Justification

Gemeinsamer Bundesausschuss

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

of 2 April 2020

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for 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 elotuzumab (Empliciti®) was listed for the first time on 1 June 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 23 August 2019, elotuzumab received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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, 12 December 2008, p. 7).

On 19 September 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient atezolizumab with the new therapeutic indication "Empliciti 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 (see sections 4.2 and 5.1)" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 January 2020, 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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of elotuzumab.

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

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

2.1.1 Approved therapeutic indication of elotuzumab (Empliciti®) in accordance with the product information

Empliciti 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 (see sections 4.2 and 5.1).

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

- 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

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

or

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In principle, the chemotherapeutic agents cyclophosphamide, melphalan, doxorubicin, pegylated liposomal doxorubicin, carmustine, and vincristine; the immunomodulators lenalidomide and pomalidomide; the proteasome inhibitors bortezomib, carfilzomib, and ixazomib; the histone deacetylase inhibitor panobinostat; the monoclonal antibodies daratumumab and elotuzumab; the glucocorticoids dexamethasone, prednisolone and prednisone; and the immunostimulant interferon alfa-2b are approved in the therapeutic indication. The marketing authorisation is partly linked to (specified) combination partners as well as to the type of previous therapy.

On 2. A non-medicinal therapy cannot be considered in the present therapeutic indication. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for patients at the time of the current therapy.

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

- Panobinostat – resolution of 17 March 2016
- Pomalidomide – resolution of 17 March 2016
- Elotuzumab – resolution of 1 December 2016
- Ixazomib – resolution of 6 July 2017
- Carfilzomib – resolution of 15 February 2018
- Daratumumab – resolution of 15 February 2018

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies. Accordingly, the treatment of patients who have already received two previous therapies

will primarily be based on the active ingredients bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, panobinostat, and pomalidomide.

In the benefit assessment on pomalidomide in combination with dexamethasone, with resolution of 17 March 2016, a hint for a considerable additional benefit in the treatment of patients with relapsed and refractory multiple myeloma after two previous therapies (including lenalidomide and bortezomib) was found for which dexamethasone (high dose) is the patient-individual therapy according to the doctor's instructions. For patients for whom dexamethasone (high dose) is not the patient-individual therapy according to the doctor's instructions, an additional benefit is not proven. With resolution of 1 December 2016, the additional benefit of elotuzumab in combination with lenalidomide and dexamethasone was evaluated with a hint for a minor additional benefit. For carfilzomib, a resolution of 15 February 2018 found a hint for a considerable additional benefit both in combination with lenalidomide and dexamethasone and for the dual combination with dexamethasone. Also by resolution of 15 February 2018, there was an indication of a considerable additional benefit for daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone. Elotuzumab in combination with lenalidomide and dexamethasone; carfilzomib in combination with dexamethasone or lenalidomide and dexamethasone as well as daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone are already approved for the treatment of patients with only one previous line of therapy. However, the benefit assessments were based on studies in which a considerable number of patients with at least two prior therapies had been included. Accordingly, study evidence is also available for the present indication. Thus, these therapeutic options are considered to be appropriate comparator therapies for the present indication.

In contrast, no additional benefit could be demonstrated for daratumumab as monotherapy in patients already treated with a protease inhibitor and an immunomodulator (resolution of 15 February 2018). For panobinostat in combination with bortezomib and dexamethasone for the treatment of patients who have received at least two prior therapies including bortezomib and an immunomodulatory substance as well as for ixazomib in combination with lenalidomide and dexamethasone, the evidence available does not allow a conclusive assessment. Accordingly, these therapeutic options are not determined to be appropriate comparator therapies.

The dual combinations of bortezomib or lenalidomide with dexamethasone continue to be given appropriate priority in the therapeutic indication. For this reason, these options are also considered to be appropriate comparator therapies in the therapeutic indication.

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 therefore regarded as 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 contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of elotuzumab is assessed as follows.

Hint for a considerable additional benefit

Justification:

The ELOQUENT-3 study was included in the present benefit assessment. The ELOQUENT-3 study is an ongoing, open-label, randomised, controlled Phase II study comparing a triple combination of elotuzumab, pomalidomide, and dexamethasone (E-Pd) with the dual combination of pomalidomide and dexamethasone (Pd).

