Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Mogamulizumab (Mycosis Fungoides, Sézary Syndrome)

of 3 December 2020

Contents

1. Legal basis

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

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 of the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not 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, Nos. 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 selling prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. In accordance with 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 in accordance with 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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 provided is assessed exclusively on the basis of the pivotal 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 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 of 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 forms 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 mogamulizumab in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 June 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 12 June 2020.

Mogamulizumab for the treatment of mycosis fungoides (MF) or Sézary syndrome (SS) is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half 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 by the G-BA on the basis of the pivotal studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess 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 September 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 assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-11) prepared by the IQWiG, and the statements submitted in the written statements and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for 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 set aside in the benefit assessment of mogamulizumab.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of mogamulizumab (Poteligeo) in accordance with the product information

Poteligeo is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.

Therapeutic indication of the resolution (resolution of 3 December 2020):

See therapeutic indication according to marketing authorisation

2.1.2 Extent of the additional benefit and significance of the evidence

Adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy

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

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

Hint for a non-quantifiable additional benefit because the scientific data does not allow quantification

Justification:

For the benefit assessment of the active ingredient mogamulizumab, the pharmaceutical company presents the open-label, randomised, MAVORIC Phase III pivotal study. This is a completed, multi-centre study that was conducted in 11 countries and 59 study centres.

The MAVORIC study included adult patients with histologically confirmed MF or SS in whom at least one previous systemic treatment (e.g. interferon, denileukin diftitox, bexarotene, photopheresis, antineoplastic chemotherapy) had failed. Psoralen plus ultraviolet light therapy (PUVA) was not considered a systemic therapy. When included in the study, patients should have had a tumour stage of IB-IV.

The 372 patients included in the study were randomised to the mogamulizumab (N = 186) or vorinostat arm (N = 186) at a ratio of 1:1. The randomisation was stratified by type (MF/SS) and stage of disease (IB or II/III or IV).

The patients had a median age of 63 years at the time of study inclusion. At the start of study, the disease affected the skin of all patients and, in most of the patients, the lymph nodes and blood. Over 80% of the patients included in the study had ≥ 2 previous systemic therapies at the start of study.

Patients randomised to the vorinostat arm of the study also had the option to be further treated with mogamulizumab in the case of disease progression or intolerable toxicity. In total, 136 patients (73.1%) who were originally randomised to the vorinostat arm switched to the mogamulizumab arm.

During the randomised treatment period, the mean number of cycles was 6.0 in the mogamulizumab arm and 3.0 in the vorinostat arm. The median duration of exposure was about twice as long for mogamulizumab (170 days) than for vorinostat (84 days).

The primary endpoint of the study was progression-free survival (PFS). Furthermore, overall survival, endpoints on morbidity, health-related quality of life, and adverse events, among others, were surveyed.

Two data cut-offs are available for the study. The first data cut-off of 31 December 2016 was an *a priori* planned primary effectiveness analysis (after 241 PFS events). There is also a data cut-off for the end of study on 2 March 2019, for which results are available for the overall survival endpoint and the side effects endpoint category. For these endpoints, the results of the data cut-off of 2 March 2019 are used. For the other endpoints of the endpoint category morbidity and health-related quality of life, the assessment is based on the results of the data cut-off of 31 December 2016.

Uncertainties in the MAVORIC study

The comparator vorinostat used in the study is not approved in Germany. An application for authorisation has been submitted to the European Medicines Agency (EMA). However, because of the lack of comparison with an active comparator and unresolved questions on efficacy and safety resulting in a negatively assessed benefit-risk profile, this was withdrawn on 13 February 2009[2]. However, the written statements received indicate that vorinostat is used in individual cases in Germany. In accordance with the statements of the clinical experts in the written statement procedure, in the present therapeutic indication, several therapeutic options, including approved medicinal products, are used in clinical practice against the background of a heterogeneous patient collective. Overall, it can be assumed that the comparator vorinostat used in the study does not reflect the standard of care in Germany.

