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 Belantamab mafodotin (reassessment after the deadline: multiple myeloma, at least 4 prior therapies, monotherapy)

of 5 October 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient belantamab mafodotin (Blenrep) to be assessed for the first time on 14 September 2020. For the resolution of 4 March 2021 made by the G-BA in this procedure, a limitation up to 1 September 2022 was pronounced. At the pharmaceutical company's request, this limitation was extended until 1 April 2023 by the resolution of the G-BA of 17 November 2022.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product Blenrep recommences when the deadline has expired.

The pharmaceutical company submitted the dossier for the benefit assessment to the G-BA in due time on 31 March 2023 (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO).

Belantamab mafodotin for the treatment of multiple myeloma (at least 4 prior therapies, monotherapy) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs.

The Committee for Medicinal Products for Human Use (CHMP) of the EMA decided against the extension of the marketing authorisation for belantamab mafodotin in its expert's report of 15 September 2023. The legally binding decision on the prolongation of the marketing authorisation shall be taken by the Commission. Until the Commission reaches a decision, belantamab mafodotin remains a reimbursable medicinal product within the meaning of Section 35a SGB V.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 3 July 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-05) 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 studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7,

sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of belantamab mafodotin.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Belantamab mafodotin (Blenrep) in accordance with the product information

Blenrep is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Therapeutic indication of the resolution (resolution of 21 September 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

The G-BA classifies the extent of the additional benefit of belantamab mafodotin to be assumed solely from a legal point of view according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V on the basis of the criteria in Section 5, paragraph 7 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. An additional benefit is present according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, but is non-quantifiable since the scientific data does not allow a quantification.

Justification:

For the benefit assessment of the active ingredient belantamab mafodotin, the pharmaceutical company submits the still ongoing, randomised, open-label, multicentre phase III study DREAMM-3 comparing belantamab mafodotin versus pomalidomide in combination with dexamethasone as well as the pivotal, non-controlled phase II study DREAMM-2.

DREAMM-3 study

The DREAMM-3 study is an open-label, randomised, multicentre phase III study comparing belantamab mafodotin with pomalidomide in combination with dexamethasone. This study enrolled patients with relapsed/ refractory multiple myeloma who had previously received 2 or more lines of therapy, including at least two consecutive cycles of lenalidomide and a PI, and who had documented disease progression or no response within 60 days of completion of the last treatment.

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

A total of 325 patients were enrolled in the study and randomised in a 2:1 ratio to either treatment with belantamab mafodotin (N = 218) or pomalidomide in combination with dexamethasone (N = 107). Randomisation was stratified by previous anti-CD38 monoclonal antibody treatment (yes/ no), ISS stage (I/II or III) and number of previous lines of treatment (≤ 3 versus > 3). Treatment with the study medication was given until disease progression, death, unacceptable toxicities, withdrawal of consent, lost to follow-up or end of study.

PFS is defined as the primary endpoint of the study. Other patient-relevant endpoints include overall survival as well as other endpoints in the categories of morbidity, health-related quality of life and side effects.

Patient recruitment started in April 2020. The study has not yet been completed. For the present assessment, the results of the primary data cut-off from 12.09.2022 are relevant.

For the present benefit assessment, a sub-population 5L+ was formed, which was tailored according to the marketing authorisation. This includes only 44 subjects ($n_{belantamab\ mafodotin}$ = 29; $n_{Pom/Dex}$ = 15). For many of the demographic and disease-specific baseline characteristics, patients in the treatment arms were comparable. However, differences are shown between the study arms for ISS stage, prior stem cell transplantation and in terms of the number of prior lines of therapy. Due to the observed imbalances of some baseline characteristics and against the background that the selection criteria of the sub-population are only partially taken into account by the stratification factors, it is unclear whether structural equality between the treatment arms in the sub-population can be assumed.

DREAMM-2 study

The DREAMM-2 study is a multicentre phase II study to evaluate the efficacy and safety of two doses of belantamab mafodotin in patients with multiple myeloma who have received 3 or more prior lines of therapy, are refractory to a proteasome inhibitor and an immunomodulatory agent, and have failed treatment with an anti-CD38 antibody. The median age of the study participants at start of study was 65 years. The study was conducted in 8 countries and 58 study sites, including Germany.