Patients with relapsed and refractory multiple myeloma who had received at least 2 prior therapies were enrolled. Patients had to have suffered a relapse after treatment with lenalidomide or a proteasome inhibitor or had to be refractory to therapy with at least one of these active ingredients. In addition, therapy refractoriness compared with the last previous therapy had to be present.

In total, the study includes 117 randomised patients. Neither patients nor study personnel are blinded to the treatment. In the ELOQUENT-3 study, the randomisation of patients was stratified according to the number of prior lines of therapy (2–3 versus ≥ 4) and stage according to the international staging system (ISS stage) at the start of study (I–II versus III) A change from comparator therapy to intervention therapy is not possible.

In the study, treatment with the study medication was carried out according to the product information.

2 data cut-offs are available for the study. The first data cut-off took place after a pre-defined number of progression events for the primary endpoint progression-free survival. The 2nd data cut-off was requested by the European Medicines Agency (EMA) as part of the approval process to obtain current data on overall survival. The 2nd data cut-off is the basis of the present benefit assessment. For this data cut-off, results for the relevant endpoint categories mortality, morbidity, and side effects are available.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival, there is a statistically significant difference in favour of E-Pd compared with Pd (hazard ratio (HR): 0.54 [95% confidence interval (CI): 0.30; 0.96]; p value 0.034). The median survival time was not achieved in the patient group receiving E-Pd at the 2nd data cut-off of 29 November 2018.

This is assessed as a significant prolongation of overall survival under elotuzumab in combination with pomalidomide and dexamethasone. There is, therefore, a considerable additional benefit for this endpoint.

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 by any cause. Progression is defined in accordance with the response criteria of the International Myeloma Working Group (IMWG).

For PFS, there is a statistically significant difference in favour of elotuzumab (hazard ratio (HR): 0.499 [95% confidence interval (CI): 0.325; 0.765]; p value 0.0011). The patients in the E-Pd group have a progression-free survival advantage of 5.55 months (median) over patients in the Pd group.

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

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on additional benefit remains unaffected.

Health status (surveyed using EQ-5D VAS)

In the ELOQUENT-3 study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company presented both continuous evaluations (mean difference compared with the start of study) and responder analyses for the time to deterioration for this endpoint.

As a minimal important difference (MID) the pharmaceutical company defines a change of 7 or 10 points as a sensitivity analysis and refers in this respect to the study by Pickard *et al.*, 2007. This responder analysis was not used in the IQWiG dossier evaluation because the study underlying the derivation of the MID (Pickard *et al.*, 2007) of the IQWiG was classified as unsuitable to validate the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. In addition, the IQWiG does not consider the ECOG-PS and FACT-G anchors used in the study to be suitable for the derivation of MID. Against the background that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean differences and taking into account that the validation study in question has already been used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology. Based on an MID of 7 points and an MID of 10 points, the responder analyses show no statistically significant difference between the E-Pd and Pd treatment arms.

For the evaluations of the change from the baseline of the EQ-5D VAS, the pharmaceutical company presents an MMRM analysis. This evaluation based on mean differences also shows no statistically significant difference between the treatment groups.

Thus, an additional benefit of elotuzumab combination therapy compared with pomalidomide and dexamethasone for the endpoint health status is not proven.

Symptomatology (surveyed using the MDASI-MM questionnaire)

In the ELOQUENT-3 study, the MDASI-MM questionnaire was used to record the symptomatology. The MDASI-MM is a questionnaire for assessing the severity of symptoms and the impairment of daily life through symptoms in patients with multiple myeloma. The benefit assessment included the 2 overarching scores for severity of symptoms and impairment of daily life through symptomatology.

For the endpoints severity symptoms and impairment of daily life through symptoms, there is no statistically significant difference between the treatment groups. Accordingly, an additional benefit of elotuzumab combination therapy compared with pomalidomide in combination with dexamethasone for the endpoint category symptomatology is not proven.

Quality of life

In the ELOQUENT-3 study, the endpoint health-related quality of life was assessed with the symptom interference score of the MDASI-MM questionnaire. However, this does not fully cover the dimension of health-related quality of life. There are therefore no suitable data to assess the endpoint category quality of life.

Side effects

Adverse events (AE) in total

Adverse events occurred at least once in almost all patients regardless of the treatment arm. The results on the endpoint "Adverse events" (AE) are presented only as a supplement because the operationalisation of side effects also includes events that are not patient-relevant.

