Gemeinsamer Bundesausschuss

Justification

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

of 16 March 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure is the first placing on the (German) market of the active ingredient selinexor on 1 October 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 27 September 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2023 on the G-BA website (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 selinexor 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, as well the addendum drawn up by the G-BA on the benefit assessment. 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 selinexor.

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 Selinexor (Nexpovio) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 16 March 2023):

See therapeutic indication according to marketing authorisation.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for selinexor in combination with bortezomib and dexamethasone:

- Bortezomib in combination with pegylated liposomal doxorubicin

  or
- Bortezomib in combination with dexamethasone

  or
- Lenalidomide in combination with dexamethasone

  or
- Elotuzumab in combination with lenalidomide and dexamethasone

  or
- Carfilzomib in combination with lenalidomide and dexamethasone

  or
- Carfilzomib in combination with dexamethasone

  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 G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. For the therapeutic indication of relapsed or refractory multiple myeloma, irrespective of the line of therapy, in addition to selinexor, medicinal products with the following active ingredients are in principle approved:

Belantamab mafodotin, bortezomib, carfilzomib, carmustine, ciltacabtagene autoleucel, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, idecabtagen vicleucel, isatuximab, ixazomib, lenalidomide, melphalan, melphalan flufenamide, panobinostat, pomalidomide, prednisolone, prednisone, teclistamab[2] and vincristine.

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

on 2. It is assumed that high-dose chemotherapy with stem cell transplant is not an option for patients at the time of therapy with selinexor in combination with bortezomib and dexamethasone. Therefore, a non-medicinal treatment cannot be considered in the present therapeutic indication.

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

- Ixazomib – resolution of 21 April 2022
- Isatuximab – resolution of 4 November 2021
- Daratumumab – resolutions of 15 February 2018 and of 3 February 2022 and of 15 September 2022
- Carfilzomib – resolutions of 15 February 2018 and of 15 July 2021
- Elotuzumab – resolution of 1 December 2016
- Pomalidomide – resolution of 5 December 2019

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

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

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

Due to different toxicity profiles relevant to therapy, the dual combinations of bortezomib and lenalidomide will continue to be given appropriate importance, i.e. even after introducing of new treatment options. In contrast, monotherapy with bortezomib is no longer recommended as a therapeutic alternative in relevant

[2] Currently unavailable in Germany

guidelines due to its proven inferiority in terms of overall survival and is therefore not considered an appropriate comparator therapy.

For carfilzomib, the resolution of 15 February 2018 found a hint for a considerable additional benefit in the benefit assessments both in combination with lenalidomide and dexamethasone versus lenalidomide plus dexamethasone and for the dual combination with dexamethasone versus bortezomib plus dexamethasone. Both combination therapies are determined to be equally appropriate comparator therapies.

In the benefit assessment of daratumumab, proof of a considerable additional benefit was declared for the combination therapy with lenalidomide and dexamethasone versus lenalidomide + dexamethasone and for the combination therapy with bortezomib and dexamethasone versus bortezomib + dexamethasone by resolution of 15 September 2022. These two combination therapies are also determined to be equally appropriate comparator therapies.

By resolution of 1 December 2016, a hint for a minor additional benefit was identified for elotuzumab in combination with lenalidomide and dexamethasone compared with lenalidomide in combination with dexamethasone for patients after at least one prior therapy. This combination is also determined to be an equally appropriate comparator therapy.

In contrast, an additional benefit of carfilzomib in combination with daratumumab and dexamethasone compared to carfilzomib and dexamethasone for patients with multiple myeloma after at least one prior therapy is not proven (resolution of 15 July 2021).

Pomalidomide is indicated in combination with bortezomib and dexamethasone in patients with at least one prior therapy, including lenalidomide. In the corresponding benefit assessment with resolution of 5 December 2019, no additional benefit could be identified for this combination in the designated patients compared with bortezomib in combination with dexamethasone.

By resolution of 4 November 2021, it was determined that an additional benefit of the combination therapy isatuximab + carfilzomib + dexamethasone, compared to the combination therapy carfilzomib + dexamethasone was not proven, as no relevant differences in patient-relevant endpoints were shown.

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

The combination therapy of daratumumab with pomalidomide and dexamethasone was approved in June 2021 for adults after one prior therapy as well as after at least two prior therapies and with disease progression during or after the last therapy. Likewise, by resolution of 3 February 2022, the G-BA did not identify any additional benefit for patients after prior therapy compared to the appropriate comparator therapy.

