Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Resolutions on the benefit assessment of medical products with new active ingredients according to section 35a SGB V Belantamab mafodotin (multiple myeloma, at least 4 prior therapies, monotherapy)

From 4. March 2021

Contents

1. Legal basis

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

For medicinal products for the treatment of a rare disease (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 11,1 st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation 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 evaluation 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 Ordinance on the Benefit Assessment of Pharmaceuticals (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 €50 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, subsection 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 legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). 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 relevant date for the first placing on the market of the active ingredient Belantamab mafodotin in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15. September 2020. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 14. September 2020.

Belantamab mafodotin for the treatment of multiple myeloma is authorised as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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 authorisation 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 15. December 2020 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-22) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG.

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

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

2.1 Additional benefit of the medicinal product

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

Blenrep 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

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

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 from the 04.03.2021):

see approved therapeutic indication

2.1.2 Extent of the additional benefit and the 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:

hint for a non-quantifiable additional benefit, because the scientific data does not allow a quantification.

Justification:

To determine the benefit assessment of the active ingredient belantamab mafodotin, the pharmaceutical company presented the pivotal, uncontrolled, randomised phase II DREAMM-2 Study. Because there are no data from direct comparing studies, the pharmaceutical company presents additionally in the written statement procedure an indirect comparison between belantamab mafodotin and selinexor plus dexamethasone, and an indirect comparison between belantamab mafodotin and "conventional care "using the bridge comparator selinexor plus dexamethasone[2].

DREAMM-2 study

The DREAMM-2 study consist of an ongoing, multi-centre study to assess the efficacy and safety of two dosages of belantamab mafodotin in patients with multiple myeloma that were pretreated with 3 or more therapy lines, are refractory towards one PI and one IMiD, and the treatment with one anti-CD38 antibody failed. The average age of the participants was 65 years at the start of the study. The study was held in 8 countries and 58 study centres, including Germany.

The study included 196 patients randomised 1:1 to the two study arms 2,5 mg/kg body weight (N = 97) or 3,4 mg/kg body weight (N = 99). Participants of another cohort were treated with belantamab mafodotin in the dosage form of a lyophilisate with a dosage of 3,4 mg/kg body weight (N = 25). This cohort was initiated once the recruitment for the first 2 cohorts that were treated with a previously frozen solution was finished, and the lyophilisate dosage form was available.

The benefit assessment applies only to a single treatment cohort (N = 97) of the DREAMM-2 study, in which belantamab mafodotin was used in the SmPC compliant dosage of 2,5 mg/kg body weight; appropriated controls are missing. In accordance with the inclusion criteria, the participants had to present failure in at least 3 prior anti-myeloma therapies. Because 95 % of the included patients from the evaluation-relevant cohort already had done ≥ 4 therapies before the start of the study, the relevant study population essentially corresponds to the therapeutic indication.

[2] Suvannasankha A et al. Assessing Efficacy via Indirect Comparison of Single-Agent Belantamab Mafodotin in DREAMM-2 versus STORM or MAMMOTH Studies in relapsed / refractory Multiple Myeloma (Poster No. MM-209, SOHO 8th Annual Meeting). 2020 12.09.2020

The recruitment of patients started in June 2018. The treatment with belantamab mafodotin is carried out until disease progression, death or in unacceptable toxicities. The primary endpoint of the study is the overall response rate (ORR).

The DREAMM-2 study additionally included a sub-study on ophthalmic examinations, in which 30 of the included patients should participate. The study aimed to investigate the effect of steroid eye drops on corneal events.

The DREAMM-2 study has not yet been completed. It ends when 60% of participants have died, their consent has been withdrawn or are lost to follow-up, and all patients with corneal events have been observed for up to 12 months after the last treatment dose.

Three data cut-offs are available. The first data cut-off on 21 June 2019 is the primary analysis that took place 6 months after randomising the last test subject to one of the two dosages of the previously frozen solution. The second data cut-off on 20 September 2019 and the third data cut-off on 31 January 2020 were requested by the European Medicines Agency (EMA). An update of the OS analysis is planned for the end of the study when 60% of the participants have died or lost to follow-up or withdrew the consent and if all patients with corneal events were observed up to 12 months after the last dose.