Serious AE, discontinuation because of adverse events

For the endpoints "serious adverse events" (SAE) and "therapy discontinuation because of AE", there are no statistically significant effects between the treatment groups.

Severe AE (CTCAE grade 3–4)

For the endpoint "severe AE" (CTCAE grade 3–4), an effect modification is shown by the characteristic number of previous lines of therapy. For patients with 2 or 3 previous lines of therapy, there is a statistically significant effect to the benefit of E-Pd compared with Pd. For patients with 4 or more previous lines of therapy, there is no statistically significant difference between the treatment groups.

Specific adverse events

For the specific AE anaemia and neutropoenia, there is a statistically significant difference to the advantage of E-Pd.

In the overall view of the results on side effects, there are statistically significant differences in severe AE (CTCAE grade 3 to 4) for patients with 2 or 3 previous lines of therapy and in detail for the specific adverse events neutropoenia and anaemia. These show positive effects of E-Pd compared with Pd. In the overall consideration of all endpoints, a slight advantage of E-Pd compared with Pd was found in the category of side effects.

Overall assessment/conclusion

For the assessment of the additional benefit of E-Pd for the treatment of patients with relapsed and refractory multiple myeloma who have already received at least two previous therapies, including lenalidomide and a proteasome inhibitor, and have demonstrated disease progression under the last therapy, results from the ELOQUENT-3 study on mortality (overall survival), morbidity, and side effects are available.

For overall survival, the ELOQUENT-3 study shows an advantage of E-Pd over Pd; this is classified as considerable.

In the morbidity category, there is no statistically significant difference between the treatment arms for the endpoints health status and symptomatology.

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

In the overall view of the results on side effects, there are statistically significant differences in severe AE (CTCAE grade 3 to 4) for patients with 2 or 3 previous lines of therapy and in detail for the specific adverse events neutropoenia and anaemia. These show positive effects of E-

Pd compared with Pd. In the overall consideration of all endpoints, a slight advantage of E-Pd compared with Pd was found in the category of side effects.

In the overall view, the G-BA concludes that E-Pd has a considerable additional benefit compared with 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 have demonstrated progression on the last therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the randomised, controlled, open ELOQUENT-3 Phase II study.

At the endpoint level, the bias risk of bias for the endpoints overall survival is estimated to be low. Uncertainties exist in that the results on the overall survival endpoint from the ELOQUENT-3 study are still not particularly meaningful, especially because of the low event rates in the study arms so far and the relatively short observation period. In the E-Pd study arm, the median survival time had not yet been achieved on 29 November 2018. To date, 62% of the planned 78 events for overall survival in the ELOQUENT-3 study have occurred. The broad confidence interval for the effect estimator hazard ratio reflects the low precision of the estimate.

Because of the open study design, there is a high risk of bias for the results for the endpoints on health status and symptomatology from the endpoint category morbidity. Furthermore, the return rates of the questionnaires used to survey these endpoints differ between the 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, it cannot be assessed to what extent therapy with E-Pd compared with Pd affects the quality of life of the patients.

The risk of bias for the endpoints on side effects (SAE, severe AE (CTCAE grade 3 or 4), discontinuation because of AE, and specific AE) is considered high.

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

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of elotuzumab in combination with pomalidomide and dexamethasone has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The present assessment is based on an interim evaluation of the currently ongoing ELOQUENT-3 study. The data on overall survival show a low number of events at the time of the present data cut-off of 29 November 2018. For the still ongoing study, the final analysis is pending after reaching 78 deaths.

Against the background that further overall survival data that may be relevant for assessing the additional benefit of elotuzumab combination therapy for patients with relapsed and refractory multiple myeloma are expected, it is justified to limit the duration of this resolution until further scientific evidence becomes available to assess the additional benefit of elotuzumab.

Conditions of the limitation

For the renewed benefit assessment after the deadline, the results of the final analysis after reaching 78 events in the overall survival endpoint from the currently ongoing ELOQUENT-3 study should be presented in the dossier on all endpoints used to demonstrate an additional benefit for patients with relapsed and refractory multiple myeloma.

For this purpose, the G-BA considers a limitation of the resolution until 1 July 2021 to be appropriate.

In principle, an extension may be granted if it is justified and clearly demonstrated that the period of the limitation is not sufficient.