Accordingly, the combination therapies carfilzomib + daratumumab + dexamethasone, pomalidomide + bortezomib + dexamethasone, isatuximab + carfilzomib + dexamethasone, ixazomib + lenalidomide + dexamethasone and daratumumab +

pomalidomide + dexamethasone are not determined to be appropriate comparator therapies.

According to its authorisation status and the available evidence, 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, daratumumab in combination with pomalidomide and dexamethasone, and also melphalan flufenamide in combination with dexamethasone and the monotherapies with daratumumab, belantamab mafodotin, idecabtagen vicleucel and ciltacabtagene autoleucel are only indicated after at least two or more prior therapies, which means that there is a relevant difference in the treatment setting compared to subjects who have received at least one prior therapy. The above treatment options are therefore not considered as appropriate comparator therapy.

According to the recommendations from guidelines and taking into account the respective authorisation status, the following combinations are equally appropriate comparator therapies for patients with multiple myeloma who have received at least one prior therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin
- Bortezomib in combination with dexamethasone
- Lenalidomide in combination with dexamethasone
- Elotuzumab in combination with lenalidomide and dexamethasone
- Carfilzomib in combination with lenalidomide and dexamethasone
- Carfilzomib in combination with dexamethasone
- Daratumumab in combination with lenalidomide and dexamethasone
- Daratumumab in combination with bortezomib and dexamethasone.

When selecting the appropriate comparator therapy, the special situation of refractory patients must be taken into account.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

The benefit assessment is based on the results of the randomised, open-label, actively controlled phase III BOSTON study. The study compares selinexor in combination with bortezomib and dexamethasone to bortezomib and dexamethasone.

Adults with relapsed and/or refractory multiple myeloma with 1 to 3 prior therapies were enrolled. A total of 402 patients were randomised to the two treatment arms (test arm: N = 195, control arm: N = 207). Stratification was according to the Revised International Staging Systems (R-ISS) for screening (I/II vs III), the number of prior lines of therapy (1 vs > 1) and prior treatment with a proteasome inhibitor (No vs Yes).

Patients were required to have an Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) of 0 - 2, with the majority of patients having an ECOG-PS of 0 or 1. Patients must not have discontinued bortezomib therapy in the past due to toxicity (CTCAE grade ≥ 3). In addition, at least 6 months had to have passed since the last bortezomib therapy before starting the study medication. About 70% of the study population (69% in the intervention arm, 70% in the control arm) had received prior treatment with bortezomib. In 9% of patients in the intervention arm and 14% of patients in the control arm, there was refractoriness to the prior bortezomib therapy.

Patients in the BOSTON study were treated until disease progression, unacceptable toxicity, withdrawal of consent, death or end of the study.

Treatment with selinexor in combination with bortezomib and dexamethasone in 5-week cycles largely complied with the requirements in the product information of selinexor.

The treatment in the control arm with bortezomib in combination with dexamethasone was given for 8 cycles according to the product information. Subsequently, the patients were treated in a 5-week cycle.

The BOSTON study started in June 2017 and ended in June 2022. It was conducted at 123 study sites in 21 countries across Europe, North America, Asia and Australia, with the majority of patients being of European descent (83% in the test arm, 80% in the control arm).

There are a total of three data cut-offs in the dossier:

- Data cut-off of 15 February 2021 with data on mortality, morbidity and health-related quality of life (request by CHMP)
- Data cut-off of 22 March 2022 with mortality data (request by CHMP)
- Data cut-off of 5 June 2022 with data on side effects (assessment due to end of study)

In the context of the written statement procedure, the pharmaceutical company states that only the endpoints already presented in the dossier were collected for these data cut-offs. Against this background, data on mortality from the data cut-off of 22 March 2022, data on morbidity and health-related quality of life from the data cut-off of 15 February 2021 and data on side effects from the data cut-off of 5 July 2022 are used for the present assessment.

On the control arm of the BOSTON study

Treatment in the control arm with bortezomib in combination with dexamethasone did not comply with the requirements in the product information of bortezomib for all patients. According to the product information, bortezomib in combination with dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have undergone at least 1 prior therapy and who have already undergone or are ineligible for haematopoietic stem cell transplant. Accordingly, treatment should be given for 4 cycles; if there is a response or stable disease is achieved, the combination can be given for a maximum of 4 further cycles.

