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
Isatuximab (Multiple myeloma, at least 2 prior therapies, combination with pomalidomide and dexamethasone)

of 4 November 2021

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient isatuximab (Sarclisa) was listed for the first time on 1 February 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 28 September 2020, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for isatuximab in the therapeutic indication "in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma after at least two prior therapies" in accordance with Section 35a paragraph 5b SGB V.

In its session on 20 November 2020, the G-BA approved the application to postpone the relevant date in accordance with Section 35a paragraph 5b SGB V.

The benefit assessment of isatuximab in the therapeutic indication "in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma after at least two

prior therapies" starts at the same time as the benefit assessment of isatuximab in the new indication "in combination with carfilzomib and dexamethasone for the treatment of multiple myeloma after at least one prior therapy", at the latest within four weeks after marketing authorisation of the new therapeutic indication "in combination with carfilzomib and dexamethasone for the treatment of multiple myeloma after at least one prior therapy" in accordance with Chapter 5, Section 8, number 2 VerfO, at the latest six months after the relevant date of the therapeutic indication "in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma after at least two prior therapies". The start of the six-month period is determined as the date of the first placing on the market of the medicinal product with the therapeutic indication "in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma after at least two previous therapies".

On 15 April 2021, isatuximab received the extension of the marketing authorisation for the therapeutic indication "in combination with carfilzomib and dexamethasone for the treatment of multiple myeloma after at least one prior therapy" to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, of 12.12.2008, p. 7).

On 10 May 2021, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient isatuximab with the therapeutic indication

"Sarclisa is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. "

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 16 August 2021, 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 isatuximab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of isatuximab.

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:

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

2.1.1 Approved therapeutic indication of isatuximab (Sarclisa®) in accordance with the product information

Sarclisa is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

Sarclisa is indicated in combination with carfilzomib 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 04.11.2021):

Sarclisa is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Adults with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy</u>

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- Bortezomib in combination with dexamethasone

or

- Lenalidomide in combination with dexamethasone

or

- Pomalidomide in combination with dexamethasone

or

- Elotuzumab in combination with lenalidomide and dexamethasone

or

- Elotuzumab in combination with pomalidomide 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 Federal Joint Committee has already determined the patient-relevant benefit 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. The following medicinal products are approved for the present therapeutic indication besides isatuximab:

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

The marketing authorisations are in part linked to (specified) combination partners and to the type of the prior therapies.

on 2. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for patients at the time of current therapy. Therefore, a non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication.

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

- Panobinostat – resolution of 17 March 2016
- Pomalidomide - resolutions of 17 March 2016 and 5 December 2019
- Elotuzumab - resolutions of 1 December 2016 and 2 April 2020
- Ixazomib – resolution of 6 July 2017
- Carfilzomib - resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolution of 15 February 2018

- Belantamab mafodotin - resolution of 4 March 2021

on 4. The general state of medical knowledge, on which the findings of the G-BA are based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication. 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 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.

In accordance with the authorisation status and the underlying evidence, the treatment of adults who have already received two prior therapies is primarily focused on the agents bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, panobinostat and pomalidomide.

In the benefit assessment of pomalidomide in combination with dexamethasone, the resolution of 17 March 2016 determined a hint for a considerable additional benefit in the treatment of patients with relapsed and refractory multiple myeloma after at least two prior therapies, including lenalidomide and bortezomib, for whom dexamethasone (high-dose) represents the patient-individual therapy according to the doctor's instructions. For patients for whom dexamethasone (high-dose) does not represent the patient-individual therapy according to the doctor's instructions, an additional benefit is not proven.

For elotuzumab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma after at least two prior therapies, including lenalidomide and a proteasome inhibitor, a hint for a considerable additional benefit over pomalidomide in combination with dexamethasone was identified by resolution of 2 April 2020. For elotuzumab in combination with pomalidomide and dexamethasone, a reassessment after the deadline will be carried out in parallel to the present benefit assessment procedure.

In addition, by resolution of 1 December 2016, evidence of 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 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. In contrast, an additional benefit for carfilzomib in combination with daratumumab and dexamethasone compared with carfilzomib and dexamethasone is not proven (resolution of 15 July 2021). Therefore, this combination is not considered as an appropriate comparator therapy.

Also, in a resolution dated 15 February 2018, an indication of a considerable additional benefit was determined for daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone compared with lenalidomide in combination with dexamethasone or bortezomib in combination with dexamethasone.