In accordance with Section 3, paragraph 1, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 7 VerfO, the procedure for the benefit assessment of the medicinal product elotuzumab shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of elotuzumab in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for the medicinal product elotuzumab can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 – 4 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient elotuzumab.

The therapeutic indication assessed here is as follows: Empliciti 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 (see sections 4.2 and 5.1).

The G- BA determined 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 to be appropriate comparator therapies. For the assessment, the pharmaceutical company presents the ongoing, open-label, randomised, controlled Phase II study in which a triple combination of E-Pd is compared with the double combination Pd.

For overall survival, the study shows a considerable advantage of E-Pd compared with Pd.

In the overall consideration of all endpoints, neither an advantage nor a disadvantage of E-Pd compared with Pd was found in the morbidity category.

No suitable data on health-related quality of life are available. Thus, it cannot be assessed to what extent therapy with E-Pd with Pd affects the quality of life of the patients.

In the overall consideration of all endpoints, a slight advantage of E-Pd compared with Pd was found in the category of side effects.

From the uncertainties described, a hint for an additional benefit of E-Pd can be derived.

In the overall view, there is a hint for a considerable additional benefit for E-Pd compared with Pd in the treatment of patients with relapsed and refractory multiple myeloma who have

received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and have demonstrated progression on the last therapy.

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).

This resolution is based on approx. 2300 patients from the resolutions on pomalidomide and panobinostat of 2016 and resolution on daratumumab of 2018. A rate of increase in 5-year prevalence (from 2009 to 2014) of 1.43% will be applied to this number of approx. 2300 patients determined in 2016. This results in 2470 patients for 2019 in the SHI target population.

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 November 2019):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2020).

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

The annual treatment costs shown refer to the first year of treatment.

Treatment duration:

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”, the time intervals between individual treatments, and for the maximum treatment duration if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Elotuzumab	Cycle 1 & 2: On Day 1, 8, 15, and 22 of a 28-day cycle From Cycle 3: On Day 1 of a 28-day cycle	2 11	4 1	19
Pomalidomide	On Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone i.v.	Cycle 1 & 2: On Day 1, 8, 15, and 22 of a 28-day cycle From Cycle 3: On Day 1 of a 28-day cycle	2 11	4 1	19
Dexamethasone, oral	On Day 1, 8, 15, and 22 of a 28-day cycle	13	4	52
Appropriate comparator therapy				
Bortezomib in combination with dexamethasone				
Bortezomib	On Day 1, 4, 8, and 11 of a 21-day cycle	4–8	4	16–32
Dexamethasone	On Day 1, 2, 4, 5, 8, 9, 11, and	4–8	8	32–64

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	12 of a 21-day cycle			
Lenalidomide in combination with dexamethasone				
Lenalidomide	On Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone	Cycle 1–4: on Day 1–4, 9–12, and 17–20 of a 28-day cycle From Cycle 5: On Day 1 through 4 of a 28-day cycle	4 9	12 4	84
Pomalidomide in combination with dexamethasone				
Pomalidomide	On Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone	On Day 1, 8, 15, and 22 of a 28-day cycle	13	4	52
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	Cycle 1 & 2: on Day 1, 8, 15, and 22 of a 28-day cycle From Cycle 3: on Day 1 and Day 15 of a 28-day cycle	2 11	4 2	30
Lenalidomide	On Day 1–21 of a 28-day cycle	13	21	273

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Dexamethasone	On Day 1, 8, 15, and 22 of a 28-day cycle	13	4	52
Carfilzomib in combination with lenalidomide and dexamethasone				
Carfilzomib	Cycle 1–12: on Day 1, 2, 8, 9, 15, and 16 of a 28-day cycle From Cycle 13: on Day 1, 2, 15, and 16 of a 28-day cycle	12 1	6 4	76
Lenalidomide	On Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone	On Day 1, 8, 15, and 22 of a 28-day cycle	13	4	52
Carfilzomib in combination with dexamethasone				
Carfilzomib	On Day 1, 2, 8, 9, 15, and 16 of a 28-day cycle	13	6	78
Dexamethasone	On Day 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle	13	8	104
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	28 day cycle Cycle 1 and 2:	2 4	4 2	23

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	every 7 days Cycle 3–6: every 14 days From Cycle 7: every 28 days	7	1	
Lenalidomide	On Day 1–21 of a 28-day cycle	13	21	273
Dexamethasone[2]	On Day 1, 8, 15, and 22 of a 28-day cycle	13	0–3	29
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	21-day cycle Cycle 1–3: every 7 day Cycle 4–8: every 21 days From Cycle 9: every 28 days	15	3 1	21
Bortezomib	On Day 1, 4, 8, and 11 of a 21-day cycle	8	4	32
Dexamethasone[2]	On Day 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle	8	8	53

[2] On the days of the daratumumab infusion, the dose of dexamethasone was given as pre-medication before the infusion.