Prior stem cell transplant or ineligibility for stem cell transplant was not an inclusion criterion of the BOSTON study. About 35% of the patients in the study were pretreated with a stem cell transplant. In the dossier, the pharmaceutical company did not provide any detailed information in this regard. Nor did the pharmaceutical company provide any detailed information regarding ineligibility for stem cell transplant. Within the framework of the written statement procedure, the pharmaceutical company submitted characteristics of the patients with and without stem cell transplant, which refer to the start of the BOSTON study and are therefore not suitable for assessing the potential suitability for stem cell therapy in an earlier line of therapy.

In addition, the patients in the control arm of the BOSTON study could be treated for more than 8 cycles. No information was available in the dossier on the percentage of patients who received more than 8 cycles of bortezomib + dexamethasone. The pharmaceutical company submitted these data subsequently within the framework of the written statement procedure. The percentage of patients treated with more than 8 cycles of bortezomib-containing therapy was higher in the comparator arm of the BOSTON study than in the intervention arm (65% vs 39%). However, the comparator arm also included patients who received bortezomib (34%) as subsequent therapy in the context of treatment switching (patients switched from the comparator arm to the intervention arm).

In the German S3 guideline[3], re-therapy with bortezomib is recommended for patients who have had a partial remission (PR), very good PR or complete remission (CR) for at least 12 months after the end of the prior therapy and who tolerated the prior therapy well. In contrast, the S3 guideline recommends a change in the treatment regimen in the case of a short progression-free survival or a relapse occurring during ongoing (maintenance) therapy. Within the framework of the written statement procedure, the clinical experts also tend to recommend re-therapy with an alternative proteasome inhibitor (PI) in the case of re-therapy with a PI, in the case of pretreatment with bortezomib, especially carfilzomib.

The data submitted by the pharmaceutical company in the context of the written statement procedure show that in the comparator arm, due to treatment switching, the combination therapy of selinexor in combination with bortezomib and dexamethasone was predominantly used as a bortezomib-containing subsequent therapy, while the patients in the intervention arm predominantly received bortezomib-free subsequent therapies.

The treatment switching permitted in the BOSTON study took place at an early stage, according to the data submitted in the written statement procedure, both in the total

[3] Guideline programme in oncology. S3 guideline Diagnostics, therapy and after-care for patients with monoclonal gammopathy of uncertain significance (MGUS) or multiple myeloma [online]. 2022 [accessed: 21.02.2023]

population and in all subgroups investigated (according to sex, age and R-ISS), so that the interpretability of the results presented is difficult.

The results of the BOSTON study are to be considered as being significantly biased especially due to the high percentage of patients who switched to a selinexor-containing therapy, as well as due to the early timing of the treatment switch. The clinical experts further justify the high risk of bias in their view in the context of the written statement procedure with the fact that for a large percentage of the patients enrolled in the BOSTON study, also due to bortezomib prior therapy, the regimen of bortezomib and dexamethasone used in the control arm, which was largely not administered in accordance with the product information, was not suitable for the reasons mentioned above.

Extent and probability of the additional benefit

Mortality

Overall survival

Overall survival was defined in the BOSTON study as the time from randomisation to death, regardless of the underlying cause.

For the endpoint of overall survival, there is no statistically significant difference between selinexor in combination with bortezomib and dexamethasone compared to bortezomib in combination with dexamethasone.

Thus, for overall survival, no advantage or disadvantage of selinexor in combination with bortezomib and dexamethasone over bortezomib in combination with dexamethasone can be determined. The result for this endpoint is to be considered as being significantly biased due to the reasons mentioned above.

In addition, the data from the pharmaceutical company's dossier show an effect modification by the age characteristic (< 65 years, ≥ 65 years) for the endpoint of overall survival: For older patients ≥ 65 years, there is a statistically significant positive effect of selinexor in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone, while for younger patients < 65 years, there is a statistically significant negative effect. This effect modification is not evident in other patient individual endpoints.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the BOSTON study. It is operationalised as the first occurrence of partial disease (PD) in the period from randomisation or death from any cause, whichever occurred earlier. PD was centrally determined by an IRC according to the IMWG response criteria.