In the benefit assessment of ixazomib in combination with lenalidomide and dexamethasone, the resolution of 6 July 2017 concluded that there was an additional benefit for people with relapsed and refractory multiple myeloma after at least one prior therapy compared to lenalidomide and dexamethasone, but that this benefit was not quantifiable. The period of validity of the relevant resolution of 6 July 2017 was limited until 1 November 2021. Therefore, this combination is also not considered as an appropriate comparator therapy.

Also, in adults who have received two prior therapies, the dual combinations of bortezomib and doxorubicin (pegylated, liposomal), bortezomib and dexamethasone, lenalidomide and dexamethasone, carfilzomib and dexamethasone, and pomalidomide and dexamethasone are given appropriate priority due to different toxicity profiles that may be relevant to therapy. For this reason, these options are considered to be the appropriate comparator therapy.

Elotuzumab in combination with lenalidomide and dexamethasone, carfilzomib in combination with dexamethasone or lenalidomide and dexamethasone, and daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone are already approved for the treatment of patients with only one prior line of therapy. However, the benefit assessments were based on studies in which patients with at least two previous therapies had been included to a considerable extent. Accordingly, study evidence is also available for the present indication. Thus, these treatment options are considered to be the appropriate comparative therapy for the present patient group.

Taking into account the available evidence and the respective authorisation status, the therapy options daratumumab in monotherapy (resolution of 15 February 2018), panobinostat in combination with bortezomib and dexamethasone (resolution of 17 March 2016), belantamab mafodotin (4 March 2021) and selinexor are not considered as appropriate comparator therapy. The same applies to the newly approved therapy options isatuximab in combination with carfilzomib and dexamethasone as well as daratumumab in combination with pomalidomide and dexamethasone, for which benefit assessments are being conducted in parallel to the present benefit assessment procedure.

In the overall review of the evidence, bortezomib in combination with pegylated liposomal doxorubicin, bortezomib in combination with dexamethasone, lenalidomide in combination with dexamethasone, pomalidomide in combination with dexamethasone, elotuzumab in combination with lenalidomide and dexamethasone, elotuzumab in combination with pomalidomide and dexamethasone, carfilzomib in combination with lenalidomide and dexamethasone, carfilzomib in combination with dexamethasone, daratumumab in combination with lenalidomide and dexamethasone or daratumumab in combination with bortezomib and dexamethasone are considered equally appropriate therapeutic options in the present therapeutic indication.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of isatuximab in combination with pomalidomide and dexamethasone is assessed as follows:

For the treatment of relapsed and refractory multiple myeloma in adults who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and who showed disease progression on the last therapy, there is a hint for a minor additional benefit.

Justification:

The benefit assessment of the active ingredient isatuximab is based on the ongoing pivotal ICARIA-MM study. This is an open-label, randomised, controlled, multicentre phase III study comparing the triple combination of isatuximab, pomalidomide and dexamethasone (Isa-Pd) with the dual combination of pomalidomide and dexamethasone (Pd).

The study will evaluate adults with refractory or relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor. For study enrolment, patients had to have relapsed or be refractory to therapy or have developed intolerable toxicity after treatment with lenalidomide or a proteasome inhibitor. In addition, there had to be therapy refractarity regarding the last previous therapy. Patients with primary refractory myeloma and with a general condition according to an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) > 2 were excluded.

Of a total of 307 patients, 154 were assigned to the intervention arm and 153 to the control arm. Randomisation was stratified by age (< 75 years vs ≥ 75 years) and number of prior therapies (2 or 3 vs ≥ 4 lines of therapy). A change from the comparative therapy to the intervention therapy is not possible.

At start of study, 66% of patients had 2 or 3 prior lines of therapy and 34% had more than 3 prior lines of therapy. Revised International Staging System (R-ISS) stage I was present in 23% of patients, R-ISS stage 2 in 64%, and R-ISS stage III in 13%.

For the ICARIA-MM study, 2 data cut-offs are available. The first data cut-off is the primary data cut-off with analyses on the primary endpoint PFS, overall survival, symptomatology, health-related quality of life (11 October 2018), and side effects (22 November 2018). In addition, based on Protocol Amendment 6 on 1 October 2020, a second overall survival data cut-off was conducted after reaching 90% of the 220 deaths required for the final analysis. Analyses regarding overall survival and side effects are available for the second data cut-off. For the endpoint categories morbidity and health-related quality of life in the present benefit assessment, the results of the 1st data cut-off are used, and for overall survival and side effects, the results of the 2nd data cut-off are used due to the longer observation period.

Extent and probability of the additional benefit

Mortality

Overall mortality

For the endpoint overall mortality no statistically significant difference was detected between the treatment arms.