Usage and consumption:

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[3]

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Elotuzumab	10 mg/kg = 770 mg 20 mg/kg = 1,540 mg	770 mg 1,540 mg	2 × 400 mg – 4 × 400 mg	8 – 11	16 × 400 mg – 44 × 400 mg
Pomalidomide	4 mg	4 mg	1 × 4 mg	273	273 × 4 mg
Dexamethasone i.v.	8 mg	8 mg	1 × 8 mg	19	19 × 8 mg
Dexamethasone	28 mg – 40 mg	28 mg 40 mg	1 × 20 mg + 1 × 8 mg 1 × 40 mg	19 33	19 × 20 mg + 19 × 8 mg 33 × 40 mg
Appropriate comparator therapy					
Bortezomib in combination with dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 × 2.5 mg	16 – 32	16 × 2.5 mg – 32 × 2.5 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	32 – 64	32 × 20 mg – 64 × 20 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	84	84 × 40 mg
Pomalidomide in combination with dexamethasone					
Pomalidomide	4 mg	4 mg	1 × 4 mg	273	273 × 4 mg

[3] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Dexamethasone	40 mg	40 mg	1 × 40 mg	52	52 × 40 mg
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	10 mg/kg = 770 mg	770 mg	2 × 400 mg	30	60 × 400 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	28 mg – 40 mg	28 mg 40 mg	1 × 20 mg + 1 × 8 mg 1 × 40 mg	30 22	30 × 20 mg + 30 × 8 mg 22 × 40 mg
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	On Day 1 and 2 of cycle 1: 20 mg/m² subsequently 27 mg/m²	38 mg – 51.3 mg	1 × 10 mg + 1 × 30 mg 1 × 60 mg	74	2 × 10 mg + 2 × 30 mg 74 × 60 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	52	52 × 40 mg
Carfilzomib in combination with dexamethasone					
Carfilzomib	On Day 1 and 2 of cycle 1: 20 mg/m² subsequently 56 mg/m²	38 mg – 106.4 mg	1 × 10 mg + 1 × 30 mg 1 × 60 mg + 1 × 30 mg + 2 × 10 mg	78	76 × 60 mg + 78 × 30 mg + 154 × 10 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	104	104 × 20 mg
Daratumumab in combination with lenalidomide and dexamethasone					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Daratumumab	16 mg/kg	1232 mg	3 × 400 mg + 1 × 100 mg	23	69 × 400 mg + 23 × 100 mg
Lenalidomide	25 mg	25 mg	1 × 25 mg	273	273 × 25 mg
Dexamethasone	40 mg	40 mg	1 × 40 mg	29	29 × 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	16 mg/kg	1232 mg	3 × 400 mg + 1 × 100 mg	21	21 × 100 mg 63 × 400 mg
Bortezomib	1.3 mg/m^2	2.47 mg	1 × 2.5 mg	32	32 × 2.5 mg
Dexamethasone	20 mg	20 mg	1 × 20 mg	53	53 × 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 Sections 130 and 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 product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Elotuzumab	1 PIK	€ 1,557.64	€ 1.77	€ 85.68	€ 1,470.19
Pomalidomide	21 HC	€ 9,647.26	€ 1.77	€ 550.38	€ 9,095.11
Dexamethasone 8 mg[4]	10 SFI	€ 20.11	€ 1.77	€ 0.72	€ 17.62