Doses of 2.5 and 3.4 mg/kg body weight (BW) were studied in 2 parallel cohorts or treatment arms. Allocation to the 2 doses was randomised. Treatment with belantamab mafodotin was given until disease progression, death or the occurrence of unacceptable toxicities. A total of 221 patients were enrolled in the study, 97 of whom were in the treatment cohort relevant to the assessment, in which the previously frozen belantamab mafodotin solution was used at the PI-compliant dosage of 2.5 mg/kg BW. The DREAMM-2 study lacks appropriate controls. According to the inclusion criteria, study participants had to have failed at least 3 previous anti-myeloma therapies. Since 95% of the patients included in the cohort relevant for the assessment had already received ≥ 4 therapies prior to start of study, the relevant study population essentially corresponds to the therapeutic indication.

The primary endpoint of the study was the overall response according to the independent review committee. Other patient-relevant endpoints included overall survival and endpoints on symptomatology and health status. In addition, endpoints of the categories health-related quality of life and side effects were collected.

Patient recruitment started in June 2018. The study has been completed. For the present assessment, the results of the final data cut-off from 31.03.2022 are relevant.

On the expert's report of the Committee for Medicinal Products for Human Use (CHMP) of the EMA dated September 2023

The Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended at its session of September 2023 that the conditional marketing authorisation for belantamab mafodotin should not be renewed.

As no comparator data were available at the time of the initial marketing authorisation of belantamab mafodotin, a further study was requested by the CHMP to confirm safety and efficacy. From the CHMP's point of view, the efficacy of belantamab mafodotin could not be confirmed in this study (DREAMM-3 study). Therefore, the CHMP recommended to the European Commission not to renew the marketing authorisation in the EU.

At the time of the present resolution on the benefit assessment of belantamab mafodotin after the expiry of the limited period of validity of the resolution on the initial benefit assessment of belantamab mafodotin, a decision by the European Commission in this regard is still pending.

Mortality

The overall survival is defined in the DREAMM-2 and DREAMM-3 studies as the time from randomisation to death from any cause.

There is no statistically significant difference in overall survival between the study arms at the primary data cut-off of the DREAMM-3 study from 12 September 2022.

In the assessment-relevant sub-population of the DREAMM-3 study, 16 subjects (55%) died in the belantamab mafodotin arm and 4 subjects (27%) died in the pomalidomide/ dexamethasone arm. The median survival time in the intervention arm is 9.5 months (95% CI: [5.1; n.c.]), while it has not yet been reached in the control arm. As of the final data cut-off of the DREAMM-2 study on 31 March 2022, a median survival time of 15.3 months was observed with belantamab mafodotin. In this respect, it is striking that the median survival time in the belantamab mafodotin arm of the DREAMM-3 study is significantly shorter. Explanations for the divergent results of the two studies on median survival time under belantamab mafodotin are currently unavailable.

When assessing the results on overall survival of the DREAMM-3 study, the low precision of the estimate (wide confidence interval) and the low event rate due to the still short observation period at the present primary data cut-off must be taken into account.

Furthermore, despite stratified analysis on overall survival by ISS stage and line of therapy in the DREAMM-3 study, uncertainties remain with regard to structural equality between treatment groups due to the small sub-population 5L+.

Morbidity

Progression-free survival (PFS)

Progression-free survival is the primary endpoint of the DREAMM-3 study. PFS is defined in the DREAMM-2 and DREAMM-3 studies as the time from randomisation to the earliest date of documented progressive disease or death from any cause, whichever occurs first.

There is no statistically significant difference in PFS between the study arms in the 5L+ sub-population of the DREAMM-3 study.

The PFS endpoint is a composite endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed

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

Symptomatology (EORTC QLQ-C30 / EORTC QLQ-MY20/IL52)

Disease symptomatology was assessed in the DREAMM-2 and DREAMM-3 studies using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20. For some patients in the DREAMM-3 study, the EORTC IL52 was used instead of the full EORTC QLQ-MY20, and thus only the "disease symptoms" domain of the EORTC QLQ-MY20 was collected. In the course of the study, the response to the full EORTC QLQ-MY20 was introduced. The study participants who had already completed the IL52 continued to complete it. There is no information on the number of study participants affected by this.

For both studies, the pharmaceutical company submits responder analyses for the percentage of patients with a change of ≥ 10 points for the time to deterioration and for the time to improvement.

Taking into account the expected progressive course of the disease, the evaluations on deterioration are used for the present benefit assessment.

Only the corresponding evaluations of the symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-MY20 (only the subscale "disease symptoms") of the DREAMM-3 study at the data collection time point of week 4 are included, as the respective return rates were over 70% at this data collection time point. Furthermore, there were significant differences in return rates between the treatment arms. Furthermore, the percentage of missing values is high in both study arms.

The evaluations at week 4 are descriptive and only provide information about the respective percentage of subjects with a deterioration by ≥ 10 points compared to week 4. With regard to the evaluations used, it should also be noted that at the data collection time point of week 4, the patients generally only received belantamab mafodotin over one treatment cycle, so that an assessment of the effect of belantamab mafodotin compared to pomalidomide and dexamethasone on the symptomatology is not possible.

Due to the uncertainties mentioned regarding the results of the EORTC QLQ-C30 and EORTC QLQ-M20/IL52 questionnaires on symptomatology used for the benefit assessment, these are estimated to be not assessable.

Cancer symptomatology (PGIS / PGIC)

The endpoint "severity of cancer symptomatology" is recorded in the DREAMM-3 study using PGIS and PGIC.

Due to the low return rates in the belantamab mafodotin arm, which were below 70% at all data collection time points, the results of these PRO questionnaires are not presented and not used.

General health status (EQ-5D VAS)

The health status is assessed in the DREAMM-3 study using the EQ-5D visual analogue scale (VAS).

Due to the low return rates in the belantamab mafodotin arm, which were below 70% at all data collection time points, the results for the EQ-5D VAS are not presented and not used.

Quality of life

Health-related quality of life was assessed in the DREAMM-2 and DREAMM-3 studies using the functional scales and the global health status scale of the cancer-specific questionnaire EORTC QLQ-C30 and the myeloma-specific additional module EORTC QLQ-MY20.

For both studies, the pharmaceutical company submits responder analyses for the percentage of patients with a change of ≥ 10 points for the time to deterioration and for the time to improvement.

Taking into account the expected progressive course of the disease, the evaluations on deterioration are used for the present benefit assessment.

Only the corresponding evaluations for the functional scales and the global health status scale of the EORTC QLQ-C30 of the DREAMM-3 study at the data collection time point of week 4 are included, as the respective return rates for these evaluations were above 70%. Furthermore, there were significant differences in return rates between the treatment arms. Furthermore, the percentage of missing values is high in both study arms.

The evaluations at week 4 are descriptive and only provide information about the respective percentage of subjects with a deterioration by ≥ 10 points compared to week 4.

Since, analogous to symptomatology, only data on the EORTC QLQ-C30 at week 4 can be used for health-related quality of life, an assessment of the effect of belantamab mafodotin compared to Pom/Dex on quality of life is not possible.

Due to the uncertainties mentioned regarding the results of the EORTC QLQ-C30 questionnaire on health-related quality of life used for the benefit assessment, these are estimated to be not assessable.

Side effects

According to the study protocol, the endpoints in the side effects category were to be collected from the start of treatment until 45 days (DREAMM-2) or until at least 70 days (DREAMM-3) after the last study medication.

The median duration of observation was 2.5 months in the belantamab mafodotin arm and 7.4 months in the pomalidomide arm in the DREAMM-3 study and 4.7 months in the belantamab mafodotin arm in the DREAMM-2 study.

The median treatment duration was 2.1 months in the belantamab mafodotin arm and 6.6 months in the pomalidomide arm in the DREAMM-3 study and 9.3 weeks in the belantamab mafodotin arm in the DREAMM-2 study.

Total adverse events (AEs)

In both the belantamab mafodotin arms of the DREAMM-2 and DREAMM-3 studies and the pomalidomide arm of the DREAMM-3 study, AEs occurred in almost all patients.

Serious adverse events (SAE); severe adverse events (CTCAE grade ≥ 3); therapy discontinuation due to adverse events

In the DREAMM-3 study, there was no statistically significant difference between the treatment arms for the endpoints of SAEs, severe AEs and therapy discontinuation due to AEs based on the time-to-event analyses.

In the DREAMM-2 study, AEs of CTCAE grade ≥ 3 were documented in 84% of subjects treated with belantamab mafodotin and SAEs in 45%.

AEs of special interest

AEs of special interest were defined as corneal events, thrombocytopenia and infusion-related reactions in both studies.