Thus, no additional benefit is determined for the endpoint overall survival with Isa-Pd.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the ICARIA-MM study. PFS was defined as the time between randomisation and the date of first documented disease progression or death from any cause, whichever occurred earlier. Disease progression was assessed according to the International Myeloma Working Group (IMWG) criteria.

There is a statistically significant difference between treatment arms for the benefit of isatuximab in combination with pomalidomide and dexamethasone (Isa-Pd) versus pomalidomide in combination with dexamethasone (Pd).

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

Symptomatology

Disease symptomatology will be assessed in the ICARIA-MM study using the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20. The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points and ≥ 15% of the scale range for the time to 1st deterioration and time to permanent deterioration and for time to 1st improvement and time to permanent improvement.

For the present evaluation, responder analyses for the percentage of patients with a change of ≥ 10 points are used to assess effects on symptomatology.

The improvement of disease-specific symptomatology may represent a separate therapeutic goal in the present indication. However, on the basis of the information provided by the pharmaceutical company in the dossier for the benefit assessment and the analyses presented in the written statement procedure, it can be stated that in the overall consideration of the baseline values at the start of the study and the available responder analyses, the percentage of patients with a deterioration exceeds the percentage of patients with an improvement to a relevant extent. Against this background and taking into account the expected progressive course of the disease, the evaluations on deterioration are used for the present benefit assessment.

With regard to the evaluations for the time to permanent deterioration, it was unclear on the basis of the information provided by the pharmaceutical company on the operationalisation

of the endpoints in the dossier for the benefit assessment, among other things, how patients were included in the evaluation who had a (then one-time) deterioration at the last survey time point.

Within the framework of the written statement procedure, the pharmaceutical company submitted, among other things, additional information and sensitivity analyses for the time until permanent deterioration. In these additional analyses, patients with a (then one-time) deterioration at the last survey time point were counted as non-responders.

The subsequently submitted sensitivity analyses on permanent deterioration are consistent with the results on permanent deterioration from the pharmaceutical company's dossier, which means that the evaluations submitted with the dossier are considered adequate.

Overall, suitable evaluations are thus available both for the period up to 1st deterioration as well as for the time until permanent deterioration. Although both operationalisations are considered to be patient-relevant, the present evaluation is based on the evaluations for the time until permanent deterioration, since deterioration that lasts over a period of time is considered to be more relevant to patients due to its permanence.

With regard to the permanent deterioration of disease symptomatology, there were statistically significant differences between the treatment arms for pain and diarrhoea to the advantage of Isa-Pd over Pd. However, uncertainties remain with regard to the results. Accordingly, the EORTC survey time points are not suitable to capture the effects of infusion-related reactions on symptomatology, as the assessment was conducted before the medication was administered and the infusion-related reactions therefore do not fall within the time period queried by the questionnaire.

Health status

Health status is assessed in the ICARIA-MM study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company submitted responder analysis operationalised as time to 1st deterioration and time to permanent deterioration and time to 1st improvement and time to permanent improvement. Analyses were performed on response criteria ≥ 7 points, ≥ 10 points, and 15% of the scale range (0-100).

Taking into account the comments in the section "Symptomatology" on improvement as well as deterioration, the evaluations on the permanent deterioration of the health status are used for the present benefit assessment.

For none of the response criteria a statistically significant difference was detected between the treatment arms.

Overall, in the endpoint category morbidity, there are advantages for Isa-Pd over Pd in the disease symptomatology of pain and diarrhoea. Uncertainties remain, as the effects of infusion-related reactions on symptomatology do not fall within the time period queried by the questionnaire.

Quality of life

In the ICARIA-MM study, health-related quality of life was assessed using the functional scales and the global health status scale (overall assessment) of the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20. The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points and ≥ 15% of the scale range for the time to 1st deterioration and time

to permanent deterioration and for time to 1st improvement and time to permanent improvement.

For the present evaluation, responder analyses for the percentage of patients with a change of ≥ 10 points are used to assess the effects on health-related quality of life.

Taking into account the comments in the section "Symptomatology" on improvement as well as deterioration, the evaluations on the permanent deterioration of quality of life are used for the present benefit assessment.

Statistically significant differences between treatment arms in favour of Isa-Pd over Pd are shown for global health status and role function. However, uncertainties remain with regard to the results. Accordingly, the EORTC survey time points are not suitable to capture the effects of infusion-related reactions on quality of life, as the survey was conducted before the medication was administered and the infusion-related reactions therefore do not fall within the time period queried by the questionnaire.

Overall, in the endpoint category quality of life, there are thus advantages for Isa-Pd over Pd for global health status and role function. Uncertainties remain, since the effects of infusion-related reactions on quality of life do not fall within the time period queried by the questionnaire.