[4] Fixed reimbursement rate

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Dexamethasone 8 mg[4]	100 TAB	€ 123.13	€ 1.77	€ 8.86	€ 112.50
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0	€ 116.84
Dexamethasone 40 mg[4]	50 TAB	€ 187.76	€ 1.77	€ 0	€ 185.99
Appropriate comparator therapy					
Bortezomib	1 PIJ	€ 1,183.73	€ 1.77	€ 55.65	€ 1,126.31
Carfilzomib 10 mg	1 PIF	€ 222.08	€ 1.77	€ 11.68	€ 208.63
Carfilzomib 30 mg	1 PIF	€ 644.12	€ 1.77	€ 35.05	€ 607.30
Carfilzomib 60 mg	1 PIF	€ 1,277.20	€ 1.77	€ 70.10	€ 1,205.33
Daratumumab 100 mg	1 CIS	€ 506.73	€ 1.77	€ 27.44	€ 477.52
Daratumumab 400 mg	1 CIS	€ 1,979.57	€ 1.77	€ 109.78	€ 1,868.02
Dexamethasone 8 mg[4]	10 SFI	€ 20.11	€ 1.77	€ 0.72	€ 17.62
Dexamethasone 8 mg[4]	100 TAB	€ 123.13	€ 1.77	€ 8.86	€ 112.50
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0	€ 116.84
Dexamethasone 40 mg[4]	50 TAB	€ 187.76	€ 1.77	€ 0	€ 185.99
Elotuzumab	1 PIK	€ 1,557.64	€ 1.77	€ 85.68	€ 1,470.19
Lenalidomide	21 HC	€ 8,175.19	€ 1.77	€ 466.31	€ 7,707.11
Pomalidomide	21 HC	€ 9,647.26	€ 1.77	€ 550.38	€ 9,095.11
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIK = powder for the preparation of an injection solution concentrate; PIJ = powder for the preparation of an injection solution; PIF powder for the preparation of an infusion solution; TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services:

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the SHI in accordance with Section 12, paragraph 7 AM-RL (information as accompanying medication in

the product information of the prescription medicinal product) are not subject to the current medicinal product price regulation. Instead, for these, in accordance with Section 129, paragraph 5a SGB V when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Medicinal product to be assessed: Elotuzumab in combination with pomalidomide and dexamethasone							
Elotuzumab							
Dexamethasone 8 mg i.v.	10 SFI	€ 20.11	€ 1.77	€ 0.72	€ 17.62	19	€ 33.48
Dimetindene i.v. 1 mg/10 kg i.v.	5 SFI	€ 18.62	€ 1.77	€ 1.97	€ 14.88	19	€ 113.09
Ranitidine 50 mg i.v.	5 CIS	€ 15.08	€ 1.77	€ 0.19	€ 13.12	19	€ 49.86
Appropriate comparator therapy							
Elotuzumab in combination with lenalidomide and dexamethasone							
Elotuzumab							
Dexamethasone 8 mg i.v.[5]	10 SFI	€ 20.11	€ 1.77	€ 0.72	€ 17.62	30	€ 52.87
Dimetindene i.v. 1 mg/10 kg	5 SFI	€ 18.62	€ 1.77	€ 1.97	€ 14.88	30	€ 178.56
Ranitidine 50 mg i.v.	5 CIS	€ 15.08	€ 1.77	€ 0.19	€ 13.12	30	€ 78.72
Daratumumab in combination with lenalidomide and dexamethasone							
Daratumumab in combination with bortezomib and dexamethasone							
Dexamethasone 20 mg i.v.[5]	5 × 4 mg SFI	€ 13.98	€ 1.77	€ 0.23	€ 11.98	1	€ 11.98
Dexamethasone 20 mg[5]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84	22	€ 51.41

[5] Fixed reimbursement rate

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/year	Costs/patient/year
Paracetamol 500–1,000 mg[5]	20 × 500 mg TAB	€ 1.50	€ 0.08	€ 0.06	€ 1.36	23	€ 1.56 – 3.13
Dimetindene i.v. 1 mg/10 kg	5 SFI	€ 18.62	€ 1.77	€ 1.97	€ 14.88	23	€ 136.90
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; TAB = tablets							

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 10. Supplementary Agreement to the Agreement on Pricing of Substances and Preparations of Substances of 1 March 2020), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 February 2019.

On 19 September 2019, 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 2 VerfO.

By letter dated 20 September 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient elotuzumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 December 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 January 2020. The deadline for submitting written statements was 23 January 2020.

The oral hearing was held on 10 February 2020.

By letter dated 10 February 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 March 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 February 2019	Determination of the appropriate comparator therapy
Working group Section 35a	5 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	10 February 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 February 2020 4 March 2020 18 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken