator therapy				
Carfilzomib in combination with lenalidomid 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 Following year 52
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
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

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
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
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 Following year 52
Elotuzumab in combination with lenalidomid 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 Following year 26
Lenalidomide	Day 1–21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52
Daratumumab in combination with lenalidomid and dexamethasone				
Daratumumab	Week 1–8: 1 × a week Week 9–24: every 2 weeks From week 25: every 4 weeks	1st year: 23 Following year: 13	1	1st year: 23 Following year: 13
Lenalidomide	Day 1–21 28-day cycle	13 cycles	21	273
Dexamethasone	1 × per week	52	1	52
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1–9: 1 × per week Week 10–24: every 3 weeks From Week 25: every 4 weeks”	1st year: 21 Following year: 13	1	1st year: 21 Following year: 13

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8 cycles	8	64

Usage and 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). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[2].

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Pomalidomide in combination with bortezomib and dexamethasone					
Pomalidomide	4 mg	4 mg	1 × 4 mg	238	238 × 4 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 × 2.5 mg +	1st year 50 Following year 34	1st year 50 × 2.5 mg Following year 34 × 2.5 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	1st year 100 Following year 68	1st year 100 × 20 mg Following year 68 × 20 mg
Appropriate comparator therapy					
Carfilzomib in combination with lenalidomid and dexamethasone					

[2] Federal health reporting. Average body measurements of the population (2017, both sexes), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Carfilzomib	1st Cycle Day 1, 2 20 mg/m² Afterwards 27 mg/m²	1. Cycle Day 1, 2 38 mg Afterwards 51.3 mg	1. Cycle Day 1, 2 1 × 10 mg + 1 × 30 mg Afterwards 1 × 60 mg	1st year 76 Following year 52	1st year 2 × 10 mg + 2 × 30 mg + 74 × 60 mg Following year 52 × 60 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	52	52 × 40 mg
Carfilzomib in combination with dexamethasone					
Carfilzomib	1. Cycle Day 1, 2 20 mg/m² Afterwards 56 mg/m²	1. Cycle Day 1, 2 38 mg Afterwards 106.4 mg	1. Cycle Day 1, 2 1 × 10 mg + 1 × 30 mg Afterwards 2 × 10 mg + 1 × 30 mg + 1 × 60 mg	78	1st year 154 × 10 mg + 78 × 30 mg + 76 × 60 mg Following year 156 × 10 mg + 78 × 30 mg + 78 × 60 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	104	104 × 20mg
Bortezomib in combination with pegylated, liposomal doxorubicin					
Bortezomib	1.3 mg/m²	2.47 mg	1 × 2.5 mg	32	32 × 2.5 mg +
Doxorubicin (pegylated, liposomal)	30 mg/m²	57 mg	1 × 50 mg 1 × 20 mg	8	8 × 50 mg + 8 × 20 mg
Bortezomib in combination with dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 × 2.5 mg	16 – 32	16–32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	32 – 64	32 – 64 × 20 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	1st year 84 Following year 52	1st year 84 × 40 mg Following year 52 × 40 mg
Elotuzumab in combination with lenalidomid and dexamethasone					
Elotuzumab	10 mg/kg	770 mg	2 × 400 mg	1st year 30 Following year 26	1st year 60 × 400 mg Following year 52 × 400 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 x

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
					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 × 8 mg + 1 × 20 mg or 1 × 40 mg	52	1st year 30 × 8 mg + 30 × 20 mg + 22 × 40 mg Following year 26 × 8 mg + 26 × 20 mg + 26 × 40 mg
Daratumumab in combination with lenalidomid and dexamethasone					
Daratumumab	16 mg/kg	1,232 mg	3 × 400 mg + 1 × 100 mg	1st year: 23 Following year: 13	1st year: 69 × 400 mg + 23 × 100 mg Following year: 39 × 400 mg + 13 × 100 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	52	52 × 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	16 mg/kg	1,232 mg	3 × 400 mg + 1 × 100 mg	1st year: 21 Following year: 13	1st year: 63 × 400 mg + 21 × 100 mg Following year: 39 × 400 mg + 13 × 100 mg
Bortezomib	1.3 mg/m^2	2.47 mg	1 × 2.5 mg	32	32 × 2.5 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	64	64 × 20 mg

Costs:

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 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.

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pomalidomide 4 mg	21 HC	€ 9,647.20	€ 1.77	€ 550.38	€ 9,095.05
Bortezomib 2.5 mg	1 PIJ	€ 1,183.67	€ 1.77	€ 55.65	€ 1,126.25
Dexamethasone 20 mg[3]	50 TAB	€ 118.55	€ 1.77	€ 0.00	€ 116.78
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PIJ	€ 1,183.67	€ 1.77	€ 55.65	€ 1,126.25
Carfilzomib 10 mg	1 PIJ	€ 222.02	€ 1.77	€ 11.68	€ 208.57
Carfilzomib 30 mg	1 PIJ	€ 644.06	€ 1.77	€ 35.05	€ 607.24
Carfilzomib 60 mg	1 PIJ	€ 1,277.14	€ 1.77	€ 70.10	€ 1,205.27
Daratumumab 100 mg	1 IFC	€ 506.67	€ 1.77	€ 27.44	€ 477.46
Daratumumab 400 mg	1 IFC	€ 1,979.51	€ 1.77	€ 109.78	€ 1,867.96
Dexamethasone 8 mg[5]	100 TAB	€ 123.07	€ 1.77	€ 8.87	€ 112.43
Dexamethasone 20 mg[5]	20 TAB	€ 53.75	€ 1.77	€ 0.00	€ 51.98
Dexamethasone 20 mg[5]	50 TAB	€ 118.55	€ 1.77	€ 0.00	€ 116.78
Dexamethasone 40 mg[5]	50 TAB	€ 187.70	€ 1.77	€ 0.00	€ 185.93
Pegylated liposomal doxorubicin 20 mg	1 IFC	€ 762.00	€ 1.77	€ 41.58	€ 718.65
Pegylated liposomal doxorubicin 50 mg	1 IFC	€ 1,877.59	€ 1.77	€ 103.96	€ 1,771.86
Elotuzumab 400 mg	1 PIS	€ 1,557.58	€ 1.77	€ 85.68	€ 1,470.13
Lenalidomide 25 mg	21 HC	€ 8,175.13	€ 1.77	€ 466.31	€ 7,707.05
Abbreviations: HC = hard capsules; IFC = concentrate for the preparation of an infusion solution; PIJ = powder for the preparation of an injection solution; PIS = powder for the preparation of an infusion solution; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 November 2019