Side effects

According to the study protocol of the ICARIA-MM study, laboratory values were only reported as an adverse event (AE) if they led to discontinuation of treatment or resulted in dose modification, or were a serious AE (SAE) or adverse event of special interest (AESI). This potentially led to incomplete coverage of AEs, especially severe AEs.

The results of the endpoint category side effects on which the present benefit assessment is based are consequently subject to uncertainties, especially with regard to severe AEs.

Adverse events (AEs) in total

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

Serious AEs (SAE)

There were no statistically significant differences between the treatment arms.

Severe AEs (CTCAE grade ≥ 3)

For the time to onset of severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference between treatment arms to the disadvantage of Isa-Pd versus Pd.

Therapy discontinuations due to AEs (≥ 1 active ingredient component)

In the dossier for the benefit assessment, only evaluations of the time to discontinuation of all active ingredient components were presented.

Within the framework of the written statement procedure, the pharmaceutical company also submitted evaluations of the time until discontinuation of at least one active ingredient component, which are considered appropriate for the present assessment, since patients could continue to be treated with the remaining active ingredients after discontinuation of individual active ingredients.

Based on the evaluations of time to discontinuation of at least one active ingredient component, there is no statistically significant difference between treatment arms.

Specific AEs

For AE bronchitis (PT) and severe AE (CTCAE grade ≥ 3) blood and lymphatic system disorders (SOC), there are statistically significant differences between the treatment arms to the disadvantage of Isa-Pd versus Pd.

The pharmaceutical company submitted different operationalisations in the dossier for the benefit assessment for specific AE infusion-related reactions. The operationalisations are not suitable for making statements on the endpoint infusion-related reactions. Due to an IV administration only in the intervention arm, events related to an infusion under the study medication could in principle only be recorded in the intervention arm. In addition, the underlying individual symptoms associated with the diagnosis of an infusion reaction were not included in the overall AE evaluation of Treatment-Emergent Adverse Events (TEAE). As a consequence, this leads to an incomplete recording of the events in the affected symptoms (such as PT Dyspnoea and PT Cough) in the submitted evaluations on PT / SOC.

Additionally, the classification into severity grades for the PT made by the pharmaceutical company was not based on the specific CTCAE criteria for the individual symptoms. Thus, there is a potential underestimation of the number of patients with severe AEs (CTCAE grade ≥ 3) in the intervention arm.

As a result, no usable data are available for the endpoint infusion-related reactions due to the uncertainties mentioned above for any of the operationalisations presented.

In the overall view of the results on side effects, there is a disadvantage for Isa-Pd compared to Pd for serious adverse events (CTCAE grade ≥ 3) and in detail for the specific adverse events bronchitis and blood and lymphatic system disorders (CTCAE grade ≥ 3).

<u>Overall assessment</u>

For the assessment of the additional benefit of isatuximab in combination with pomalidomide and dexamethasone (Isa-Pd), results from the open-label, randomised, controlled study ICARIA-MM are available for the endpoint categories mortality, morbidity, quality of life, and side effects.

In the ongoing study, the triple combination Isa-Pd is compared with the dual combination of pomalidomide and dexamethasone (Pd).

For overall survival, there is no statistically significant difference between the treatment arms.

For the patient-reported endpoints, the pharmaceutical company provided evaluations of both time to first-time and sustained improvement and time to first-time and sustained deterioration based on the EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D VAS measurement tools. In the overall view of the baseline values at the start of the study and the available responder analyses, the percentage of patients with a deterioration exceeds the percentage of patients with an improvement to a relevant extent. Against this background and taking into account the expected progressive course of the disease, the evaluations on deterioration are used for the present benefit assessment. Since a deterioration that persists over a period of time is considered to be more relevant for patients than a first-time deterioration due to its

permanence, the present assessment is based on the analyses of the time to permanent deterioration.

In the endpoint category morbidity, there are advantages for Isa-Pd over Pd in the symptoms pain and diarrhoea, for the endpoint category health-related quality of life there are advantages for Isa-Pd in global health status and role functioning.

In terms of side effects, Isa-Pd showed a disadvantage in serious adverse events (CTCAE grade ≥ 3) compared to Pd. In detail, with regard to the specific adverse events bronchitis and blood and lymphatic system disorders (CTCAE grade ≥ 3), there are disadvantages for Isa-Pd compared to Pd.