PFS is statistically significantly prolonged with selinexor in combination with bortezomib and dexamethasone compared to bortezomib in combination with dexamethasone.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is assessed according to IMWG response criteria and thus, not in a symptom-related manner but by means of laboratory parametric, imaging, and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

Data on morbidity and health-related quality of life are potentially relevant for the interpretation of the PFS result, especially when, as in the present case, disease progression based on laboratory, imaging and haematological findings is associated with effects on morbidity and/or quality of life. However, no assessable data on morbidity and health-related quality of life are available from the BOSTON study. Thus, it is not possible to assess whether the prolonged PFS is associated with a benefit with respect to these endpoints.

In addition, there is no statistically significant effect on overall survival, so the effect on PFS does not translate into an improvement in overall survival based on these data.

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

Symptomatology

Symptomatology was assessed in the BOSTON study using EORTC QLQ-C30 and EORTC QLQ-CIPN20.

The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 15% of the scale range for the time to 1st clinically relevant deterioration. In addition, the pharmaceutical company submits evaluations of the continuous data on the weekly rate of change using a linear mixed effect model, in which a linear adjustment is made. With this model, different data collection time point can thus also be taken into account.

In principle, both operationalisations can be suitable for making statements about the additional benefit. In the present case, however, both evaluation methods are unsuitable due to the very different data collection time points as well as a strongly different number of data collections between the two study arms.

In the intervention arm, the data collection is conducted on day 1 of each 5-week cycle. In the control arm, the data collection is carried out on the day 1 of each 3-week cycle, or on day 1 of each 5-week cycle from the 9th cycle. Thus, by week 21, there are only 4 data collection points in the intervention arm, but 7 data collection points in the control arm, which can pose a risk of bias.

Against this background, additional analyses with the same number of data collections in both study arms would have been necessary to derive an additional benefit, but the pharmaceutical company did not submit these in the written statement procedure.

The results presented for the endpoints of symptomatology assessed by EORTC QLQ-C30 and symptomatology assessed by EORTC QLQ-CIPN20 are therefore not assessable.

Health status

The health status is assessed in the BOSTON study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company submitted responder analysis, operationalised as time to 1st deterioration of ≥ 15% of the scale range. In addition, the pharmaceutical company submits evaluations of the continuous data on the weekly rate of change using a linear mixed effect model, in which a linear adjustment is made. With this model, different data collection time points can thus also be taken into account.

Taking into account the comments in the "Symptomatology" section regarding the different data collection time points in the two study arms, the results for the endpoint of health status are unsuitable for the present benefit assessment.

In the overall consideration of the endpoint category morbidity, no suitable data are available.

Quality of life

Health-related quality of life was assessed in the BOSTON study using the EORTC QLQ-C30.

The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 15% of the scale range for the time to 1st clinically relevant deterioration. In addition, the pharmaceutical company submits evaluations of the continuous data on the weekly rate of change using a linear mixed effect model, in which a linear adjustment is made. With this model, different data collection time points can thus also be taken into account.

Taking into account the comments in the "Symptomatology" section regarding the different data collection time points in the two study arms, the results on health-related quality of life are unsuitable for the present benefit assessment.

Thus, in the overall assessment of the endpoint category of health-related quality of life, no assessable data are available.

Side effects

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Serious AEs (SAE) and severe AEs (CTCAE grade ≥ 3)

For the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference between the treatment arms to the disadvantage of selinexor in combination with bortezomib and dexamethasone.

Therapy discontinuations due to AEs

For the endpoint of therapy discontinuations due to AEs, no statistically significant difference was detected between the treatment groups.

Specific AEs

For the specific AEs gastrointestinal disorders (severe AEs) and cataract (severe AEs), there was a statistically significant difference between the treatment arms to the disadvantage of selinexor in combination with bortezomib and dexamethasone.

For the endpoints of cardiac disorders (AEs), respiratory, thoracic and mediastinal disorders (SAEs), blood and lymphatic system disorders (severe AEs), general disorders and general disorders and administration site conditions (severe AEs) and metabolism and nutrition disorders (severe AEs), there was a statistically significant difference to the disadvantage of selinexor + bortezomib + dexamethasone compared with bortezomib + dexamethasone.

With regard to the specific AE of peripheral neuropathies, there is a discrepant operationalisation in the dossier compared to the study report. In the study report, the peripheral neuropathies were operationalised by a Synonym Recoded Preferred Term, whereas in the dossier, coding was done via Dictionary-Derived Terms. No justification was provided for the deviation from the prespecified approach. These ambiguities could not be clarified in the written statement procedure either. The results for the specific AE of peripheral neuropathies are therefore assessed as non-interpretable.

In the overall assessment of the endpoint category of side effects, there are disadvantages for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and specific AEs for selinexor in

combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone. These disadvantages are considered significant for patients. For the endpoint of therapy discontinuations due to AEs, however, there was no difference between the treatment arms.

Overall assessment/ conclusion

For the assessment of the additional benefit of selinexor in combination with bortezomib and dexamethasone in adults with multiple myeloma who have received at least one prior therapy, results on mortality, morbidity, quality of life and side effects are available from the open-label, randomised controlled trial BOSTON. The completed study compared selinexor in combination with bortezomib and dexamethasone to bortezomib in combination with dexamethasone.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms. The result for this endpoint is to be considered as significantly biased.

This is due in particular to a high percentage of patients in the control arm of the study who switched to a selinexor-containing therapy at an early stage. In addition, there are doubts about the extent to which the bortezomib-containing treatment regimen applied was suitable in the present treatment setting, in which a relevant percentage of patients had received bortezomib prior therapy.

In the overall analysis of the results on morbidity, no suitable data are available. The data on the patient-reported endpoints in the categories of morbidity (collected using the EORTC QLQ-C30, EORTC QLQ-CIPN20 and EQ-5D VAS) and health-related quality of life (collected using the EORTC QLQ-C30) are not assessable due to the very different data collection time points and a very different number of data collections between the two study arms.

In the endpoint category of side effects, there are statistically significant differences in the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3) as well as in specific AEs between the treatment arms to the disadvantage of the intervention. In contrast, there were no differences in therapy discontinuations due to AEs between the treatment arms.

In the overall analysis of all results, there are only disadvantages of selinexor in combination with bortezomib and dexamethasone compared to bortezomib in combination with dexamethasone, which consist of an increase in side effects.

However, taking into account the clinical relevance, these disadvantages are not of a magnitude that would justify a lower benefit in the overall assessment of all endpoints.

Overall, there is no evidence of additional benefit of selinexor in combination with bortezomib and dexamethasone for adults with multiple myeloma who have received at least one prior therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Nexpovio with the active ingredient selinexor.

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

The following combination therapies were determined as 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 lenalidomide and dexamethasone

  or
- Carfilzomib in combination with lenalidomide and dexamethasone

  or
- Carfilzomib in combination with dexamethasone

  or
- Daratumumab in combination with lenalidomide and dexamethasone

  or
- Daratumumab in combination with bortezomib and dexamethasone

For the proof of an additional benefit, results from the open-label, randomised controlled trial BOSTON were presented for mortality, morbidity, health-related quality of life and side effects.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms. The result for this endpoint is to be considered as significantly biased.

This is due in particular to a high percentage of patients in the control arm of the study who switched to a selinexor-containing therapy at an early stage. In addition, there are doubts about the extent to which the bortezomib-containing treatment regimen applied was suitable in the present treatment setting, in which a relevant percentage of patients had received bortezomib prior therapy.

In the overall analysis of the results on morbidity, no suitable data are available. The data on the patient-reported endpoints in the categories of morbidity and health-related quality of life are not assessable due to very different data collection time points and a strongly different number of data collections between the two study arms.

In the endpoint category of side effects, there are disadvantages for SAEs and severe AEs (CTCAE grade ≥ 3) as well as for specific AEs. In contrast, there were no differences in therapy discontinuations due to AEs between the treatment arms.

In the overall analysis of all results, there are only disadvantages of selinexor in combination with bortezomib and dexamethasone compared to bortezomib in combination with dexamethasone, which consist of an increase in side effects.

However, taking into account the clinical relevance, these disadvantages are not of a magnitude that would justify a lower benefit in the overall assessment of all endpoints.

Overall, there is no evidence of additional benefit of selinexor in combination with bortezomib and dexamethasone for adults with multiple myeloma who have received at least one prior therapy.