[2] https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/vorinostat-msd

Mortality

Overall survival

In the MAVORIC study, overall survival was defined as the time from the day of randomisation to death by any cause, censored to the last date when the person was known to be alive.

There was no statistically significant difference between the treatment arms.

Morbidity

Progression-free survival (PFS)

In the MAVORIC study, PFS was defined as the time from the day of randomisation to documented disease progression in at least one of the compartments potentially affected by MF or SS (i.e. skin, blood, lymph nodes, and internal organs) or to death by any cause. The criteria were based on the Modified Severity Weighted Assessment Tool (mSWAT) (skin), imaging procedures (lymph nodes, internal organs), and laboratory parameters (blood). In addition to the assessment of the investigator, the progression was determined in an independent, blinded review.

For the endpoint PFS, there is a statistically significant advantage for treatment with mogamulizumab compared with control therapy.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was identified as an independent endpoint via the endpoint overall survival.

Disease progression in the compartments lymph nodes, internal organs and blood according to the operationalisation was not surveyed in symptom-related manner but rather by means of imaging procedures and laboratory parameters. Thus, the survey of disease progression in these areas is based on asymptomatic findings and is assessed as not directly relevant to the patient.

Disease progression in the skin compartment was surveyed using the mSWAT. For the assessment of skin changes, a distinction was made between patches, plaques, and tumours. The mSWAT was calculated by multiplying the proportions of diseased skin areas (% of total body surface area) by the weighting factors (1 for patches, 2 for plaques, and 4 for tumours) and forming a common score.

The skin changes associated with the clinical presentation in the form of patches, plaques, and tumours represent a burden for the affected patient because of the external visibility and the functional restriction. The change in the skin is to be considered patient-relevant if it is shown to be a relevant change through appropriate operationalisation.

According to the written statements of professional societies, the assessment of skin response by means of the mSWAT is a standardised procedure, which is recommended as a measurement method by professional societies and is the standard instrument for recording cutaneous disease burden both in clinical practice and in clinical studies.

Nevertheless, there is a lack of information on the (evidence-based) foundation of the weighting factors used for the type of skin lesion (patches, plaques, tumours) as well as on the rationale for representing skin lesions of different prognosis in a combined score. Furthermore, there is no information on the interrater reliability.

There is thus some doubt as to whether the mSWAT measurement tool used to assess skin response is sufficiently valid and reliable to reflect cutaneous disease burden.

Taking into account the written statements of the professional societies as well as the burden on the patient, the changes in the skin measured with the mSWAT in this rare indication are presented in the present assessment.

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

Cutaneous symptomatology – complete response of the skin

Complete skin response was defined as a complete resolution of all skin symptoms in accordance with mSWAT. The data was recorded by the investigator at baseline and every four weeks until the end of treatment. The complete response of the skin was evaluated by the investigator as well as in an independent blinded review. The assessment of a complete response had to be confirmed after at least four weeks.

Against the backdrop of the well externally visible, often painful, and/or itchy skin symptomatology, the endpoint complete response is considered patient-relevant. Taking into account the patient's burden associated with the disease, the change in the skin measured with the mSWAT – notwithstanding the uncertainties mentioned above – is assessed as patient-relevant for the assessment of the complete skin response; which is considered significant in this indication.

For the endpoint, there was no statistically significant difference between the treatment arms.

Cutaneous symptomatology – response of the skin

The response of the skin was defined as a complete or partial response of the skin. The endpoint is therefore a combined endpoint consisting of endpoints in the morbidity category. The endpoint component "complete response" was assessed as an independent endpoint.

Complete skin response was defined as a complete regression of all skin symptoms and partial response as a 50–99% regression of skin symptomatology. The skin response was assessed by the investigator as well as in an independent blinded review. The assessment of a complete or partial response had to be confirmed after at least four weeks.

Against the background of the externally visible, often painful and/or itchy skin symptomatology and the associated noticeable burden for the patient, a regression of ≥ 50% in this indication is generally considered a relevant change in the skin symptomatology and assessed as relevant for the patient.

The pharmaceutical company has submitted evaluations in accordance with mSWAT for the assessment of the cutaneous disease burden.

