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 (after at least 4 prior therapies, combination with 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 was 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. 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 dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

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

See therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

Appropriate comparator therapy for selinexor in combination with dexamethasone:

A patient-individual therapy under selection of:

- Bortezomib monotherapy
- Bortezomib + pegylated liposomal doxorubicin
- Bortezomib + dexamethasone
- Carfilzomib + lenalidomide and dexamethasone
- Carfilzomib + dexamethasone
- Daratumumab + lenalidomide + dexamethasone
- Daratumumab + bortezomib + dexamethasone
- Daratumumab monotherapy

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

- Daratumumab + pomalidomide + dexamethasone
- Elotuzumab + lenalidomide + dexamethasone
- Elotuzumab + pomalidomide + dexamethasone
- Isatuximab + pomalidomide + dexamethasone
- Ixazomib + lenalidomide + dexamethasone
- Lenalidomide + dexamethasone
- Panobinostat + bortezomib and dexamethasone
- Pomalidomide + bortezomib and dexamethasone
- Pomalidomide + dexamethasone
- Cyclophosphamide (in combination with other antineoplastic medicinal products)
- Melphalan
- Doxorubicin
- Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)
- Vincristine
- Dexamethasone
- Prednisolone
- Prednisone
- Best supportive care

taking into account prior therapies as well as the severity and duration of the response.

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. In addition to selinexor, the following active ingredients are approved for the present therapeutic indication:

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 current therapy. Therefore, a non-medicinal treatment cannot be considered in the present therapeutic indication.

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

- Idecabtagen vicleucel – resolution of 16 June 2022
- Belantamab mafodotin – resolution of 4 March 2021
- Carfilzomib – resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolutions of 15 February 2018, 3 February 2022 and 15 September 2022
- Elotuzumab – resolutions of 1 December 2016 and 16 December 2021
- Isatuximab – resolutions of 4 November 2021
- Ixazomib – resolution of 6 July 2017
- Panobinostat – resolution of 17 March 2016
- Pomalidomide – resolutions of 17 March 2016 and 5 December 2019

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

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.

The evidence is limited for patients who have received at least four lines of prior therapy. A uniform treatment standard cannot be derived from the available evidence. National and international guidelines generally refer to patient-individual therapy, which is influenced by various factors. According to the S3 guideline, the response and tolerability of prior myeloma therapy play a key role in the choice of therapy.

With regard to the relapsed disease situation, the S3 guideline initially states that a triplet therapy with two new substances (monoclonal antibody, immunomodulatory agent, proteasome inhibitor) and a steroid should be used for patients in the first relapse. Furthermore, with reference to the respective approved therapeutic indications of the active ingredients, the guideline on the therapy of the 1st to 3rd relapse states that regarding each combination therapy all product classes are generally

[2] Currently unavailable in Germany.

used and combined in individual order. This is also done against the background that a therapeutic advantage of triplet therapies over doublet therapies is countered by an increased therapy toxicity, so that they are unsuitable for all patients. According to the S3 guideline, patients with 4 or more prior therapies should be examined to see whether a triplet therapy is reasonable and possible. Furthermore, there is a recommendation that a therapy with classical cytostatic agents should also be examined.

With regard to the treatment setting with at least four prior therapies, the scientific-medical societies focus on a heterogeneous patient collective. It also follows that an individual therapy has to be chosen for the treatment setting, which is determined by patient-related factors, whereby the prior therapies and the response to them also play an important role here. If the patients showed an adequate and long response to a therapy, a re-therapy can in principle also be considered according to the scientific-medical societies. The renewed use of immunomodulating substances or proteasome inhibitors in later lines of therapy is also recommended, whereby another preparation of the respective substance class should be used preferentially. In addition to combination therapies with novel active ingredients, the scientific-medical societies also refer to classical cytostatic agents.

Overall, all approved active ingredients and combinations of active ingredients thereof can be considered.