In the overall analysis of the results on the patient-relevant endpoints, the advantages of Isa-Pd in the endpoint categories morbidity and health-related quality of life are offset by a disadvantage in the side effects. The disadvantage in serious adverse events (CTCAE grade ≥ 3) is considered moderate and does not reach a magnitude that would call into question the positive effects of Isa-Pd in disease-specific symptomatology and health-related quality of life.

Overall, the G-BA concludes that isatuximab in combination with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma in adults who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and who showed disease progression during the last therapy, has a minor additional benefit compared with pomalidomide in combination with dexamethasone.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing, open-label, randomised controlled phase III ICARIA-MM study.

The risk of bias at the study level is rated as low.

Since the benefit assessment is based on the results of only one study, only indications of an additional benefit can be derived with regard to the reliability of the results.

For the endpoint overall survival, the risk of bias is rated as low.

Due to the open-label study design, the results on the patient-reported outcomes in particular are to be regarded as potentially highly biased and thus of limited significance.

The results on patient-reported endpoints are also subject to uncertainty because the effects of infusion-related reactions on morbidity and quality of life do not fall within the time period queried by the questionnaire.

Furthermore, due to potentially incomplete recording of adverse events, especially severe adverse events (CTCAE grade ≥ 3), and lack of usable data on infusion-related reactions, there are uncertainties regarding the results of the endpoint category side effects.

All in all, the available data are subject to uncertainties, which leads to a limitation of the reliability of data. The reliability of data for the additional benefit is classified in the category "hint".

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Sarclisa with the active ingredient isatuximab in combination with pomalidomide and dexamethasone.

Isatuximab is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

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

- Bortezomib in combination with pegylated liposomal doxorubicin

or

- Bortezomib in combination with dexamethasone

or

- Lenalidomide in combination with dexamethasone

or

- Pomalidomide in combination with dexamethasone

or

- Elotuzumab in combination with lenalidomide and dexamethasone

or

- Elotuzumab in combination with pomalidomide 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

Results are available from the open-label, randomised, controlled ICARIA-MM study comparing isatuximab in combination with pomalidomide and dexamethasone (Isa-Pd) to pomalidomide and dexamethasone (Pd).

There is no statistically significant difference for the overall survival.

In the time to permanent deterioration, there are advantages for Isa-Pd in the endpoint category morbidity in the symptoms of pain and diarrhoea and in health-related quality of life in global health status and role functioning.

In terms of side effects, Isa-Pd showed a disadvantage in serious adverse events (CTCAE grade ≥ 3). The disadvantage is considered moderate and does not reach a magnitude that would call into question the positive effects in disease-specific symptomatology and health-related quality of life.

Uncertainties remain for the patient-reported endpoints, as effects of infusion-related reactions on morbidity and quality of life do not fall within the time period queried by the questionnaire, and for side effects due to potentially incomplete coverage and missing data on infusion-related reactions.

Overall, the G-BA concluded that there is a hint for a minor additional benefit for isatuximab in combination with pomalidomide and dexamethasone compared with pomalidomide in combination with dexamethasone.

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

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

The resolution is based on the information from the dossier of the pharmaceutical company.

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 Sarclisa (active ingredient: isatuximab) at the following publicly accessible link (last access: 7 October 2021):

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

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for healthcare professionals and blood banks contains instructions on how to manage the risk of isatuximab interfering with blood typing (indirect antihuman globulin test or indirect Coombs test). Isatuximab-induced interference with blood typing may persist for approximately 6 months after the last infusion of the medicinal product; therefore, healthcare professionals should advise patients to carry their patient identification card with them until 6 months after the end of treatment.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2021).

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

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient or patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Isatuximab in combination with pomalidomide and dexamethasone				
Isatuximab	Cycle 1: on 1, 8, 15 and 22 28-days cycle from cycle 2 onwards: at 1 and 15 28-days cycle	13 cycles	2 - 4	1st year: 28
Pomalidomide	on day 1 - 21 of an 28-days cycle	13 cycles	21	273
Dexamethasone	on 1, 8, 15 and 22 28-days cycle	13 cycles	0 - 2	24
Appropriate comparator therapy				
Carfilzomib in combination with lenalidomide and dexamethasone				
Carfilzomib	1st -12th cycle Day 1, 2, 8, 9, 15, 16 from 13th cycle Day 1, 2, 15, 16 28-days cycle	13 cycles	1st -12th cycle 6	1st year 76
Lenalidomide	Day 1 - 21 28-days cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-days cycle	13 cycles	4	52
Carfilzomib in combination with dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-days cycle	13 cycles	6	78