In the DREAMM-3 study, there was a statistically significant difference for corneal events of any severity to the disadvantage of belantamab mafodotin versus Pom/Dex.

In the DREAMM-2 study, corneal events and keratopathies of any severity were the most common AEs of special interest.

OSDI (Ocular Surface Disease Index)

For both studies, ocular toxicity is additionally presented in the endpoint category of side effects by means of OSDI at week 4. The evaluations on the later post-baseline visits are not taken into account due to too low return rates (< 70%). Furthermore, there were significant differences in return rates between the treatment arms.

In the DREAMM-2 study, there is a slight numerical mean deterioration in OSDI from baseline to week 4.

In the DREAMM-3 study, a descriptive evaluation was performed on the percentage of subjects with deterioration by ≥ 15% of the scale range in the OSDI at week 4. The percentage of missing values that were not included in the analysis was high in both study arms.

Overall, no conclusions on the long-term ocular toxicity of belantamab mafodotin can be derived from the available results at week 4.

PRO-CTCAE (Patient-Reported Outcomes Common Terminology Criteria for Adverse Events)

The PRO-CTCAE is not considered in the benefit assessment due to the operationalisation in the DREAMM-2 and DREAMM-3 studies and the associated ambiguities. On the one hand, the selection of items from the PRO-CTCAE library is not sufficiently justified in some cases and it remains unclear whether this was done a priori. On the other, due to the 7-day reference period of the questions on symptomatic AEs, it can be assumed that events that occurred are not fully taken into account in the results of the PRO-CTCAE.

<u>Overall assessment</u>

The present assessment is a new benefit assessment after the expiry of the limitation of the initial resolution of the G-BA of 4 March 2021 for belantamab mafodotin for the treatment of adult patients with multiple myeloma who have already received at least four therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 monoclonal antibody, and who show disease progression on the last therapy.

For the new benefit assessment, the final data of the label-enabling, single-arm phase II study DREAMM-2 and the data of the primary data cut-off of the open-label, randomised DREAMM-3 study comparing belantamab mafodotin versus pomalidomide and dexamethasone are available. For the new benefit assessment, the sub-population 5L+ from the DREAMM-3 study, which was tailored according to the marketing authorisation or the product information, was used. Compared to the total population of the DREAMM-3 study (325 subjects), this sub-population comprises only 44 subjects (belantamab mafodotin = 29; Pom/Dex = 15). With

regard to the DREAMM-2 study, the benefit assessment refers to the treatment cohort in which belanatmab mafodotin was used in the dosage compliant with the product information.

The pharmaceutical company submitted data on mortality, morbidity, quality of life and side effects for both studies.

However, the data of the DREAMM-2 study do not allow for a comparative assessment due to the single-arm study design.

In the assessment-relevant sub-population of the DREAMM-3 study, there was no statistically significant difference between belantamab mafodotin and pomalidomide/ dexamethasone in terms of overall survival. In this regard, 16 subjects (55%) died in the belantamab mafodotin arm and 4 (27%) in the pomalidomide/ dexamethasone arm. The median survival time in the intervention arm is 9.5 months (95% CI: [5.1; n.c.]), while it has not yet been reached in the control arm. When assessing this result, the low precision of the estimate (wide confidence interval) and the low event rate due to the still short observation period for the present primary data cut-off of the DREAMM-3 study must be taken into account. In addition, uncertainties arise with regard to structural equality between the treatment groups due to the small sub-population 5L+.

In the morbidity category, symptomatology (using EORTC QLQ-C30 and EORTC QLQ-MY20/IL52), cancer symptomatology (using PGIS/PGIC) and general health status (using EQ-5D VAS) are recorded. With regard to cancer symptomatology (using PGIS/PGIC) and health status (using EQ-5D VAS), the results are not used in the belantamab mafodotin arm due to the low return rates of the respective assessment tools. With regard to symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-MY20/IL52), due to the low return rates in the belantamab mafodotin arm and the significant differences in return rates between the treatment arms, only the results for week 4 from the DREAMM-3 study can be used for the benefit assessment. Due to the resulting uncertainties regarding the assessment of the effect of belantamab mafodotin compared to pomalidomide and dexamethasone on symptomatology, the data are considered not assessable. Overall, no assessable data are available in the endpoint category of morbidity.

For health-related quality of life (assessed using the EORTC QLQ-C30 and EORTC QLQ-MY20), only the results of the EORTC QLQ-C30 functional scales of the DREAMM-3 study at week 4 could be used for the benefit assessment due to low return rates in the belantamab mafodotin arm and the significant differences in return rates between the treatment arms. Due to the resulting uncertainties regarding the assessment of the effect of belantamab mafodotin compared to pomalidomide and dexamethasone on health-related quality of life, the data are estimated to be not assessable.

For the results on side effects, the DREAMM-3 study did not show any relevant differences between the treatment arms for the benefit assessment. In detail, the adverse events of special interest show a disadvantage for corneal events of belantamab mafodotin compared to pomalidomide and dexamethasone.

The Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended at its session of September 2023 that the conditional marketing authorisation for belantamab mafodotin should not be renewed. In the CHMP's view, the study requested as part of the conditional marketing authorisation did not confirm the efficacy of belantamab mafodotin (DREAMM-3 study).

In the overall assessment, the G-BA determines a non-quantifiable additional benefit of belantamab mafodotin solely from a legal perspective according to Section 35a, paragraph 1, sentence 11, 1st half of sentence SGB V.

Significance of the evidence

This assessment is based on the results of the single-arm phase II DREAMM-2 study and the open-label, randomised DREAMM-3 study comparing belantamab mafodotin with pomalidomide and dexamethasone. Only the treatment cohort of the DREAMM-2 study, in which belantamab mafodotin was used in the dosage compliant with the product information and the 5L+ sub-population of the DREAMM-3 study, which was tailored according to the marketing authorisation and the product information, are relevant for the benefit assessment.

The single-arm data from the DREAMM-2 study do not allow for a comparative assessment.

For the DREAMM-3 study, a high risk of bias can be assumed due to the open-label study design. In addition, the study population relevant to the assessment is only a very small sub-population 5L+ of the total number of patients enrolled in the DREAMM-3 study, tailored to the indication. As the selection criteria of the sub-population were only partially taken into account by the stratification factors and against the background of the observed imbalances of some baseline characteristics, it is unclear whether structural equality between the treatment groups in the sub-population can be assumed. As a result, the significance of the results is limited by the small number of patients included in the sub-population.

In addition, uncertainties arise for all endpoints of the DREAMM-3 study.

With regard to the assessment of the results on overall survival, the low precision of the estimate (wide confidence interval) and the low event rate due to the still short observation period at the present primary data cut-off must be taken into account.

Due to too low return rates in the belantamab mafodotin arm and due to too low return rates in the belantamab mafodotin arm and clear differences in the return rates between the treatment groups, the data on the endpoints of morbidity and health-related quality of life cannot be used at all or only at week 4. Furthermore, the percentages of missing values of the respective evaluations for the patient-reported endpoints are high in both study arms. Taking into account the uncertainties mentioned above, it is not possible to assess the effect of belantamab mafodotin compared to pomalidomide and dexamethasone on symptomatology and quality of life. Thus, there are no assessable data for the evaluation of morbidity (disease symptomatology, cancer symptomatology, general health status) and quality of life. Statements on morbidity and quality of life are given a high priority, especially in the palliative treatment setting presented here.

Furthermore, the median treatment duration and median duration of observation are very short, especially in the belantamab mafodotin arm of the DREAMM-3 study, leading to uncertainties in particular regarding the estimation of long-term effects of belantamab mafodotin compared to pomalidomide and dexamethasone on all endpoints.

The overall assessment gives a hint for the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient belantamab mafodotin due to the expiry of the limitation of the resolution of 4 March 2021.

Belantamab mafodotin was approved under "conditional marketing authorisation" as an orphan drug.

The present assessment relates to the use of belantamab mafodotin for the treatment of multiple myeloma in the following patient population:

Adults with multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and

an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy

For the renewed benefit assessment, the pharmaceutical company submits the final data of the label-enabling, single-arm phase II study DREAMM-2 and the data of the primary data cut-off of the open-label, randomised DREAMM-3 study comparing belantamab mafodotin versus pomalidomide and dexamethasone.

For the new benefit assessment, the sub-population 5L+ from the DREAMM-3 study, which was tailored according to the marketing authorisation or the product information, was used. Compared to the total population of the DREAMM-3 study (325 subjects), this sub-population comprises only 44 subjects (belantamab mafodotin = 29; Pom/Dex = 15).

With regard to the DREAMM-2 study, the benefit assessment refers to the treatment cohort in which belantamab mafodotin was used in the dosage compliant with the product information.

Due to the single-arm study design, the data of the DREAMM-2 study do not allow for a comparative assessment.

In the assessment-relevant sub-population of the DREAMM-3 study, there was no statistically significant difference between belantamab mafodotin and pomalidomide/ dexamethasone in terms of overall survival.

There are no assessable data for the evaluation of morbidity (disease symptomatology, cancer symptomatology, general health status) and quality of life. Statements on morbidity and quality of life are given a high priority, especially in the palliative treatment setting presented here.

For the results on side effects, the DREAMM-3 study did not show any relevant differences between the treatment arms for the benefit assessment. In detail, the adverse events of special interest show a disadvantage for corneal events of belantamab mafodotin compared to pomalidomide and dexamethasone.

The Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended at its session of September 2023 that the conditional marketing authorisation for belantamab mafodotin should not be renewed. In the CHMP's view, the study requested as part of the conditional marketing authorisation did not confirm the efficacy of belantamab mafodotin (DREAMM-3 study).

In the overall assessment, the G-BA determines a non-quantifiable additional benefit of belantamab mafodotin solely from a legal perspective according to Section 35a, paragraph 1, sentence 11, 1st half of sentence SGB V.

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 belantamab mafodotin (resolution of 4 March 2021). Based on the data currently available, a number of 570 to 1,130 patients is estimated by resolution of 4 March 2021. It is assumed that the true number of patients tends to be closer to the upper limit of the range.

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 Blenrep (active ingredient: belantamab mafodotin) at the following publicly accessible link (last access: 28 June 2023):

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

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

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional measures to risk minimisation, the pharmaceutical company should provide training materials for all belantamab mafodotin prescribing, dispensing and administering medical professionals as well as patients.

The training material for medical professionals includes a guideline for corneal side effects and a guideline for eye examination. The guideline for corneal side effects contains information on the safety risk of these side effects and on appropriate risk minimisation measures. The guideline for eye examination also contains instructions to facilitate communication between the patient's treating physician and ophthalmologist.

The patient training material includes a guideline regarding corneal side effects for patients, a patient card and a pharmacy card for eye drops. The guideline informs patients that corneal side effects can occur during treatment with belantamab mafodotin and also contains information about the prescribed eye examinations and measures to be taken upon occurrence of the corneal side effects. The patient card, which shows that the patient is being treated with belantamab mafodotin and contains the contact information of the haematologist/ oncologist and the ophthalmologist, should be presented to the healthcare professional during follow-up examinations. Presentation of the pharmacy card for eye drops to the pharmacy is to ensure receipt and correct use of eye drops containing preservative-free tear substitute.

This medicinal product was approved under "conditional marketing authorisation". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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: 01 September 2023).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and 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				
Belantamab mafodotin	Continuously, every 21 days	17.4	1	17.4

Consumption:

The active ingredient belantamab mafodotin is dosed depending on body weight. For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[2]

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					
Belantamab mafodotin	2.5 mg/ kg BW = 192.5 mg	192.5 mg	2 × 100 mg	17.4	34.8 × 100 mg

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Belantamab mafodotin	1 PCI	€ 5,742.21	€ 2.00	€ 556.54	€ 5,183.67
Abbreviations: PCI = powder for concentrate for solution for infusion					

LAUER-TAXE® last revised: 1 September 2023

2 Federal Statistical Office (2018). Microcensus 2017 - Questions on health - Body measurements of the population. https://www.gbe-bund.de/gbe/ (Accessed: 08.08.2023).

Costs for additionally required SHI services:

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

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

No additionally required SHI services are taken into account for the cost representation.

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication)

and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called indetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGBV.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

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

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

3. Bureaucratic costs calculation

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

4. Process sequence

On 31 March 2023, the pharmaceutical company submitted a dossier for the benefit assessment of belantamab mafodotin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 3 July 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 7 August 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 September 2023 and on 26 September 2023, and the proposed resolution was approved.

At its session on 5 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 June 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	2 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 August 2023	Conduct of the oral hearing
Working group Section 35a	16 August 2023 6 September 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	12 September 2023 26 September 2023	Concluding discussion of the draft resolution
Plenum	5 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 5 October 2023

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

Prof. Hecken