For the benefit assessment of the endpoint categories Mortality and Side effects, the cut-off data with the longest observation period (13-month update) are used.

indirect comparisons

For the indirect comparison between belantamab mafodotin and "conventional care", the Pharmaceutical company makes an indirect comparison with Bucher via the bridge comparator Selinexor plus Dexamethasone. In this comparing exists a matching-adjusted indirect comparison (MAIC) on the belantamab mafodotin side, which the pharmaceutical company conducts between belantamab mafodotin and selinexor plus dexamethasone, and on the "conventional care" a publication from Costa et al.[3], which compares the overall survival of selinexor plus dexamethasone (Chari et al..[4]) with the overall survival in the "conventional care" cohort done as part of the MAMMOTH study.

to the matching-adjusted indirect comparison between belantamab mafodotin and selinexor plus dexamethasone

A matching-adjusted indirect comparison (MAIC) was performed to compare the overall survival between belantamab mafodotin and selinexor plus dexamethasone. For this, data were collected from the DREAMM-2 study for belantamab mafodotin and the STORM study (Chari, et al., 2019; part 2) for selinexor plus dexamethasone. The patient characteristics used for the matching were selected depending on availability based on clinical expert opinions.

on the indirect comparison according to Bucher between belantamab mafodotin and conventional care via the bridge comparator selinexor plus dexamethasone

In the last step, a further indirect comparison between Bucher and the bridge comparator selinexor plus dexamethasone was performed to compare the overall survival between belantamab mafodotin and conventional care. For this, the HR reported by Costa et al. for the overall survival from selinexor plus dexamethasone versus conventional care and the HR adjusted to MAIC from belantamab mafodotin versus selinexor plus dexamethasone.

Assessment of the indirect comparisons

The indirect comparisons presented are not sufficiently valid for several reasons to be used to quantify the additional benefit of belantamab mafodotin.

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[3] Costa LJ et al. Overall survival of triple class refractory, penta-exposed multiple myeloma (MM) patients treated with selinexor plus dexamethasone or conventional care: a combined analysis oft he STORM and Mammoth studies. Blood. 2019; 134: 3125

[4] Chari A et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. J New England Journal of Medicine. 2019; 381(8): 727-38

Due to the lack of information, it remains unclear to what extent the included patient populations are comparable between the included studies.

Regarding the patients' conventional care treatment from the MAMMOTH study, there is no specific information on the type and scope of this treatment.

The selection of the adjustment and matching factors taken into account for the indirect comparisons is not named or justified in the pharmaceutical company's explanations. It is noted that some prognostically important baseline characteristics could not be considered as confounders in the MAIC analysis for the indirect comparison between belantamab mafodotin and selinexor plus dexamethasone because relevant information was not available. In addition, for the comparison of belantamab mafodotin and conventional care, only an indirect comparison according to Bucher with the bridge comparator selinexor plus dexamethasone was carried out, which is based on the assumption of a uniform distribution of the effect modifiers. This assumption was not justified and cannot be tracked due to a lack of relevant information. Overall, it cannot be ruled out that relevant factors will not be taken into account and lead to distortions in the results.

The indirect comparison according to Bucher between belantamab mafodotin and conventional care using the bridge comparator selinexor plus dexamethasone only yields results on overall survival, but not on other patient-relevant endpoints.

Overall, the remaining uncertainties are so serious that the presented indirect comparisons between belantamab mafodotin and selinexor plus dexamethasone and between belantamab mafodotin and conventional care via the bridging comparator selinexor plus dexamethasone cannot be used for the benefit assessment. Regardless of this, results for only one patient-relevant endpoint are not sufficient.

Selinexor plus dexamethasone is a new treatment option. The CHMP issued a corresponding positive opinion in January 2021. The formal marketing authorisation by the EU Commission is currently pending.

About the results of the DREAMM-2 study

Mortality

The overall survival is defined as the time from randomisation to death from any cause.

As of the data cut-off of the 13-month update on 31 January 2020, 48 (49%) of the 97 belantamab mafodotin-treated study patients had died. The median survival time was 13.7 months.

Since no comparable data are available, no statement on the extent of the additional benefit can be made based on these results.

Morbidity

EORTC QLQ-C30 symptom scales and individual symptom items of the QLQ-C30 as well as the symptom scales of the QLQ-MY20

The EORTC QLQ-C30 and QLQ-MY20 were done in the DREAMM-2 study every 6 weeks during the treatment period and at the end of treatment. Return rates could only be tracked for the 21 June 2019 and 20 September 2019 data cut-offs. No information is available on this for the 13-month update.

Return rates (data cut-off on 20 September 2019) related to the ITT population decreased from baseline at 77% to all post-baseline visits below 70%.

Due to the low return rates, the EORTC questionnaires' results are not used for the benefit assessment.

Consequently, no statement on the extent of the additional benefit for morbidity can be derived from the results of the DREAMM-2 study.

Quality of life

In the DREAMM-2 study, the functional scales and global scale for health status/quality of life of the EORTC QLQ-C30 as well as the functional scales of the QLQ-MY20 and the NEI VFQ-25 questionnaire were used to record the quality of life.

Analogous to the patient-reported endpoints of morbidity, the return rates for the EORTC questionnaires were so low that no valid results could be derived from them.

The NEI VFQ-25 was used in the DREAMM-2 study to assess the impact of potential corneal events on function and health-related quality of life. Due to the descriptive nature of the results, the very short observation period of 3 weeks and the lack of control, no valid statements can be made about the effects of belantamab mafodotin on quality of life.

Consequently, no statement on the extent of the additional benefit for quality of life can be derived from the results of the DREAMM-2 study.

Side effects

The results on side effects relate to the 95 patients of the Full Safety Set population. This population includes all patients who received at least one dose of the study medication. AEs from the time of initiation of therapy up to 45 days after the last study medication were taken into account in the evaluations. Information on the treatment duration for the data cut-off on 31 January 2020 is not available. A median of 3 treatment cycles and a maximum of 17 cycles were administered, one cycle lasting 21 days according to the protocol, but delayed administration of the medication was possible.

Adverse events (AE) in total

The results for the endpoint adverse events are only presented as a supplement. Almost every patient suffered an adverse event (93 patients (98%)).

Serious adverse events (SAEs)

40 out of 95 of the patients (42%) had at least one serious adverse event (SAE). Pneumonia and pyrexia were the most common, each occurring in 7% of patients.

Severe adverse events (CTCAE grade ≥ 3)

80 out of 95 of the patients (84%) had at least one severe AE with CTCAE grade ≥ 3. The most common AEs with a severity of ≥ 3 were keratopathies; AEs of the blood (including preferred terms: anaemia, thrombocytopenia, decreased platelet count, neutropenia, decreased neutrophil count, decreased lymphocyte count) and pneumonia.

Therapy discontinuation because of adverse events

9% of patients discontinued therapy due to adverse events.

AE of special interest

In the DREAMM-2 study, infusion-related reactions, thrombocytopenia, neutropenia and corneal events were defined as AEs of special interest. Infusion-related events occurred in 21% of patients. Thrombocytopenia was observed in 38% of the patients. 15% of patients had neutropenia.

The corneal events were assessed both based on the CTCAE classification scale and a classification scale[5] developed by GSK. According to the GSK scale, 72% of patients treated had corneal events, with almost half of these patients exhibiting simultaneous symptoms of blurred vision and dry eyes. Almost 50% of all patients had corneal events grade 3 or 4 on the GSK scale. Using the CTCAE classification, keratopathy was documented in 71% of the patients. 31% of these patients had severe keratopathy. Blurred vision and dry eyes, according to CTCAE were observed in 25% and 15% of the treated patients, respectively, with the proportion of patients with severe events being low. No serious corneal events according to CTCAE occurred.

OSDI (Ocular Surface Disease Index)

The OSDI was used in the DREAMM-2 study to record the eye toxicity of belantamab mafodotin. Using the OSDI, patients evaluate the frequency of eye irritation and its effect on vision. The pharmaceutical company presented the results of the OSDI for the endpoint category quality of life. Since not all relevant dimensions of quality of life (physical, psychological and social) are mapped with the instrument and symptomatic eye toxicities of the study medication are recorded with the OSDI in the DREAMM-2 study, the endpoint for the endpoint category safety is used.
Due to their descriptive character, the very short observation period of 3 weeks and the lack of control, the results of the OSDI do not allow any valid conclusions.

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

The PRO-CTCAE is an instrument for recording patient-reported side effects. It is used to evaluate the symptomatic side effects that cancer patients experience in the course of therapy studies. The PRO-CTCAE consists of a library with 124 items on 78 CTCAE symptoms and 80 PRO-CTCAE terms.
The PRO-CTCAE is not considered in the benefit assessment due to the operationalisation in the DREAMM-2 study and the associated ambiguities. In its written statement, the pharmaceutical company added the information missing in the benefit assessment on the PRO-CTCAE items selected a priori and a reason for the inclusion or exclusion of the items from the PRO-CTCAE library. However, due to the (assumed) reference period of the questions about the symptomatic AEs, it can still be assumed that the survey only covers the symptoms of the last week of a 3-week treatment cycle and that events that occur as a result are not fully taken into account in the results of the PRO-CTCAE.

The side effects were only investigated in a few patients in the DREAMM-2 study. The majority of the patients in the DREAMM-2 study were treated with the frozen formulation, while the commercial freeze-dried formulation was only investigated in 25 patients at the unapproved dose of 3.4 mg/kg body weight. Due to the still very limited data, it remains unclear whether the commercial formulation leads to a higher frequency and severity of the side effects. Outstanding results of the ongoing DREAMM-3 study are intended to generate additional findings in this regard.[6]

Since the results of the DREAMM-2 study on side effects are based on uncontrolled data, no comparative statements can be made.

<u>Overall assessment</u>

For the benefit assessment of belantamab mafodotin to treat adult patients 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

[5]G-BA dossier assessment on belantamab mafodotin; page 24 table 5: contains a concrete description of the impairments according to the corresponding severity levels of the GSK scale for corneal events.
[6] European Medicines Agency. Assessment report: BLENREP. 23 July 2020, pages 106 and 118

monoclonal antibody, and who have demonstrated disease progression on the last therapy, results from the uncontrolled DREAMM-2 study on overall survival and side effects are available.

Data on morbidity and quality of life are also available. However, these have such low return rates that no valid results can be derived from them. The data are classified as not assessable.

Despite this, a comparative assessment of the study results is not possible due to the single-arm design of the DREAMM-2 study.

The results of indirect comparisons between belantamab mafodotin and selinexor plus dexamethasone as well as between belantamab mafodotin and conventional care via the bridging comparator selinexor plus dexamethasone in the written statement procedure cannot be used to derive an additional benefit because the extent to which the included patient populations are comparable between the included studies remains unclear, and it cannot be ruled out that relevant adjustment and matching factors are not taken into account and lead to biases in the results.

A quantitative assessment of the extent of the effect and quantification of the additional benefit based on the data presented is therefore not possible.

As a result, the G-BA classifies the extent of the additional benefit of belantamab mafodotin in the present indication due to the limited data based on 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 In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SBG V, because the scientific data does not allow a quantification.

Significance of the evidence

The DREAMM-2 study is a one-arm, uncontrolled study.

Data reliability is rated as a hint because only a single-arm, uncontrolled study is available, and a comparative assessment is not possible.

In the overall review, the result is a hint of a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of belantamab mafodotin finds 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 pursuant to Section 35a paragraph 1 SGB V.

Based on the pivotal single-arm phase II study DREAMM-2, no reliable conclusions can be drawn on the extent of the additional benefit due to the deficient data basis. There is a lack of sufficiently significant data to assess the additional benefit concerning overall survival, patient-relevant symptoms (morbidity), quality of life, side effects and in particular direct comparative studies.

Since clinical data from a direct comparative study of belantamab mafodotin versus pomalidomide and dexamethasone (DREAMM-3 study) are expected in the present therapeutic indication, which may be relevant for the assessment of the additional benefit of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of belantamab mafodotin.

Against the background that the medicinal product Blenrep with the active ingredient belantamab mafodotin was approved under special conditions, the European Medicines Agency requires, concerning the evidence to be provided by the pharmaceutical company, among other things, that the results of the currently still ongoing phase III DREAMM-3 study are to be submitted. The results are expected to be submitted to the EMA by July 2024[7].

In the context of the written statement procedure on the present benefit assessment, the pharmaceutical company states that a primary data cut-off of the DREAMM-3 study will take place in 2022. The European Medicines Agency demands study report submission in the second quarter of 2022. The limitation enables the expected interim results from the DREAMM-3 study to be included in the benefit assessment of the medicinal product under Section 35a SGB V in a timely manner.

For this purpose, the G-BA considers a limitation for the resolution until 1 September 2022 to be appropriate.

Conditions for the limitation:

For the renewed benefit assessment after the expiry of the deadline, the dossier should contain significant interim results for the patients in the therapeutic indication that is the subject of the assessment from the currently ongoing DREAMM-3 study on all patient-relevant endpoints that are used to demonstrate the additional benefit.

A change in the time limit can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of belantamab mafodotin recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of belantamab mafodotin (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO).

The possibility that a benefit assessment for belantamab mafodotin can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 6 VerfO) remains unaffected hereof.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the new medicinal product blenrep with the active ingredient belantamab mafodotin 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 showed disease progression during the last therapy.

Blenrep was authorised under special conditions 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.

[7] European Medicines Agency. Assessment report: BLENREP. 23 July 2020, pages 106 and 126

For the benefit assessment, the pharmaceutical company presents the results from the uncontrolled DREAMM-2 study with results on the endpoint categories of mortality, morbidity, quality of life and side effects. However, the data on morbidity and quality of life have such low return rates that no valid results can be derived from them, and the data are classified as not assessable.

The results presented by the pharmaceutical company on indirect comparisons both between belantamab mafodotin and selinexor plus dexamethasone and between belantamab mafodotin and conventional care via the bridging comparator selinexor plus dexamethasone in the written statement procedure cannot be used to derive an additional benefit because the extent to which the included patient populations are comparable between the included studies remains unclear, and it cannot be excluded that relevant adjustment and matching factors are not taken into account and lead to biases in the results. Regardless of this, results for only one patient-relevant endpoint are not sufficient.

Overall, only data from a single-arm, uncontrolled study are available, which do not allow a comparison. The data are therefore not suitable for quantifying the extent of the additional benefit.

Data reliability is rated as a hint because only a single-arm, uncontrolled study is available, and a comparative assessment is not possible.

In the overall review, belantamab mafodotin used for the treatment of adults with multiple myeloma who have already received at least four therapies and whose disease is refractory to at least one proteasome inhibitor, an immunomodulator and an anti-CD-38 monoclonal antibody, and who demonstrated disease progression on the last therapy is determined as a hint for a non-quantifiable additional benefit, because the scientific data does not allow quantification.

The validity of the resolution is limited to 1 September 2022. The limitation enables the expected interim results from the DREAMM-3 study to be included in the benefit assessment of the medicinal product under Section 35a SGB V in a timely manner.

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

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

The pharmaceutical company calculated the number of patients in the SHI target population using four derivation steps.

In the dossier assessment, the proportions of 0.7% to 2% of patients with a 5th or 5th or subsequent therapy lines transferred to all patients with multiple myeloma requiring therapy were rated as uncertain.