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-days cycle	13 cycles	8	104
Bortezomib in combination with dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21-days cycle	4 - 8 cycles	4	16 - 32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21-days cycle	4 - 8 cycles	8	32 - 64
Bortezomib in combination with pegylated liposomal doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-days cycle	8 cycles	4	32
Doxorubicin (pegylated, liposomal)	Day 4 21-days cycle	8 cycles	1	8
Lenalidomide in combination with dexamethasone				
Lenalidomide	Day 1 - 21 28-days cycle	13 cycles	21	273
Dexamethasone	1st – 4th cycle Day 1- 4, 9 - 12, 17 - 20 from 5th cycle Day 1 - 4 28-days cycle	13 cycles	1st – 4th cycle 12	1st year 84
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	1st – 2nd cycle Day 1, 8, 15, 22 from 3rd cycle Day 1, 15 28-days cycle	13 cycles	1st – 2nd cycle 4 from 3rd cycle 2	1st year 30
Lenalidomide	Day 1 - 21 28-days cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-days cycle	13 cycles	4	52
Elotuzumab in combination with pomalidomide and dexamethasone				
Elotuzumab	1st – 2nd cycle Day 1, 8, 15, 22 from 3rd cycle Day 1	13 cycles	1st – 2nd cycle 4 from 3rd cycle 1	1st year 19

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
	28-days cycle			
Pomalidomide	Day 1 - 21 of 28 day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-days cycle	13 cycles	4	52
Pomalidomide in combination with dexamethasone				
Pomalidomide	Day 1 - 21 of 28 day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-days cycle	13 cycles	4	52
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: every 14 days From week 25: every 28 days	1st year: 23 Subsequent year: 13	1	1st year: 23
Lenalidomide	Day 1 - 21 28-days cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-days cycle	13 cycles	1st year: 0 (cycle 1 – 2) 2 (cycle 3 – 6) 3 (from cycle 7)	1st year: 29
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1 - 9: 1 x every 7 days Week 10 - 24: every 21 days from week 25: once every 28 days	1st year: 21 Subsequent year: 13	1	1st year: 21
Bortezomib	Day 1, 4, 8, 11 21-days cycle	8 cycles	4	32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8 cycles	6 (cycle 1 - 3) 7 (cycle 4 – 8)	1st year: 53

Consumption:

For dosages depending on body weight or body surface, 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) [2].

Designation of the therapy	Dosage/ Application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Isatuximab in combination with pomalidomide and dexamethasone					
Isatuximab	10 mg/kg	770 mg	1 x 500 mg + 3 x 100 mg	28	1st year: 28 x 500 mg + 84 x 100 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	24	24 x 40 mg
Appropriate comparator therapy					
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² after that 27 mg/m²	1st cycle day 1, 2 38 mg after that 51.3 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg after that 1 x 60 mg	1st year 76	1st year 2 x 10 mg + 2 x 30 mg + 74 x 60 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52	52 x 40 mg
Carfilzomib in combination with dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² after that 56 mg/m²	1st cycle day 1, 2 38 mg after that 106.4 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg after that 2 x 10 mg + 1 x 30 mg + 1 x 60 mg	78	1st year 154 x 10 mg + 78 x 30 mg + 76 x 60 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	104	104 x 20 mg

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

Designation of the therapy	Dosage/ Application	Dose/ patient/ treatment days	Usage 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	32 x 2.5 mg +
Doxorubicin (pegylated, liposomal)	30 mg/m²	57 mg	1 x 50 mg 1 x 20 mg	8	8 x 50 mg + 8 x 20 mg
Bortezomib in combination with dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	16 - 32	16 - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32 - 64	32 – 64 x 20 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 84	1st year 84 x 40 mg
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	10 mg/kg	770 mg	2 x 400 mg	1st year 30	1st year 60 x 400 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	1st - 2nd cycle Day 1, 8,15, 22 28 mg from 3rd cycle Day 1, 15 28 mg Day 8, 22 40 mg	1st - 2nd cycle Day 1, 8,15, 22 28 mg from 3rd cycle Day 1, 15 28 mg Day 8.22 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52	1st year 30 x 8 mg + 30 x 20 mg + 22 x 40 mg
Elotuzumab in combination with pomalidomide and dexamethasone					
Elotuzumab	Cycle 1-2: 10 mg/kg 20 mg/kg = 1,540 mg	Cycle 1-2: 770 mg 1,540 mg	Cycle 1-2: 2 x 400 mg 4 x 400 mg	1st year 8 11	1st year 16 x 400 mg + 44 x 400 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	28 mg -	28 mg	1 x 20 mg + 1 x 8 mg	19	19 x 20 mg + 19 x 8 mg +

