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 Elotuzumab (reassessment after the deadline: multiple Myeloma, at least 2 prior therapies, combination with Pomalidomide and Dexamethasone)

of 16 December 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 benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

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

According to Section 35a paragraph 3 SGB V, the G-BA 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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient elotuzumab (Empliciti) to be assessed for the first time on 19 September 2019. For the resolution of 2 April 2020 made by the G-BA in this procedure, a time limit of 2 July 2021 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product elotuzumab recommences when the deadline has expired.

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 5 VerfO on 30 June 2021.

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 1 October 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 elotuzumab compared to 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 elotuzumab.

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 Elotuzumab (Empliciti) in accordance with the product information

Elotuzumab 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.

Therapeutic indication of the resolution (resolution of 16 December 2021):

see approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for elotuzumab in combination with pomalidomide and dexamethasone:

- 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

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

– Elotuzumab in combination with lenalidomide and dexamethasone

or

– Carfilzomib in combination with lenalidomide and dexamethasone

or

– Carfilzomib in combination with dexamethasone

or

– Daratumumab in combination with lenalidomide and dexamethasone

or

– Daratumumab in combination with bortezomib and dexamethasone

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, in principle, 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 advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

Belantamab mafodotin, bortezomib, carfilzomib, carmustine, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, idecabtagen vicleucel, interferon alfa-2b, isatuximab, ixazomib, lenalidomide, melphalan, panobinostat, pomalidomide, prednisolone, prednisone, selinexor 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 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
- Isatuximab – resolutions of 4 November 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.

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 by resolution of 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 corresponding resolution of 6 July 2017 was limited to 1 November 2021, followed by a reassessment after the deadline in parallel with the present benefit assessment procedure. 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 comparator 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), selinexor and idecabtagen vicleuce are not considered as appropriate comparator therapy. The same applies to the newly approved treatment option daratumumab in combination with pomalidomide and dexamethasone, for which the benefit assessment is being conducted in parallel to the present benefit assessment procedure.

In its resolution of 4 November, the G-BA found a hint for a minor additional benefit of isatuximab in combination with pomalidomide and dexamethasone in adults with at least two prior therapies, compared to pomalidomide in combination with dexamethasone. The therapeutic significance of this treatment option, which is still relatively new in the health care context, cannot yet be conclusively assessed. Also by resolution of 4 November 2021, no additional benefit was identified for isatuximab in combination with carfilzomib and dexamethasone in adults with at least one prior therapy, compared to carfilzomib in combination with dexamethasone. These treatment options are not considered as appropriate comparator therapy.

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. The resolution was limited until 1 July 2021, and the corresponding reassessment after the deadline is the subject of the present assessment.

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, 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 treatment 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 elotuzumab in combination with pomalidomide and dexamethasone is assessed as follows:

There is a hint for a considerable additional benefit of elotuzumab 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 have demonstrated disease progression on the last therapy.

Justification:

For the proof of an additional benefit of elotuzumab in combination with pomalidomide and dexamethasone, the pharmaceutical company presented the results of the ELOQUENT-3 study.

ELOQUENT-3 is a multicentre, open-label, randomised controlled phase II study, comparing the triple combination of elotuzumab, pomalidomide and dexamethasone (E-Pd) with the dual combination of pomalidomide and dexamethasone (Pd). Adult patients with relapsed and refractory multiple myeloma, who had received at least 2 prior therapies, were enrolled in the ongoing study, which started in March 2016. For this, patients had to have relapsed after treatment with lenalidomide or a proteasome inhibitor or be refractory to treatment with at least one of these active ingredients. In addition, there had to be treatment refractoriness to most recent prior therapy.

The 117 patients enrolled were randomised 1:1 to the intervention arm (E-Pd; N = 60) and to the comparator arm (Pd; N = 57), stratified by number of prior lines of therapy (2 to 3 vs ≥ 4) and by International Staging System (ISS) stage at the start of study (I to II vs III). A change from the comparator therapy to the intervention therapy is not possible.

ELOQUENT-3 is conducted in 39 study sites across Asia, Europe and North America.

3 data cut-offs are available for the study. The first data cut-off of 21.02.2018 was predefined after reaching a specified number of events for the primary endpoint of progression-free survival. The 2nd data cut-off of 29.11.2018 was requested by the European Medicines Agency

(EMA) as part of the marketing authorisation process to obtain updated data on overall survival. The 3rd data cut-off was predefined after occurrence of 78 deaths on 22.02.2021 (final analysis of overall survival). This data cut-off was still pending at the time of the initial assessment by the G-BA. For the present benefit assessment, the results of this 3rd data cut-off were used.