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

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

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

The resolution is based on the number of patients from the last resolution on multiple myeloma after at least one prior therapy (daratumumab (15 September 2022)). The figures were already used as a basis for other resolutions on multiple myeloma after at least one prior therapy (resolutions on ixazomib dated 21 April 2022, resolutions on carfilzomib dated 15 July 2021, 15 February 2018; initial resolution on daratumumab dated 15 February 2018 and resolution on elotuzumab dated 1 December 2016). An update of the data basis, especially with regard to the changed treatment setting is considered necessary.

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 Nexpovio (active ingredient: selinexor) at the following publicly accessible link (last access: 6 February 2023):

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

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

2.4 Treatment costs

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

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2023).

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

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies

from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Selinexor in combination with dexamethasone and bortezomib				
Selinexor	Day 1, 8, 15, 22, 29 35-day cycle	10.4	5	52.0
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23, 29, 30 35-day cycle	10.4	10	104.0
Bortezomib	Day 1, 8, 15, 22 35-day cycle	10.4	4	41.6
Appropriate comparator therapy				
Bortezomib in combination with pegylated liposomal doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8.0	4	32.0
Doxorubicin (pegylated, lysosomal)	Day 4 21-day cycle	8.0	1	8.0
Bortezomib in combination with dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	4.0 - 8.0	4	16.0 - 32.0
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21-day cycle	4.0 - 8.0	8	32.0 - 64.0
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	13.0	1st -12th cycle 6	1st year 76.0
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0
Carfilzomib in combination with dexamethasone				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13.0	6	78.0
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-day cycle	13.0	8	104.0
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	1st year: 23.0	1	1st year 23.0
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	1st year 0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	1st year 29.0[4]
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1 - 9 1 x every 7 days Week 10 - 24 1 x every 21 days From week 25 1 x every 28 days	1st year 21.0	1	1st year 21.0
Bortezomib	Day 1, 4, 8 and 11 21-day cycle	8.0	4	32.0
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8.0	6 (cycle 1 - 3) 7 (cycle 4 - 8)	53.0[4]
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1, 15	13.0	1st - 2nd cycle 4 From 3rd cycle 2	1st year 30.0

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	28-day cycle			
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0
Lenalidomide in combination with dexamethasone				
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	1st - 4th cycle Day 1 - 4, 9 - 12, 17 - 20 From 5th cycle Day 1 - 4 28-day cycle	13.0	1st - 4th cycle 12 From 5th cycle 4	1st year 84.0

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 applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[5].

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Selinexor in combination with dexamethasone and bortezomib					
Selinexor	100 mg	100 mg	5 x 20 mg	52.0	260.0 x 20 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	104.0	104.0 x 20 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	41.6	41.6 x 2.5 mg
Appropriate comparator therapy					

[5] 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	Average annual consumption by potency
Bortezomib in combination with pegylated liposomal doxorubicin					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
Doxorubicin (pegylated, lysosomal)	30 mg/m²	57 mg	1 x 20 mg 1 x 50 mg	8.0	8 x 20 mg 8 x 50 mg
Bortezomib in combination with dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	16.0 - 32.0	16 x 2.5 mg - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32.0 - 64.0	32 x 20 mg - 64 x 20 mg
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 27 mg/m²	1st cycle day 1, 2 38 mg Thereafter 51.3 mg	1st cycle Day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 1 x 60 mg	1st year 76.0	1st year 2 x 10 mg + 2 x 30 mg + 74 x 60 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Carfilzomib in combination with dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 56 mg/m²	1st cycle day 1, 2 38 mg Thereafter 106.4 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78.0	1st year 154 x 10 mg + 78 x 30 mg + 76 x 60 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	104.0	104 x 20 mg
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 23.0	1st year: 23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 29.0	1st year: 29 x 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year:	1st year:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
				21.0	21 x 1,800 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	53.0	53 x 20 mg
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	10 mg/kg	770 mg	2 x 400 mg	1st year: 30.0	1st year: 60 x 400 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8, 22 40 mg	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8, 22 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52.0	1st year 30 x 8 mg + 30 x 20 mg + 22 x 40 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 84.0	1st year: 84 x 40 mg

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Selinexor 20 mg	20 FCT	€ 10,954.09	€ 2.00	€ 1,066.80	€ 9,885.29
Dexamethasone 20 mg[6]	50 TAB	€ 118.85	€ 2.00	€ 0.00	€ 116.85
Bortezomib 2.5 mg	1 PSI	€ 185.33	€ 2.00	€ 8.26	€ 175.07
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 185.33	€ 2.00	€ 8.26	€ 175.07
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 721.45	€ 2.00	€ 89.87	€ 629.58
Pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,778.86	€ 2.00	€ 224.69	€ 1,552.17
Dexamethasone 20 mg[6]	20 TAB	€ 54.05	€ 2.00	€ 0.00	€ 52.05
Dexamethasone 20 mg[6]	50 TAB	€ 118.85	€ 2.00	€ 0.00	€ 116.85
Carfilzomib 10 mg	1 PIS	€ 196.99	€ 2.00	€ 17.63	€ 177.36
Carfilzomib 30 mg	1 PIS	€ 568.39	€ 2.00	€ 52.88	€ 513.51
Carfilzomib 60 mg	1 PIS	€ 1,125.50	€ 2.00	€ 105.75	€ 1,017.75
Lenalidomide 25 mg	21 HC	€ 64.12	€ 2.00	€ 2.51	€ 59.61
Dexamethasone 40 mg[6]	50 TAB	€ 188.00	€ 2.00	€ 0.00	€ 186.00
Daratumumab 1,800 mg	1 SFI	€ 5,809.83	€ 2.00	€ 234.65	€ 5,573.18
Dexamethasone 20 mg[6]	10 TAB	€ 32.38	€ 2.00	€ 0.00	€ 30.38
Elotuzumab 400 mg	1 PIC	€ 1,557.88	€ 2.00	€ 146.88	€ 1,409.00
Dexamethasone 8 mg[6Fehler! Textmarke nicht definiert.]	100 Pic	€ 123.37	€ 2.00	€ 8.87	€ 112.50
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets PIS = powder for the preparation of an infusion solution, CIS = concentrate for the preparation of an infusion solution, FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 March 2023

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

[6] Fixed reimbursement rate

(e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[7]	Treatment days per year	Costs/ patient/ year
Appropriate comparator therapy					
Daratumumab *in combination with lenalidomide and dexamethasone*					
Premedication[8]					
Dexamethasone 40 mg, oral	€ 188.00[6] 50 x 40 mg	€ 186.00 [€ 2.00; € 0.00]	€ 3.72	1st year 23	1st year € 85.56
Paracetamol[9] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 23	1st year € 3.62 - € 6.92
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 23	1st year € 145.91
Daratumumab *in combination with bortezomib and dexamethasone*					
Premedication[8]					
Dexamethasone 20 mg, oral	€ 118.85[6] 50 x 20 mg	€ 116.85 [€ 2.00; € 0.00]	€ 2.34	1st year 21	1st year € 49.08
Paracetamol[9] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 21	1st year € 3.31 - € 6.32
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 21	1st year € 133.22
Appropriate comparator therapy					
Elotuzumab *in combination with lenalidomide and dexamethasone*					

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

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

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

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[7]	Treatment days per year	Costs/ patient/ year
Premedication[10]					
Dexamethasone 8 mg, IV	€ 20.35[6] 10 x 8 mg	€ 17.63 [€ 2.00; € 0.72]	€ 1.76	1st year 30	1. year € 52.89
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 30	1st year € 190.32
Famotidine 20 mg, oral	€ 20.15[6] 100 x 20 mg	€ 17.45 [€ 2.00; € 0.70]	€ 0.17	1st year 30	1st year € 5.24
Paracetamol[9] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 30	1st year € 4.73 - € 9.03 -

Patients receiving therapy with carfilzomib, daratumumab and lenalidomide should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[11]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

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

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Appropriate comparator therapy				
Carfilzomib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50

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

[11] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011“ https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Daratumumab Lenalidomide	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)	1	€ 89.50	€ 89.50

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Selinexor

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 26 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 September 2022, the pharmaceutical company submitted a dossier for the benefit assessment of selinexor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 September 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 selinexor.

The dossier assessment by the IQWiG was submitted to the G-BA on 23 December 2022, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2023. The deadline for submitting written statements was 23 January 2023.

The oral hearing was held on 06 February 2023.

By letter dated 7 February 2023, 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 24 February 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 October 2021	Determination of the appropriate comparator therapy
Working group Section 35a	31 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 February 2023 7 February 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 February 2023 28 February 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

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

Prof. Hecken