As part of the written statement procedure, one of the commentators submitted to the G-BA further explanations on calculating the number of patients in the SHI target population.

As part of an addendum, the G-BA commissioned the IQWiG to review and evaluate the additionally submitted calculations. In summary, the findings described below result from this assessment.

The commentator shows a new percentage of patients in the 5th. therapy line of 4% based on all patients with multiple myeloma in need of therapy. Accordingly, there are 1055 to 1133 patients in the SHI target population (mean: 1094 patients). The share value of 4% contains uncertainties comparable with that of the share value (0.7 to 2%) from the dossier. However, the data used are more up-to-date and only relate to the German health care context.

In addition, the commentator presented an alternative calculation based on an evaluation of routine SHI data with 1850 patients in the SHI target population. For the number of patients from the SHI routine data analysis, an overall overestimation of the patient numbers can be assumed.

In the overall assessment, a range of 567 to 1133 patients in the SHI target population is rated as the best possible estimate at present based on all the documents submitted, although this tends to be expected in the upper part of this range. The G-BA bases the resolution on this information on the range from 567 to 1133 patients from the assessment done by the IQWiG as part of the addendum.

The value of the lower limit results from the maximum number of patients in the SHI target population from the dossier on belantamab mafodotin, which was based on a proportion of 2% of patients with a 5th or subsequent therapy line. The value of the upper limit results from the maximum number of patients in the target population of the present assessment by the commentator, based on a proportion of 4% of patients with a 5th therapy line.

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: 14. December 2020):

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

Under the European Medicines Agency (EMA) requirements 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.

Medical professionals' training material includes a guideline for corneal side effects and a guideline for eye examination. The guideline regarding corneal side effects contains relevant information on the safety risk of keratopathy or microcystic epithelial changes of the cornea and details on how the safety risks addressed by the risk minimisation measures are minimised by appropriate monitoring. The eye examination guideline contains important information about corneal side effects associated with belantamab mafodotin, how to deal with side effects, and instructions for facilitating communication between the treating physician and the patient's ophthalmologist.

The patient training programme includes a guideline regarding corneal side effects for patients, a patient card and a pharmacy card for eye drops.

This medicinal product was approved under "special conditions". 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: 15. February 2021):

For the cost representation, only the dosages of the general case are considered. If the treatment duration is not limited, initial induction schemes are not taken into account for the presentation of costs. Patient-individual dose adjustments, e.g., side effects or comorbidities, are not considered when calculating the annual treatment costs.

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", 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)	Days of treatment/ 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 administered in doses 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).[8]

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Belantamab mafodotin	2.5 mg/kg body weight = 192,5 mg	192.5 mg	2 x 100 mg	17.4	34.8 x 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the

8 Statistisches Bundesamt (Federal Statistic Office) (2018). Mikrozensus 2017 - Fragen zur Gesundheit - Körpermaße der Bevölkerung. https://www.destatis.de/DE/Methoden/Qualitaet/Qualitaetsberichte/Bevoelkerung/mikrozensus-2017.pdf;jsessionid=B922CBC0E7D233E5ACE6BA7FAD0CC37A.internet8731?__blob=publicationFile (access: 19 November 2021):

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	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 PIE	€ 8558.80	€ 1.77	€ 488.21	€ 8,068.82
Abbreviations: PIE = Powder for concentrate for solution for infusion					

LAUER-TAXE® last revised: 15. February 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information or patient information leaflet, the differences 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.

For the cost representation no additionally required SHI services are considered.

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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application

containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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

On 14. September 2020, 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, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15. December 2020 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 written statements was 5. January 2021.

The oral hearing was held on 26. January 2021.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23. February 2021, and the draft resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8. December 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	19. January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	26. January 2021	Conduct of the oral hearing
Working group Section 35a	2. February 2021 16. February 2021	Consultation on the dossier evaluation 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	23. February 2021	Concluding consultation of the draft resolution
Plenum	4. March 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4. March 2021

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

Prof. Hecken