For skin response measured by mSWAT, there is a statistically significant difference between treatment arms to the advantage of mogamulizumab compared with vorinostat. Sensitivity analyses based on the unweighted relative proportions of skin lesions of the total body surface area (BSA) were also submitted by the pharmaceutical company within the scope of the written statement. These address the uncertainties regarding the weighting factors used. These confirm the present positive effect of mogamulizumab compared with vorinostat.

As explained, there are doubts as whether the mSWAT measurement tool used to assess skin response is sufficiently valid and reliable to reflect cutaneous disease burden. Particularly for the partial response sub-endpoint, information on the basis of the weighting factors used for the type of skin lesion (patches, plaques, tumours) as well as on the rationale for representing skin lesions of different prognosis in a combined score is essential. The sensitivity analyses cannot completely eliminate the existing uncertainties regarding the mSWAT. For these reasons, the results for this endpoint are not considered sufficiently meaningful to be used for the determination of the additional benefit.

Taking into account the written statements of the professional societies as well as the patient's burden associated with the disease, the changes in the skin measured with the mSWAT are nevertheless presented in the present assessment.

Cutaneous symptomatology – Pruritus NRS

Itching was recorded by means of the pruritus numerical rating scale (NRS); a score of 0 corresponds to no itch, and a score of 10 to the worst itch imaginable. Pruritus NRS was assessed at the start of study and then every four weeks until the end of treatment.

There are currently no externally validated, anchor-based MID available for the assessment of the Pruritus NRS. The responder analyses submitted by the pharmaceutical company are not usable because the investigation of the clinical relevance of the observed change, which is based on distribution-based procedures, is not sufficiently valid.

The pharmaceutical company also presented evaluations of the mean change from the start of study to month six based on a mixed-effect model with repeat measurements (MMRM). These are not considered because of low (< 70% of study participants) and different return rates in the treatment arms. It can also be assumed that the basic assumption of the MMRM model – missing at random – is not fulfilled for the missing values.

For the present assessment, there are usable data with sufficiently high return rates for Cycles 1 and 2 (Cycle 2: 89.3% in the intervention arm and 89.3% in the control arm) for evaluations of the mean change. However, comparative analysis is available only for Cycle 1. Based on the mean difference compared with Cycle 1, there is no statistically significant difference between the treatment groups.

Cutaneous symptomatology – symptom domains of Skindex-29

The skin symptomatology of the study participants was recorded using the symptom domain of the Skindex 29 questionnaire. Higher Skindex-29 values are associated with a more severe skin symptomatology. Skindex-29 was collected at the start of study and then every eight weeks until the end of treatment.

There are currently no externally validated, anchor-based MID available for the assessment of Skindex-29. The responder analyses submitted by the pharmaceutical company are not usable because the investigation of the clinical relevance of the observed change, which is based on distribution-based procedures, is not sufficiently valid.

The pharmaceutical company also presented evaluations of the mean change from the start of study to month six based on MMRM analyses. These are not considered because of low (< 70% of study participants) and different return rates in the treatment arms. It can also be assumed that the basic assumption of the MMRM model – missing at random – is not fulfilled for the missing values.

For the present assessment, the evaluations of the mean change Cycle 1 are used. These are based on sufficiently high return rates (83.9% in the intervention arm and 89.3% in the control arm). Based on the mean difference compared with Cycle 1, there is no statistically significant difference between the treatment groups.

Health status (EQ-5D, visual analogue scale)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The EQ-5D visual analogue scale (VAS) ranges from 0 to 100 and is employed by adult study participants to assess their health status. A value of 0 corresponds to the worst conceivable health status and a value of 100 to the best conceivable health status. EQ-5D-VAS was collected at baseline and then every eight weeks until the end of treatment.

For the benefit assessment, the pharmaceutical company presented evaluations of the mean change from the start of study to month six based on MMRM analyses as well as responder analyses. These are not considered because of low (< 70% of study participants) and different return rates in the treatment arms. It can also be assumed that the basic assumption of the MMRM model – missing at random – is not fulfilled for the missing values.

In the context of the evaluations on the mean change, the evaluations on Cycle 1 are used. These are based on sufficiently high return rates (89.9% in the intervention arm and 90.1% in the control arm).

Based on the mean difference compared with Cycle 1, there is no statistically significant difference between the treatment groups. Overall, there are no statistically significant differences between the treatment groups for the health status endpoint.

In the overall consideration of the endpoints on morbidity, neither advantages nor disadvantages can be derived for determining the additional benefit of mogamulizumab compared with vorinostat.

Quality of life

In the MAVORIC study, health-related quality of life was assessed sing the disease-specific ItchyQoL and Skindex-29 questionnaires as well as the Functional Assessment of Cancer Therapy – General (FACT-G) cross-tumour questionnaire.

ItchyQoL

The ItchyQoL is a specific measurement instrument to assess the quality of life in patients suffering from pruritus. The questionnaire was collected at the start of study and then every eight weeks until the end of treatment.

There are currently no externally validated, anchor-based MID available for the assessment of the ItchyQoL. The responder analyses submitted by the pharmaceutical company are not usable because the investigation of the clinical relevance of the observed change, which is based on distribution-based procedures, is not sufficiently valid.

The pharmaceutical company also presented evaluations of the mean change from the start of study to month six based on MMRM analyses. These are not considered because of low (< 70% of study participants) and different return rates in the treatment arms. It can also be assumed that the basic assumption of the MMRM model – missing at random – is not fulfilled for the missing values.

For the present assessment, there are usable data with sufficiently high return rates for Cycle 2 (77.9% in the intervention arm and 76.3% in the control arm) for evaluations of the mean change. However, analyses for the sub-scales are available only for Cycle 1. Based on the mean difference in the total score at Cycle 2 as well as in the “emotion”, “function”, and “symptoms” domains at Cycle 1, there is no statistically significant difference between the treatment groups.

Skindex-29

For details on the questionnaire and the analyses submitted by the pharmaceutical company, please refer to the section on the endpoint category morbidity of the endpoint “cutaneous symptomatology – symptom domain of Skindex-29”.

For the present assessment, there are usable data with sufficiently high return rates at Cycle 1 (83.9% in the intervention arm and 89.3% in the control arm) for evaluations of the mean change.

Based on the mean difference in the total score as well as in the individual domain “function”, there is no statistically significant difference between the treatment groups. For the individual domain “emotion”, there is a statistically significant difference to the advantage of mogamulizumab compared with vorinostat. The standardised mean difference in the form of Hedges’ g is used to assess the relevance of the result. The 95% confidence interval of the standardised mean difference was not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be deduced that the effect observed is relevant.

FACT-G

The tumour disease-specific questionnaire FACT-G consists of four sub-scales: physical well-being, social/familiar well-being, emotional well-being, and functional well-being.

Only the total score of the FACT-G questionnaire was considered in assessing the additional benefit because this provides a comprehensive overview of the data on the health-related quality of life of the patients. The individual FACT-G sub-scales are therefore only presented additionally.

The pharmaceutical company presented evaluations of the mean change from the start of study to month six based on MMRM analyses as well as responder analyses. These are not considered because of low (< 70% of study participants) and different return rates in the treatment arms. It can also be assumed that the basic assumption of the MMRM model – missing at random – is not fulfilled for the missing values.

For the present assessment, there are usable data with sufficiently high return rates at Cycle 1 (88.2% in the intervention arm and 92.5% in the control arm) for evaluations of the mean change.

Based on the mean difference, there is a statistically significant difference to the advantage of mogamulizumab compared with vorinostat. The standardised mean difference in the form of Hedges' g is used to assess the relevance of the result. The 95% confidence interval of the standardised mean difference was not completely outside the irrelevance range of −0.2 to 0.2. Thus it cannot be deduced that the effect observed is relevant.

In the overall analysis, there were no relevant differences (standardised mean difference in the form of Hedges' g) in health-related quality of life between the treatment groups. Overall, neither an advantage nor a disadvantage for mogamulizumab compared with vorinostat can be determined.