With regard to the therapy options belantamab mafodotin and idecabtagen vicleucel, which are explicitly approved only for a well-advanced treatment setting with three and four prior therapies, respectively, and which are also mentioned in the S3 guideline and by the scientific-medical societies, the following should be noted. For belantamab mafodotin, a hint of a non-quantifiable additional benefit was identified in the benefit assessment by resolution of the G-BA of 4 March 2021 because the scientific data basis did not allow quantification. Against the background of the still ongoing phase III DREAMM-3 study, the resolution is limited until 1 April 2023. For idecabtagen vicleucel, a hint for a non-quantifiable additional benefit was established by resolution of the G-BA of 16 June 2022 because the scientific data basis did not allow quantification. This was done against the background that no statement could be made about the extent of the additional benefit on the basis of the indirect comparisons presented. Belantamab mafodotin and idecabtagen vicleucel are not determined to be an appropriate comparator therapy for this resolution.

For isatuximab in combination with carfilzomib and dexamethasone, the benefit assessment of the G-BA did not show an additional benefit compared to carfilzomib in combination with dexamethasone (resolution of 4 November 2021). The same applies to carfilzomib in combination with daratumumab and dexamethasone, according to which an additional benefit compared to carfilzomib in combination with dexamethasone is not proven (resolution of the G-BA of 15 July 2021). The combination therapies mentioned do not qualify as an appropriate comparator therapy for the present resolution.

The active ingredient melphalan flufenamide is a new treatment option for the treatment setting after at least three prior therapies. The active ingredient was approved on 17.08.2022 and has only been available in Germany for a short time. Based on the generally accepted state of medical knowledge, melphalan flufenamide is not determined to be an appropriate comparator therapy for the present resolution.

The active ingredient ciltacabtagene autoleucel is also a new treatment option for the treatment setting after at least three prior therapies. The active ingredient was approved on 25.05.2022 and has only been available in Germany for a short time. Based on the generally accepted state of medical knowledge, ciltacabtagene autoleucel is not determined to be an appropriate comparator therapy for the present resolution.

In accordance with the recommendation of the S3 guideline, the G-BA also assumes that no further antineoplastic/myeloma-specific therapy can be considered for some patients, best supportive care being the appropriate treatment for them. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Overall, a patient-individual therapy is thus determined as the appropriate comparator therapy, selecting the above-mentioned specific therapy options and taking into account the prior therapies as well as the severity and duration of the response.

Overall, a patient-individual therapy with selection of

- Bortezomib (monotherapy),
- Bortezomib + pegylated liposomal doxorubicin,
- Bortezomib + dexamethasone,
- Carfilzomib + lenalidomide and dexamethasone,
- Carfilzomib + dexamethasone,
- Daratumumab + lenalidomide + dexamethasone,
- Daratumumab + bortezomib + dexamethasone,
- Daratumumab (monotherapy),
- Daratumumab + pomalidomide + dexamethasone,
- Elotuzumab + lenalidomide + dexamethasone,
- Elotuzumab + pomalidomide + dexamethasone,
- Isatuximab + pomalidomide + dexamethasone,
- Ixazomib + lenalidomide + dexamethasone,
- Lenalidomide + dexamethasone,
- Panobinostat + bortezomib and dexamethasone,
- Pomalidomide + bortezomib and dexamethasone,
- Pomalidomide + dexamethasone, cyclophosphamide (in combination with other antineoplastic medicinal products),
- Melphalan,
- Doxorubicin,
- Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone),
- Vincristine,
- Dexamethasone,

- Prednisolone,
- Prednisone and
- Best supportive care

is therefore determined to be the appropriate comparator therapy, taking into account prior therapies as well as the severity and duration of the response.

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.

Change of the appropriate comparator therapy

Originally, the therapy options included in the patient-individual therapy determined as the appropriate comparator therapy did not include the combination therapy "daratumumab in combination with pomalidomide and dexamethasone".

The present resolution adds the combination therapy "daratumumab in combination with pomalidomide and dexamethasone" to the selection of therapy options in the context of patient-individual therapy.

The statements of the clinical experts in the benefit assessment procedure on melphalan flufenamide also showed that in everyday clinical practice, the combination therapy pomalidomide + dexamethasone is often extended by another concomitant active ingredient in the sense of a triplet therapy. According to clinical experts, monoclonal antibodies in particular can be added.

By resolution of the G-BA of 3 February 2022, a hint for a minor additional benefit was identified for daratumumab in combination with pomalidomide and dexamethasone in patients with at least two prior therapies and disease progression on the last therapy compared to pomalidomide in combination with dexamethasone.

Taking into account the statements of the clinical experts in the benefit assessment procedure on melphalan flufenamide, "daratumumab in combination with pomalidomide and dexamethasone" is added to the selection of therapy options within the scope of the patient-individual therapy determined as the appropriate comparator therapy.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

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:

Data basis

For the benefit assessment of selinexor in adults with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who

have demonstrated disease progression on the last therapy, the pharmaceutical company submits comparisons of individual arms of different studies on selinexor in the dossier. The data presented were identified by means of an information search for further investigations with selinexor. The identified studies on selinexor are the single-arm studies STORM and XPORT-MM-028. In addition, the pharmaceutical company identifies the publications Cornell 2021[3] and Richardson 2021[4] via a bibliographic search. A randomised controlled trial for a direct comparison was not identified.

STORM study

The STORM study is the pivotal study on selinexor, which enrolled patients with multiple myeloma who were pre-treated with 4 or 5 active ingredients and were refractory to 2 or 3 product classes, or who received at least 3 prior therapies (including lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab and an alkylating agent). The STORM study is a completed, multicentre, single-arm study in which the intervention consisted of selinexor + dexamethasone. Primary endpoint of the study was the overall response rate. The pharmaceutical company presents the results of the STORM study in its dossier descriptively for the sub-population corresponding to the therapeutic indication of selinexor. For the comparison of individual arms of different studies, the pharmaceutical company uses only aggregated data from this sub-population from Cornell 2021.

XPORT-MM-028 *study*

The XPORT-MM-028 study is an ongoing, multicentre study comparing different selinexor and dexamethasone doses, among others. In 3 of the 4 treatment arms of the study, selinexor is administered in combination with dexamethasone (different doses in each case). Patients with at least 4 prior therapies and refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 antibody were enrolled. The pharmaceutical company presents the results of those patients who received selinexor in combination with dexamethasone according to the product information in a descriptive way in the dossier.

Comparator data

The pharmaceutical company does not conduct an information search for further studies on the appropriate comparator therapy. In the course of bibliographic research for Selinexor, it identifies the works of Cornell 2021 and Richardson 2021. In Cornell 2021, the results of the selinexor STORM study will be compared with results from the MAMMOTH study, in which patients received conventional therapy. In Richardson 2021, results from the STORM study are compared with results from patients who received conventional therapy from the Flatiron Health Analytic Database (FHAD). Based on this, a non-adjusted indirect comparison of individual arms of different studies is presented in the dossier. The study pool is potentially incomplete due to the lack of information procurement after further investigations for the appropriate comparator therapy.

MAMMOTH study

The MAMMOTH study is a retrospective study that enrolled patients with multiple myeloma who were refractory to daratumumab and/or isatuximab. In the study, patients with different numbers of prior therapies were compared with each other. For the unadjusted indirect comparison of individual arms of different studies, the pharmaceutical company exclusively

[3] Cornell R, Hari P, Tang S et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. Am J Hematol 2021; 96(1): E5-E8.
[4] Richardson PG, Jagannath S, Chari A et al. Overall survival with oral selinexor plus low-dose dexamethasone versus real-world therapy in triple-class-refractory multiple myeloma. eJHaem 2021; 2(1): 48-55.

uses aggregated data of a sub-population of the MAMMOTH study from Cornell 2021. Patients in this sub-population were pretreated with 5 active ingredients and refractory to 3 product classes.

FHAD

In its dossier, the pharmaceutical company also draws on results from FHAD electronic health records. For the unadjusted indirect comparison, it only considers those patients of the FHAD who correspond to the therapeutic indication of selinexor in combination with dexamethasone.

Conclusion

The presented data from the single-arm STORM and XPORT-MM-028 studies alone are unsuitable for assessing the additional benefit of selinexor as they do not allow a comparison with the appropriate comparator therapy.

The comparisons of individual arms of different studies presented by the pharmaceutical company are results of aggregated data from the Cornell 2021 publication identified by them on an unadjusted comparison of a sub-population of the STORM study with the MAMMOTH study. Secondly, they perform a non-adjusted indirect comparison of the STORM study with patient-individual data from FHAD based on the Richardson 2021 publication. They present results for the comparisons only for the endpoint of overall survival. Information on the appropriate comparator therapy is not presented in full in the dossier. The pharmaceutical company only describes that the patients in MAMMOTH and FHAD received a patient-individual therapy and names one active ingredient of the therapy regimen in each case. It is therefore not evident whether the patient-individual therapy in MAMMOTH and the FHAD correspond to the combination therapies listed by the G-BA. In addition, it cannot be ruled out that patients who are not covered by the present therapeutic indication were enrolled in the comparisons. The data submitted by the pharmaceutical company are therefore not assessable overall with regard to the question of the benefit assessment.

Irrespective of the completeness of the study pool, there are no effects for which it can be safely excluded in the present setting of an indirect comparison without bridge comparator that they do not result solely from a systematic risk of bias due to confounding variables.

Overall, the data presented are not suitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selinexor in combination with dexamethasone in adults with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory drugs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Nexpovio with the active ingredient selinexor.

Nexpovio is indicated in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

A patient-individual therapy was determined to be the appropriate comparator therapy, taking into account the prior therapies as well as the severity and duration of the response. Various combination therapies and monotherapies were determined as comparators for the patient-individual therapy. This includes a choice of treatment options approved for multiple myeloma as well as best supportive care.

For the benefit assessment, data from the single-arm STORM and XPORT-MM-028 studies on selinexor identified by the pharmaceutical company were presented descriptively in the dossier. In addition, the pharmaceutical company presented comparisons of individual arms of different studies on selinexor.

Overall, the presented descriptive data of the single-arm studies as well as the unadjusted indirect comparisons of individual arms of different studies are unsuitable to demonstrate an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of selinexor in combination with dexamethasone in adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory drugs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy is not proven.

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 pharmaceutical company shall base the determination of the number of patients in the target population on the number from the resolution on belantamab mafodotin (resolution of 4 March 2021). The number of patients used was assessed as the best possible estimate in the corresponding assessment on the basis of the entire documentation submitted at the time, whereby it tended to be expected in the upper area of the range. Selinexor is indicated in multiple myeloma with refractoryity to a higher minimum number of active ingredients compared to belantamab mafodotin. As a result, the underlying number of patients in the SHI target population may be overestimated. In the absence of better data basis and in order to enable a consistent consideration of the patient numbers, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, the G-BA considers it appropriate to use the patient numbers cited in the resolution on belantamab mafodotin of 4 March 2020.

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: 7 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

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.

Best supportive care:

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as the appropriate comparator as part of a patient-individual therapy, best supportive care is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

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 monotherapy and 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.

Treatment with ixazomib in combination with lenalidomide and dexamethasone for more than 24 cycles should be based on an individual risk-benefit assessment, as data on tolerability and toxicity beyond 24 cycles are limited.

The maximum cumulative total dose of doxorubicin is 450 - 550 mg/m^2 BSA. On this basis, an approximate treatment duration of 6 to 9 cycles is used for monotherapy with doxorubicin.

The costs incurred for prednisone and prednisolone cannot be precisely quantified due to the largely lacking dosage data in the relevant therapeutic indication.

The cost representation for the active ingredient dexamethasone as a suitable comparator in the context of a patient-individual therapy is made with reference to the treatment regimen used in the MM-003 study.[5]

[5] Miguel JS, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70380-2/fulltext

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				
Selinexor	Day 1 + 3 of a 7-day cycle	52.1	2	104.2
Dexamethasone	Day 1 + 3 of a 7-day cycle	52.1	2	104.2
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Bortezomib monotherapy				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8.0	4	32.0
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				
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	13.0	8	104.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	28-day cycle			
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[6]
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[6]
Daratumumab monotherapy (only for subjects with disease progression on last therapy)				
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
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	1st - 2nd cycle	13.0	1st - 2nd cycle	1st year

[6] 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
	Day 1, 8, 15, 22 From 3rd cycle Day 1, 15 28-day cycle		4 From 3rd cycle 2	30.0
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
Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1 28-day cycle	13.0	1st - 2nd cycle 4 From 3rd cycle 1	1st year 19.0
Pomalidomide	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
Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with disease progression on last therapy)				
Isatuximab	1st cycle Day 1, 8, 15, 22 From 2nd cycle Day 1, 15 28-day cycle	13.0	1st cycle 4 From 2nd cycle 2	1st year 28.0
Pomalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	1st cycle 0 From 2nd cycle 2	1st year 24.0
Ixazomib in combination with lenalidomide and dexamethasone				
Ixazomib	Day 1, 8, 15 28-day cycle	13.0	3	39.0
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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
Panobinostat in combination with bortezomib and dexamethasone				
Panobinostat	1st - 16th cycle Day 1, 3, 5, 8, 10, 12 21-day cycle	8.0 - 16.0	6	48.0 - 96.0
Bortezomib	1st - 8th cycle Day 1, 4, 8, 11 9th - 16th cycle Day 1, 8 21-day cycle	8.0 - 16.0	1st - 8th cycle: 4 9th - 16th cycle: 2	32.0 - 48.0
Dexamethasone	1st - 8th cycle Day 1, 2, 4, 5, 8, 9, 11, 12 9th - 16th cycle Day 1, 2, 8, 9 21-day cycle	8.0 - 16.0	1st - 8th cycle: 8 9th - 16th cycle: 4	64.0 - 96.0
Pomalidomide in combination with bortezomib and dexamethasone				
Pomalidomide	Day 1 - 14 21-day cycle	17.4	14	243.6
Bortezomib	1st - 8th cycle Day 1, 4, 8, 11 From 9th cycle Day 1, 8 21-day cycle	17.4	1st - 8th cycle 4 From 9th cycle 2	1st year 50.8
Dexamethasone	1st - 8th cycle Day 1, 2, 4, 5, 8, 9, 11, 12 From 9th cycle	17.4	1st - 8th cycle 8 From 9th cycle	1st year 101.6

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Day 1, 2, 8, 9 21-day cycle		4	
Pomalidomide in combination with dexamethasone (only for subjects with disease progression on last therapy)				
Pomalidomide	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
Cyclophosphamide (in combination with other antineoplastic medicinal products) [8]				
Cyclophosphamide	Day 1 35-day cycle	10.4	1	10.4
Melphalan	Day 1 - 4 35-day cycle	10.4	4	41.6
Carmustine	Day 1 35-day cycle	10.4	1	10.4
Vincristine	Day 1 35-day cycle	10.4	1	10.4
Prednisone	1st - 3rd cycle Day 1 - 7, 8 - 14 From 4th cycle Day 1 - 7	10.4	1st - 3rd cycle 14 From 4th cycle 7	1st year 93.8
Melphalan				
Melphalan	Continuously, 1 x every 28 days	13.0	1	13.0
Doxorubicin				
Doxorubicin	Day 1 21-day cycle	6.0 - 9.0	1	6.0 - 9.0
Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)				
Carmustine	Day 1 35-day cycle	10.4	1	10.4
Cyclophosphamide	Day 1 35-day cycle	10.4	1	10.4
Melphalan	Day 1 - 4 35-day cycle	10.4	4	41.6
Vincristine	Day 1 35-day cycle	10.4	1	10.4
Prednisone	1st - 3rd cycle Day 1 - 7, 8 - 14	10.4	1st - 3rd cycle 14	1st year 93.8

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	From 4th cycle Day 1 - 7		From 4th cycle 7	
Vincristine				
Vincristine	Continuously, 1 x every 7 days	52.1	1	52.1
Dexamethasone				
Dexamethasone [5]	Day 1-4, 9-12 and 17-20 28-day cycle	13.0	12	156.0
Daratumumab in combination with pomalidomide 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
Pomalidomide	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[6]
Prednisolone				
Prednisolone	incalculable			
Prednisone				
Prednisone	incalculable			
Best supportive care				
Best supportive care	Different from patient to patient			

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)[7].

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					
Selinexor	80 mg	80 mg	4 x 20 mg	104.2	416.8 x 20 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	104.2	104.2 x 20 mg
Appropriate comparator therapy					
Bortezomib monotherapy					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
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 - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32.0 - 64.0	32 - 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					

[7] 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
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: 21.0	1st year: 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
Daratumumab monotherapy (only for subjects with disease progression on last therapy)					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 23.0	1st year: 23 x 1,800 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	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8, 22	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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Day 8, 22 40 mg	40 mg			
Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)					
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 10 mg/kg From 3rd cycle Day 1 20 mg/kg	1st - 2nd cycle Day 1, 8, 15, 22 770 mg From 3rd cycle Day 1 1540 mg	1st - 2nd cycle Day 1, 8, 15, 22 2 x 400 mg From 3rd cycle Day 1 4 x 400 mg	1st year: 19.0	1st year: 60 x 400 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1 28 mg Day 8, 15, 22 40 mg	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1 28 mg Day 8, 15, 22 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52.0	1st year 19 x 8 mg + 19 x 20 mg + 33 x 40 mg
Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with disease progression on last therapy)					
Isatuximab	10 mg/kg	770 mg	1 x 500 mg + 3 x 100 mg	28.0	1st year: 28 x 500 mg + 84 x 100 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	24.0	24 x 40 mg
Ixazomib in combination with lenalidomide and dexamethasone					
Ixazomib	4 mg	4 mg	1 x 4 mg	39.0	39 x 4 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
Lenalidomide in combination with dexamethasone					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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
Panobinostat in combination with bortezomib and dexamethasone					
Panobinostat	20 mg	20 mg	1 x 20 mg	48.0 - 96.0	48 x 20 mg - 96 x 20 mg
Bortezomib	1.3 mg/m^2	2.47 mg	1 x 2.5 mg	32.0 - 48.0	32 x 2.5 mg - 48 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	64.0 - 96.0	64 x 20 mg - 96 x 20 mg
Pomalidomide in combination with bortezomib and dexamethasone					
Pomalidomide	4 mg	4 mg	1 x 4 mg	243.6	243.6 x 4 mg
Bortezomib	1.3 mg/m^2	2.47 mg	1 x 2.5 mg	50.8	50.8 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	101.6	101.6 x 20 mg
Pomalidomide in combination with dexamethasone (only for subjects with disease progression on last therapy)					
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Cyclophosphamide (in combination with other antineoplastic medicinal products)[8]					
Cyclophosphamide	400 mg/m^2	760 mg	1 x 1,000 mg	10.4	10.4 x 1,000 mg
Melphalan	8 mg/m^2	15.2 mg	8 x 2 mg	41.6	332.8 x 2 mg
Carmustine	20 mg/m^2	38 mg	1 x 100 mg	10.4	10.4 x 100 mg
Vincristine [10]	1.2 mg/m^2	2 mg	1 x 2 mg	10.4	10.4 x 2 mg
Prednisone	1st - 3rd cycle Day 1 - 7 40 mg/m^2 Day 8 - 14 20 mg/m^2 From 4th cycle Day 1 - 7	1st - 3rd cycle Day 1 - 7 76 mg Day 8 - 14 38 mg From 4th cycle Day 1 - 7 76 mg	1 x 50 mg 1 x 20 mg 1 x 10 mg or 2 x 20 mg	93.8	1st year 72.8 x 50 mg 114.8 x 20 mg 72.8 x 10 mg

[8] Oken MM, Harrington DP, Abramson N et al, Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma. Cancer 1997; 79(8): 1561-1567.
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/%28SICI%291097-0142%2819970415%2979%3A8%3C1561%3A%3AAID-CNCR18%3E3.0.CO%3B2-W

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	40 mg/m²				
Melphalan					
Melphalan	0.4 mg/kg	30.8 mg	1 x 50 mg	13.0	13.0 x 50 mg
Doxorubicin					
Doxorubicin[9]	60 mg/m² - 75 mg/m²	114 mg - 142.5 mg	1 x 150 mg	6.0 - 9.0	6.0 x 150 mg - 9.0 x 150 mg
Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone) [8]					
Carmustine	20 mg/m²	38 mg	1 x 100 mg	10.4	10.4 x 100 mg
Cyclophosphamide	400 mg/m²	760 mg	1 x 1,000 mg	10.4	10.4 x 1,000 mg
Melphalan	8 mg/m²	15.2 mg	8 x 2 mg	41.6	332.8 x 2 mg
Vincristine [10]	1.2 mg/m²	2 mg	1 x 2 mg	10.4	10.4 x 2 mg
Prednisone	1st - 3rd cycle Day 1 - 7 40 mg/m² Day 8 - 14 20 mg/m² From 4th cycle Day 1 - 7 40 mg/m²	1st - 3rd cycle Day 1 - 7 76 mg Day 8 - 14 38 mg From 4th cycle Day 1 - 7 76 mg	1 x 50 mg 1 x 20 mg 1 x 10 mg or 2 x 20 mg	93.8	1st year 72.8 x 50 mg 114.8 x 20 mg 72.8 x 10 mg
Vincristine					
Vincristine[10]	1.4 mg/m²	2 mg	1 x 2 mg	52.1	52.1 x 2 mg
Dexamethasone monotherapy					
Dexamethasone[5]	40 mg	40 mg	5 x 8 mg	156.0	780.0 x 8 mg
Daratumumab in combination with pomalidomide 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
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year:	1st year:

[9] Recommended maximum cumulative dose according to the product information: 450 - 550 mg/m²
[10] The single dose should not exceed 2 mg according to the product information of vincristine

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
				29.0	29 x 40 mg
Prednisolone					
Prednisolone	incalculable				
Prednisone					
Prednisone	incalculable				
Best supportive care					
Best supportive care	Different from patient to patient				

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[11]	50 TAB	€ 118.85	€ 2.00	€ 0.00	€ 116.85
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[11]	20 TAB	€ 54.05	€ 2.00	€ 0.00	€ 52.05
Dexamethasone 20 mg[11]	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

[11] Fixed reimbursement rate

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
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[11]	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[11]	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[11]	100 TAB	€ 123.37	€ 2.00	€ 8.87	€ 112.50
Pomalidomide 4 mg[11]	21 HC	€ 9,061.45	€ 2.00	€ 886.12	€ 8,173.33
Isatuximab 100 mg	1 CIS	€ 368.71	€ 2.00	€ 33.92	€ 332.79
Isatuximab 500 mg	1 CIS	€ 1,790.14	€ 2.00	€ 169.62	€ 1,618.52
Ixazomib 4 mg	3 HC	€ 6,431.26	€ 2.00	€ 624.00	€ 5,805.26
Panobinostat 20 mg	6 HC	€ 4,656.37	€ 2.00	€ 450.23	€ 4,204.14
Cyclophosphamide 1000 mg	6 PSI	€ 127.41	€ 2.00	€ 11.02	€ 114.39
Melphalan 2 mg	50 FCT	€ 56.20	€ 2.00	€ 4.26	€ 49.94
Carmustine 100 mg	1 PSS	€ 3,842.58	€ 2.00	€ 185.28	€ 3,655.30
Prednisone 50 mg[11]	50 TAB	€ 68.02	€ 2.00	€ 4.49	€ 61.53
Prednisone 20 mg[11]	100 TAB	€ 29.25	€ 2.00	€ 1.42	€ 25.83
Prednisone 10 mg[11]	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Vincristine 2 mg	1 SFI	€ 37.63	€ 2.00	€ 1.25	€ 34.38
Melphalan 50 mg	1 DSS	€ 52.29	€ 2.00	€ 3.89	€ 46.40
Doxorubicin 150 mg[11]	1 SFI	€ 418.32	€ 2.00	€ 0.00	€ 416.32
Prednisolone	incalculable				
Prednisone	incalculable				
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, PSS = powder and solvent for the preparation of an infusion solution, DDS = dry substance with solvent					

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 (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[12]	Treatment days per year	Costs/ patient/ year
Appropriate comparator therapy					
Daratumumab *in combination with lenalidomide and dexamethasone*					
Premedication[13]					
Dexamethasone 40 mg, oral	€ 188.00[11] 50 x 40 mg	€ 186.00 [€ 2.00; € 0.00]	€ 3.72	1st year 23	1st year € 85.56
Paracetamol[14] 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[13]					
Dexamethasone 20 mg, oral	€ 118.85[11] 50 x 20 mg	€ 116.85 [€ 2.00; € 0.00]	€ 2.34	1st year 21	1st year € 49.08
Paracetamol[14] 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
Elotuzumab *in combination with lenalidomide and dexamethasone*					
Premedication[15]					
Dexamethasone 8 mg, IV	€ 20.35[11] 10 x 8 mg	€ 17.63 [€ 2.00; € 0.72]	€ 1.76	1st year 30	1. year € 52.89

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

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

[14] 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.

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

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[11] 100 x 20 mg	€ 17.45 [€ 2.00; € 0.70]	€ 0.17	1st year 30	1st year € 5.24
Paracetamol[14] 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 -
***Elotuzumab** + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)*					
Premedication					
Dexamethasone 8 mg, IV	€ 20.35[11] 10 x 8 mg	€ 17.63 [€ 2.00; € 0.72]	€ 1.76	1st year 19	1st year € 33.50
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 19	1st year € 120.54
Famotidine 20 mg, oral	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 19	1st year € 3.32
Paracetamol[14] 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 19	1st year € 2.99 - € 5.72
***Daratumumab** monotherapy*					
Premedication[13]					
Methylprednisolone 60 mg - 100 mg, IV	€ 21.31 3 x 32 mg	€ 16.32 [€ 2.00; € 2.99]	€ 5.44	1st year 23	1st year € 250.24 - € 500.48
Postmedication[13]					
Methylprednisolone 20 mg, oral	€ 73.80[11] 100 x 16 mg € 29.31[11] 100 x 4 mg	€ 66.86 [€ 2.00; € 4.94] € 25.88 [€ 2.00; € 1.43]	€ 0.93	1st year 46	1st year € 42.66
Daratumumab in combination with pomalidomide and dexamethasone					

Premedication[13]					
Dexamethasone 40 mg, oral	€ 188.00[11] 50 x 40 mg	€ 186.00 [€ 2.00; € 0.00]	€ 3.72	1st year 23	1st year € 85.56
Paracetamol[14] 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

Patients receiving therapy with carfilzomib, pomalidomide, 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[16]. 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 Daratumumab Lenalidomide Pomalidomide	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)	1	€ 89.50	€ 89.50

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations

[16] 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

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.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 29 March 2022.

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 22 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 6 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
Subcommittee Medicinal products	29 March 2022	New implementation 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	Conduct of the oral hearing
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