Extent and probability of the additional benefit

Mortality

Overall survival is defined in the ELOQUENT-3 study as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, there was a statistically significant difference in favour of elotuzumab in combination with pomalidomide and dexamethasone in the total study population.

There was an effect modification by the characteristic "previous stem cell transplant" for overall survival. According to this, there was a statistically significant effect in favour of E-Pd for patients who had not previously received a stem cell transplant. However, there was no significant difference between the treatment groups for patients who had previously received a stem cell transplant.

When interpreting this result, the following relevant uncertainties come into play.

On the one hand, it should be taken into account that the previous, initial assessment of the combination E-Pd by the G-BA, based on the data cut-off of 29 November 2018 of the ELOQUENT-3 study, did not show any corresponding effect modification by the characteristic "previous stem cell transplant" for overall survival.

On the other, in view of the low sample size of the ELOQUENT-3 study, comparatively small patient numbers result for the subgroups investigated. In this respect, the clinical experts in the present written statement procedure also considered a corresponding evaluation to be hardly valid against the background of the limited number of patients.

In addition, no corresponding effect modification by the characteristic "previous stem cell transplant" occurred in comparable studies such as the ELOQUENT-2 study, in which the triple combination of elotuzumab, lenalidomide and dexamethasone (N = 321) was compared with the dual combination of lenalidomide and dexamethasone (N = 325). The ELOQUENT-2 study was a phase III study, in which patients who had received one to three prior therapies, were enrolled. There were no statistically significant differences between the treatment groups, neither for patients with a previous stem cell transplant nor for patients without one[2].

Furthermore, it should be considered that an effect modification by the characteristic "previous stem cell transplant" only resulted for the endpoint of overall survival and for none of the other endpoints of the ELOQUENT-3 study.

[2] Dimopoulos MA, Lonial S, White D, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomised ELOQUENT-2 study. Blood Cancer J. 2020 Sep 4;10(9):91. doi: 10.1038/s41408-020-00357-4. PMID: 32887873; PMCID: PMC7474076.

Against the background of the uncertainties described above, the existing data basis on the observed effect modification by the characteristic "previous stem cell transplant" are not considered sufficient to derive corresponding separate statements on the additional benefit in the overall assessment with the necessary certainty.
For the endpoint of overall survival, treatment with E-Pd in the total population of the ELOQUENT-3 study showed a prolongation of survival time, compared to treatment with Pd, which was assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

PFS was the primary endpoint of the ELOQUENT-3 study and was operationalised as time from randomisation to tumour progression or death from any cause. Progression is defined according to the response criteria of the International Myeloma Working Group (IMWG).

While data on PFS were available for the 2nd data cut-off of 29.11.2018, which formed the basis of the initial assessment of E-Pd by the G-BA, no data on PFS are available for the final analysis of overall survival with data cut-off of 22.02.2021.

Health status (assessed by EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For this endpoint of the benefit assessment, the pharmaceutical company submitted both continuous evaluations (mean difference from the start of study) and responder analyses of the time to initial deterioration on the one hand and of the time to permanent deterioration by ≥ 7, ≥ 10 and ≥ 15 points, respectively, on the other, compared to baseline.

In IQWiG's benefit assessment, the responder analyses of the time to permanent deterioration were not used because the pharmaceutical company did not provide an exact description of the operationalisation and censoring regime. In this respect, further information was provided by the pharmaceutical company during the written statement procedure for the present assessment. According to the pharmaceutical company, patients who showed a one-off deterioration and subsequently presented no further value were considered to have a permanent deterioration. However, no information was provided on how many patients were affected by this in the study arms.
The responder analyses of time to initial deterioration are used for the present assessment.

There was no statistically significant difference between the study arms for any of the three response thresholds. Thus, there are neither positive nor negative effects of elotuzumab in combination with pomalidomide and dexamethasone with regard to the health status.

Symptomatology (surveyed using the MDASI-MM questionnaire)

In the ELOQUENT-3 study, the MDASI-MM questionnaire was used to assess symptomatology. The MDASI-MM is a questionnaire designed to assess symptom severity and how symptoms affect daily life in patients with multiple myeloma.
For the benefit assessment, the pharmaceutical company submitted both continuous evaluations (mean difference from the start of study) and responder analyses of the time to

initial deterioration on the one hand and of the time to permanent deterioration by ≥ 1.5 points (15% of the scale range), on the other, compared to baseline.

For the present assessment, the respective total scores of all items (total symptom severity and symptom interference) are used for symptom severity and for impairment of daily life by symptoms. Responder analyses of time to initial deterioration are also used for symptomatology.

There was no statistically significant difference between the study arms for the endpoints of symptom severity and impairment of daily life by symptoms. Accordingly, there are neither positive nor negative effects of elotuzumab in combination with pomalidomide and dexamethasone with regard to symptomatology.

Quality of life

The endpoint of health-related quality of life was assessed in the ELOQUENT-3 study with the symptom interference score of the MDASI-MM questionnaire. However, this does not fully cover the dimension of health-related quality of life and was already assigned to the endpoint category of morbidity in the initial assessment.
Therefore, no suitable data are available for the assessment of the endpoint category of quality of life.

Side effects

Adverse events (AEs)

Endpoints in the AE category (excluding additional primary tumours) are collected up to 60 days after the last study medication.

Serious adverse events (SAE)

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

Severe AE (CTCAE grade ≥ 3)

For severe adverse events with CTCAE grade ≥ 3, there was a statistically significant difference in the benefit of E-Pd over Pd, based on the total study population. An effect modification by the characteristic "number of previous lines of therapy" was detected. For subjects with 2 or 3 previous lines of therapy, there was a statistically significant advantage for the benefit of E-Pd over Pd. For subjects with 4 or more previous lines of therapy, there was no statistically significant difference.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, no statistically significant difference was detected between the study arms.

Specific AEs

No specific AEs were identified.

In the overall assessment, concerning side effects, E-Pd showed an advantage over Pd with regard to the endpoint of severe adverse events (CTCAE grade ≥ 3). For the endpoints of

serious AE and discontinuation due to AEs, there was no statistically significant differences between the study arms. In the overall assessment of all endpoints, an advantage of E-Pd over Pd is found in the category of side effects.

Overall assessment

For the assessment of the additional benefit of elotuzumab in combination with pomalidomide and dexamethasone (E-Pd), results on mortality (overall survival), morbidity (symptomatology and health status) and side effects are available from the ELOQUENT-3 study in comparison with pomalidomide in combination with dexamethasone (Pd).

For the endpoint of overall survival, the present results show a statistically significant prolongation of survival by treatment with E-Pd compared to treatment with Pd, which is assessed as a significant improvement.

There was no statistically significant difference between the treatment arms for symptomatology (assessed by MDASI-MM) and health status (assessed by EQ-5D VAS).

No suitable data on health-related quality of life are available from the ELOQUENT-3 study.

For side effects, there is an advantage of E-Pd over Pd with regard to the endpoint of severe adverse events (CTCAE grade 3 or 4). There was no difference for the endpoints of serious AE and discontinuation due to AEs. Thus, an overall advantage of E-Pd over Pd can be observed in the category of side effects.

In the overall assessment, the G-BA concludes that there is considerable additional benefit of E-Pd compared to Pd in the treatment of patients with relapsed and refractory multiple myeloma who have already received at least two prior therapies including lenalidomide and a proteasome inhibitor and who have demonstrated disease progression on the last therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the randomised, controlled, open-label phase II ELOQUENT-3 study. The cross-endpoint risk of bias is rated as low for the study.

Although the risk of bias for the endpoint of overall survival is generally considered to be low, it must be conditionally taken into account that there is an effect modification by the characteristic "previous stem cell transplant (yes/no)" with clearly different effects for the two subgroups, albeit with an overall small number of cases. For this reason, the reliability of data of the total study population with regard to the extent of improvement in overall survival is limited.

Due to the open-label study design, there is a high risk of bias in the results for the endpoints on health status and symptomatology from the endpoint category of morbidity. In addition, the return rates of the questionnaires used to collect these endpoints differ between study arms and decrease over the course of the study.

No suitable data on health-related quality of life are available from the ELOQUENT-3 study. Thus, the extent to which the treatment with E-Pd has an effect on the patients' quality of life compared to Pd cannot be assessed.

The risk of bias for the endpoints of side effects (SAE, severe AE (CTCAE grade 3 or 4), and discontinuation due to AEs) is rated as high.

In the overall assessment of the uncertainties described above, a hint for an additional benefit of E-Pd can be derived.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient elotuzumab due to the expiry of the limitation of the resolution of 2 April 2020. Elotuzumab 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 to be:

- 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

- Carfilzomib in combination with lenalidomide and dexamethasone

or

- Carfilzomib in combination with dexamethasone

or

- Daratumumab in combination with lenalidomide and dexamethasone

or

- Daratumumab in combination with bortezomib and dexamethasone

The pharmaceutical company presents results from the open-label, randomised controlled ELOQUENT-3 study, comparing elotuzumab plus pomalidomide and dexamethasone with pomalidomide plus dexamethasone.

For the endpoint of overall survival, E-Pd showed a statistically significant advantage, which was assessed as a significant improvement .

There was no statistically significant difference for symptomatology and health status.

No suitable data on health-related quality of life are available from the ELOQUENT-3 study.

For side effects, the endpoint of severe adverse events (CTCAE grade 3 or 4) shows an advantage of E-Pd.

As a result, the G-BA found a considerable additional benefit of E-Pd compared to Pd.

The reliability of data of the additional benefit identified is classified in the "hint" category. In this regard, among other things, it is taken into account that the subgroup analyses of the characteristic "previous stem cell transplant" show an inhomogeneous effect for the endpoint of overall survival, albeit with an overall small number of cases.

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).

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of isatuximab (resolution of 4 November 2021).

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 Empliciti (active ingredient: elotuzumab) at the following publicly accessible link (last access: 18 August 2021):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 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/ 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 infusion that the dexamethasone dose is given IV as premedication before the infusion and on the other days the dexamethasone can be administered orally.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Eelotuzumab in combination with pomalidomide and dexamethasone				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 28-day cycle From 3rd cycle Day 1 28-day cycle	13 cycles	1st - 2nd cycle 4 From 3rd cycle 1	1st year 19
Pomalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15 and 22 28-day cycle	13 cycles	4	52
Appropriate comparator therapy				
Carfilzomib in combination with lenalidomide and dexamethasone				
Carfilzomib	1st -12th cycle Day 1, 2, 8, 9, 15, 16 From 13th cycle Day 1, 2, 15, 16 28-day cycle	13 cycles	1st -12th cycle 6	1st year 76
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52
Carfilzomib in combination with dexamethasone				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13 cycles	6	78
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-day cycle	13 cycles	8	104
Bortezomib in combination with dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	4 - 8 cycles	4	16 - 32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21-day cycle	4 - 8 cycles	8	32 - 64
Bortezomib in combination with pegylated liposomal doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Doxorubicin (pegylated, lysosomal)	Day 4 21-day cycle	8 cycles	1	8
Lenalidomide in combination with dexamethasone				
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	1st - 4th cycle Day 1- 4, 9 - 12, 17 - 20 From 5th cycle Day 1 - 4 28-day cycle	13 cycles	1st - 4th cycle 12	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-day cycle	13 cycles	1st - 2nd cycle 4 From 3rd cycle 2	1st year 30
Lenalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13 cycles	4	52
Pomalidomide in combination with dexamethasone				
Pomalidomide	Day 1 - 21 28-day cycle	13 cycles	21	273

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone	Day 1, 8, 15, 22 28-day 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-day cycle	13 cycles	21	273
Dexamethasone	Day 1, 8, 15, 22 28-day 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: every 28 days	1st year: 21 Subsequent year: 13	1	1st year: 21
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8 cycles	4	32
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8 cycles	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)[3].

[3] 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	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
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 - 40 mg	28 mg - 40 mg	1 x 20 mg + 1 x 8 mg 1 x 40 mg	19 33	19 x 20 mg + 19 x 8 mg + 33 x 40 mg
Appropriate comparator therapy					
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	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 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	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
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					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Bortezomib	1.3 mg/m^2	2.47 mg	1 x 2.5 mg	16 - 32	16 - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32 - 64	32 – 64 x 20 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 84	1st year 84 x 40 mg
Eelotuzumab 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
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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/m²	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
Dexamethasone	40 mg	40 mg	1 x 40 mg	24	24 x 40 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130 a 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:					
Elotuzumab 400 mg	1 PIC	€ 1,557.64	€ 1.77	€ 85.68	€ 1,470.19
Pomalidomide 4 mg	21 HC	€ 9,061.21	€ 1.77	€ 516.91	€ 8,542.53
Dexamethasone 8 mg[4]	100 TAB	€ 123.13	€ 1.77	€ 8.87	€ 112.49
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84
Dexamethasone 40 mg[4]	50 TAB	€ 187.76	€ 1.77	€ 0.00	€ 185.99
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 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