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 standard expenditure in the course of the treatment are not shown.

[3] Fixed amount

Type of service	Cost per package	Costs after deduction of statutory rebates	Cost per service[4]	Treatment days/year	Costs/patient/year
Appropriate comparator therapy					
Elotuzumab (in combination with lenalidomid and dexamethasone)					
Pre-medication[5]					
Dexamethasone 8 mg, i.v.	€ 20.05[9] 10 × 8 mg	€ 17.56 [€ 1.77 €; € 0.72]	€ 1.76	1st year 30 Following year 26	1st year € 52.68 Following year € 45.66
Dimetindene 1 mg/10 kg BW, i.v. [6]	€ 18.56 5 × 4 mg	€ 14.82 [€ 1.77 €; € 1.97]	€ 5.92	1st year 30 Following year 26	1st year € 177.84 Following year € 154.13
Ranitidine 150 mg, oral	€ 19.85[7] 100 × 150 mg	€ 17.38 [€ 1.77 €; € 0.70]	€ 0.17	1st year 30 Following year 26	1st year € 5.21 Following year € 4.52
Paracetamol[8] 500–1000 mg, oral	€ 1.50[9] 20 × 500 mg € 1.06[11] 10 x 1000 mg	€ 1.36 [€0.08; €0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 – € 0.10	1st year 30 Following year 26	1st year € 2.04 – € 2.91– Following year € 1.77– € 2.52
Daratumumab (in combination with bortezomib and dexamethasone or in combination with lenalidomide und dexamethasone)					
Pre-medication[10]					
Dexamethasone 20 mg, i.v.	€ 16.59[9] 10 × 4 mg	€ 14.38 [€ 1.77; € 0.44]	€ 7.19	1st year 22	1st year € 158.18

[4] Proportionate costs of costs per package for consumption per treatment day.
[5] According to product information on Empliciti® (last updated: August 2019)
[6] 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 the basis (average height: 1.72 m, average body weight: 77 kg).
[7] Fixed amount
[8] The dosage of 650 mg paracetamol in the pre-medication specified in the product information cannot be achieved with tablets. For this reason, a dosage of 500–1000 mg is used.
[9] Fixed amount non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance in accordance with Section 12, paragraph 7 AM-RL (information as concomitant medication in the product information of the prescription medicinal product)
are not subject to the current medicinal product price regulation. Instead, in accordance with Section 129, paragraph 5a SGB V) when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges pursuant to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.
[10] According to product information on Darzalex (last updated: June 2019)

Type of service	Cost per package	Costs after deduction of statutory rebates	Cost per service[4]	Treatment days/year	Costs/patient/year
				Following year 13	Following year € 93.47
Paracetamol[10] 500–1000 mg, oral	€ 1.50[11] 20 × 500 mg € 1.06[11] 10 x 1000 mg	€ 1.36 [€0.08; €0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 – € 0.10	1st year 22 Following year 13 1st year 22 Following year 13	1st year € 1.50 – € 2.13 Following year € 0.88– € 1.26–
Dimetindene 1 mg/10 kg BW, i.v.[8]	€ 18.56 5 × 4 mg	€ 14.82 [€ 1.77 €; € 1.97]	€ 5.92	1st year 22 Following year 13	1st year € 130.02 Following year € 77.06
Post-medication[12]					
Prednisone	€ 28.95[9] 100 × 20 mg	€ 25.76 [€ 1.77; € 1.42]	€ 0.26	1st year 22 Following year 13	1st year € 5.67 Following year € 3.35

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost presentation is based on the pharmacy retail price and the maximum surcharge for production 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

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 20 February 2018.

On 7 June 2019 the pharmaceutical company submitted a dossier for the benefit assessment of pomalidomide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 11 June 2019 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 pomalidomide.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 September 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 16 September 2019. The deadline for submitting written statements was 7 October 2019.

The oral hearing was held on 29 October 2019.

By letter dated 29 October 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 14 November 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 26 November 2019, and the proposed resolution was approved.

At its session on 5 December 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 February 2018	Determination of the appropriate comparator therapy
Working group Section 35a	23 October 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	29 October 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents

Working group Section 35a	6 November 2019 20 November 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	26 November 2019	Concluding discussion of the proposed resolution
Plenum	5 December 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 5 December 2019

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

Prof Hecken