Designation of the therapy	Dosage/ Application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	40 mg	40 mg	1 x 40 mg	33	33 x 40 mg
Pomalidomide in combination with dexamethasone					
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	52 x 40 mg
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	16 mg/kg	1,232 mg	3 x 400 mg + 1 x 100 mg	1st year: 23	1st year: 69 x 400 mg + 23 x 100 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 29	1st year 29 x 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	16 mg/kg	1,232 mg	3 x 400 mg + 1 x 100 mg	1st year: 21	1st year: 63 x 400 mg + 21 x 100 mg
Bortezomib	1.3 mg/m^2	2.47 mg	1 x 2.5 mg	32	32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	53	53 x 20 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both 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 based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Isatuximab 500 mg	1 CIS	€ 3,825.79	€ 1.77	€ 215.22	€ 3,608.80

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
Isatuximab 100 mg	1 CIS	€ 788.47	€ 1.77	€ 43.04	€ 743.66
Pomalidomide	21 HC	€ 9,061.21	€ 1.77	€ 516.91	€ 8,542.53
Dexamethasone 40 mg[3]	50 TAB	€ 187.76	€ 1.77	€ 0.00	€ 185.99
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 1,039.39	€ 1.77	€ 48.80	€ 988.82
Carfilzomib 10 mg	1 PSI	€ 222.08	€ 1.77	€ 11.68	€ 208.63
Carfilzomib 30 mg	1 PSI	€ 644.12	€ 1.77	€ 35.05	€ 607.30
Carfilzomib 60 mg	1 PSI	€ 1,277.20	€ 1.77	€ 70.10	€ 1,205.33
Daratumumab 100 mg	1 CIS	€ 467.46	€ 1.77	€ 0.00	€ 465.69
Daratumumab 400 mg	1 CIS	€ 1,827.29	€ 1.77	€ 0.00	€ 1,825.52
Dexamethasone 8 mg[3]	100 TAB	€ 123.13	€ 1.77	€ 8.87	€ 112.49
Dexamethasone 20 mg[3]	10 TAB	€ 32.14	€ 1.77	€ 0.00	€ 30.37
Dexamethasone 20 mg[3]	20 TAB	€ 53.81	€ 1.77	€ 0.00	€ 52.04
Dexamethasone 20 mg[3]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84
Dexamethasone 40 mg[3]	50 TAB	€ 187.76	€ 1.77	€ 0.00	€ 185.99
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 776.39	€ 1.77	€ 42.37	€ 732.25
Pegylated liposomal doxorubicin 50 mg	1 CIS	€ 1,912.37	€ 1.77	€ 105.94	€ 1,804.66
Elotuzumab 400 mg	1 PIC	€ 1,557.64	€ 1.77	€ 85.68	€ 1,470.19
Lenalidomide 25 mg	21 HC	€ 8,330.89	€ 1.77	€ 475.20	€ 7,853.92
Pomalidomide	21 HC	€ 9,061.21	€ 1.77	€ 516.91	€ 8,542.53
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets					

LAUER-TAXE® last revised: 15 October 2021

Costs for additionally required SHI services:

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

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.

[3] Fixed reimbursement rate

Type of service	Costs per pack	Costs after deduction of statutory rebate	Costs per services[4]	Treatment days per year	Costs / patient/ year
Medicinal product to be assessed: ***Isatuximab*** *in combination with pomalidomide and dexamethasone*					
Premedication[5]					
Dexamethasone 40 mg, IV	€ 20.11[3] 10 x 8 mg	€ 17.62 [€ 1.77; € 0.72]	€ 8.81	1st year 28	1st year € 246.68
Paracetamol[6] 500 - 1,000 mg, oral	€ 1.50[7] 20 x 500 mg € 1.06[7] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 28	1st year € 1.90 - € 2.72
Diphenhydramine 25 – 50 mg	€ 8.75[7] 50 x 50 mg	€ 7.91 [€ 0.44; € 0.40]	€ 0.08 - € 0.16	1st year 28	1st year € 2.21 - € 4.43
Appropriate comparator therapy					
Elotuzumab *in combination with lenalidomide and dexamethasone*					
Premedication[8]					
Dexamethasone 8 mg, IV	€ 20.11[3] 10 x 8 mg	€ 17.62 [€ 1.77; € 0.72]	€ 1.76	1st year 30	1st year € 52.86
Dimetindene 1 mg/10 kg bw, IV	€ 18.62 5 x 4 mg	€ 14.93 [€ 1.77; € 1.92]	€ 5.97	1st year 30	1st year € 179.16
Famotidine 20 mg, oral	€ 19.91[3] 100 x 20 mg	€ 17.44 [€ 1.77; € 0.70]	€ 0.17	1st year 30	1st year € 5.23
Paracetamol[6] 500 - 1,000 mg, oral	€ 1.50[7] 20 x 500 mg	€ 1.36 [€ 0.08; € 0.06]	€ 0.07 -	1st year 30	1st year € 2.04 - € 2.91 -

[4] Proportionate share of cost per pack for consumption per treatment day. Rounded interm result.

[5] According to the product information for Sarclisa (last revised: July 2021)

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

[7] 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 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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

Type of service	Costs per pack	Costs after deduction of statutory rebate	Costs per services[4]	Treatment days per year	Costs / patient/ year
	€ 1.06[7] 10 x 1,000 mg	€ 0.97 [€ 0.05; € 0.04]	€ 0.10		
Elotuzumab *in combination with pomalidomide and dexamethasone*					
Premedication[8]					
Dexamethasone 8 mg, IV	€ 20.11[3] 10 x 8 mg	€ 17.62 [€ 1.77; € 0.72]	€ 1.76	1st year 19	1st year € 33.48
Dimetindene 1 mg/10 kg bw, IV	€ 18.62 5 x 4 mg	€ 14.93 [€ 1.77; € 1.92]	€ 5.97	1st year 19	1st year € 113.47
Famotidine 20 mg, oral	€ 19.91[3] 100 x 20 mg	€ 17.44 [€ 1.77; € 0.70]	€ 0.17	1st year 19	1st year € 3.31
Paracetamol[6] 500 - 1,000 mg, oral	€ 1.50[7] 20 x 500 mg € 1.06[7] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 19	1st year € 1.29 - € 1.84 -
Daratumumab *in combination with lenalidomide and dexamethasone*					
Premedication[9]					
Dexamethasone 40 mg, IV	€ 20.11[3] 10 x 8 mg	€ 17.62 [€ 1.77; € 0.72]	€ 8.81	1st year 23	1st year € 202.63
Paracetamol[6] 500 - 1,000 mg, oral	€ 1.50[7] 20 x 500 mg € 1.06[7] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 23	1st year € 1.56 - € 2.23
Dimetindene 1 mg/10 kg bw, IV	€ 18.62 5 x 4 mg	€ 14.93 [€ 1.77; € 1.92]	€ 5.97	1st year 23	1st year € 137.36
Daratumumab *in combination with bortezomib and dexamethasone*					
Premedication[9]					
Dexamethasone 20 mg, IV	€ 16.65[3] 10 x 4 mg	€ 14.44 [€ 1.77; € 0.44]	€ 7.22	1st year 21	1st year € 151.62
Paracetamol[6] 500 - 1,000 mg, oral	€ 1.50[7] 20 x 500 mg € 1.06[7]	€ 1.36 [€ 0.08; € 0.06] € 0.97	€ 0.07 - € 0.10	1st year 21	1st year € 1.43 - € 2.04

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

Type of service	Costs per pack	Costs after deduction of statutory rebate	Costs per services[4]	Treatment days per year	Costs / patient/ year
	10 x 1,000 mg	[€ 0.05; € 0.04]			
Dimetindene 1 mg/10 kg bw, IV	€ 18.62 5 x 4 mg	€ 14.93 [€ 1.77; € 1.92]	€ 5.97	1st year 21	1st year € 125.41

Patients receiving therapy with carfilzomib, daratumumab and lenalidomide should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[10]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

In deviation from this, additional 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	Unit cost	Costs/ patient/ year
Appropriate comparator therapy				
Carfilzomib Daratumumab Lenalidomide	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[11]	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[12]	1	€ 89.50	€ 89.50

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but instead follow the rules for calculating in the Hilfstaxe. The cost

[10] "Update of the S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.:021/011", https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Hepatitis_B_Virusinfektionen_Prophylaxe_Diagnostik_Therapie_2011-abgelaufen.pdf

representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 7 May 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 August 2021.

On 10 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 2 VerfO.

By letter dated 12 May 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient isatuximab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 16 August 2021. The deadline for submitting written statements was 6 September 2021.

The oral hearing was held on 27 September 2021.

By letter dated 29 September 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by IQWiG was submitted to the G-BA on 15 October 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and 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 26 October 2021, and the proposed resolution was approved.

At its session on 4 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 May 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	10 August 2021	New determination of the appropriate comparator therapy
Working group Section 35a	22 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	27 September 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	6 October 2021 20 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	26 October 2021	Concluding discussion of the draft resolution
Plenum	4 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 November 2021

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

Prof. Hecken