[4] 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
Daratumumab 400 mg	1 CIS	€ 1,827.29	€ 1.77	€ 0.00	€ 1,825.52
Dexamethasone 8 mg[4]	100 TAB	€ 123.13	€ 1.77	€ 8.87	€ 112.49
Dexamethasone 20 mg[4]	10 TAB	€ 32.14	€ 1.77	€ 0.00	€ 30.37
Dexamethasone 20 mg[4]	20 TAB	€ 53.81	€ 1.77	€ 0.00	€ 52.04
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84
Dexamethasone 40 mg[4]	50 TAB	€ 187.76	€ 1.77	€ 0.00	€ 185.99
Pegylated liposomal doxorubicin 20 mg	1 CIS	€ 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 4 mg	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					

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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[5]	Treatment days per year	Costs/ patient/ year
Medicinal product to be assessed: ***Elotuzumab*** *in combination with pomalidomide and dexamethasone*					
Premedication[6]					
Dexamethasone 8 mg, IV	€ 20.11[4] 10 x 8 mg	€ 17.62 [€ 1.77; € 0.72]	€ 1.76	1st year 19	1st year € 33.48

[5] Proportionate share of cost per pack for consumption per treatment day. Rounded interim result.
[6] According to the product information for Empliciti (last revised: December 2020)

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[5]	Treatment days per year	Costs/ patient/ year
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[4] 100 x 20 mg	€ 17.44 [€ 1.77; € 0.70]	€ 0.17	1st year 19	1st year € 3.31
Paracetamol[7] 500 - 1,000 mg, oral	€ 1.50[8] 20 x 500 mg € 1.06[8] 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 -
Appropriate comparator therapy					
Elotuzumab *in combination with lenalidomide and dexamethasone*					
Premedication[6]					
Dexamethasone 8 mg, IV	€ 20.11[4] 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[4] 100 x 20 mg	€ 17.44 [€ 1.77; € 0.70]	€ 0.17	1st year 30	1st year € 5.23
Paracetamol[7] 500 - 1,000 mg, oral	€ 1.50[8] 20 x 500 mg € 1.06[8] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 30	1st year € 2.04 - € 2.91 -
Daratumumab *in combination with lenalidomide and dexamethasone*					

[7] 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.

[8] 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.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[5]	Treatment days per year	Costs/ patient/ year
Premedication[9]					
Dexamethasone 40 mg, IV	€ 20.11[4] 10 x 8 mg	€ 17.62 [€ 1.77; € 0.72]	€ 8.81	1st year 23	1st year € 202.63
Paracetamol[7] 500 - 1,000 mg, oral	€ 1.50[8] 20 x 500 mg € 1.06[8] 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[4] 10 x 4 mg	€ 14.44 [€ 1.77; € 0.44]	€ 7.22	1st year 21	1st year € 151.62
Paracetamol[7] 500 - 1,000 mg, oral	€ 1.50[8] 20 x 500 mg € 1.06[8] 10 x 1,000 mg	€ 1.36 [€ 0.08; € 0.06] € 0.97 [€ 0.05; € 0.04]	€ 0.07 - € 0.10	1st year 21	1st year € 1.43 - € 2.04
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.

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

[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

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

3. Bureaucratic costs 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.

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

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

4. Process sequence

At its session on 12 February 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 24 August 2021.

On 30 June 2021, the pharmaceutical company submitted a dossier for the benefit assessment of elotuzumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 5 VerfO.

By letter dated 1 July 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 elotuzumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 October 2021. The deadline for submitting written statements was 22 October 2021.

The oral hearing was held on 8 November 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 7 December 2021, and the proposed resolution was approved.

At its session on 16 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 February 2019	Determination of the appropriate comparator therapy
	24 August 2021	New determination of the appropriate comparator therapy
Working group Section 35a	3 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	8 November 2021	Conduct of the oral hearing
Working group Section 35a	17 November 2021 1 December 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	7 December 2021	Concluding discussion of the draft resolution
Plenum	16 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 December 2021

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

Prof. Hecken