<u>Side effects</u>

Total adverse events (AE)

Almost all study participants experienced AE. The results are presented additionally.

Serious AE (SAE)

For the endpoint SAE, there are no statistically significant differences between the treatment arms.

Severe AE (CTCAE grade ≥ 3)

In terms of severe adverse events (CTCAE grade ≥ 3), there is a statistically significant difference to the advantage of mogamulizumab compared with vorinostat. In detail, there are statistically significant differences in the advantage of mogamulizumab compared with vorinostat with regard to blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3), including thrombocytopoenia (PT, CTCAE grade ≥ 3); gastrointestinal disorders (SOC, CTCAE ≥ 3); general disorders and administration site conditions (SOC, CTCAE ≥ 3), including fatigue (PT, CTCAE ≥ 3).

Therapy discontinuations because of AE

In terms of therapy discontinuations because of AE, there is a statistically significant difference to the advantage of mogamulizumab compared with vorinostat. In the intervention arm, an AE that led to therapy discontinuation occurred after a median of 53.5 months. In the control arm, the median time to the event was not yet reached.

In the present assessment, the results on therapy discontinuations because of AE are considered sufficiently valid and are used for the assessment.

The overall results on side effects show relevant advantages for mogamulizumab compared with vorinostat for severe AEs (CTCAE grade ≥ 3) and therapy discontinuations because of AEs.

Overall assessment

For the assessment of the additional benefit of mogamulizumab for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy, there are results for the endpoint categories mortality, morbidity, quality of life, and side effects.

The assessment is based on the MAVORIC study in which mogamulizumab was compared with vorinostat. Vorinostat is not approved in Germany; however, according to the written statements received, it is used in Germany in individual cases. In accordance with the statements of the clinical experts in the written statement procedure, in the present therapeutic indication, several therapeutic options, including approved medicinal products, are used in clinical practice against the background of a heterogeneous patient collective. Overall, it can be assumed that the comparator vorinostat used in the study does not reflect the standard of care in Germany.

In the evaluation of the endpoint overall survival, there was no statistically significant difference between the treatment arms.

In the overall consideration of the endpoints on morbidity, neither advantages nor disadvantages can be derived for determining the additional benefit of mogamulizumab compared with vorinostat.

Data on health-related quality of life are also available for the present assessment. For the disease-specific questionnaires ItchyQoL and Skindex-29 as well as for the cross-tumour disease questionnaire FACT-G, there are no relevant differences (standardised mean difference in the form of Hedges' g) between the treatment groups.

With regard to side effects, there is a relevant, but no more than minor, advantage of mogamulizumab compared with vorinostat in terms of severe adverse events (CTCAE grade ≥ 3) and therapy discontinuations because of adverse events.

Because of the limitations in the significance of the present study for the reality of care in Germany, from the perspective of the G-BA, there are major uncertainties in the interpretation of the study results. These are estimated to be so significant that, despite the relevant advantages with respect to side effects, they do not allow a quantification of the extent of the additional benefit overall.

In the overall assessment, a non-quantifiable additional benefit for mogamulizumab compared with vorinostat in the treatment of adult patients with MF or SS who have received at least one prior systemic therapy is determined because the scientific data basis does not allow quantification.

Significance of the evidence

This assessment is based on results from the open-label, randomised, controlled MAVORIC Phase III study. The risk of bias at the study level is estimated to be low.

Because of the open study design and the resulting lack of blinding for subjective endpoint assessment, the patient-reported endpoints on morbidity and health-related quality of life are classified as highly biased. Furthermore, their significance is limited because of the low return rates and the resulting short observation period. Overall, the available data basis is subject uncertainties, which leads to a downgrading of the significance of the evidence for the overall assessment. The significance of the evidence for the additional benefit identified must therefore be classified as a "hint".

2.1.3 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Poteligeo with the active ingredient mogamulizumab. Poteligeo was approved as an orphan drug. Mogamulizumab is indicated for the treatment of adult patients with mycosis fungoides or Sézary syndrome who have received at least one prior systemic therapy.

The pharmaceutical company presents the open-label, randomised MAVORIC Phase III study in which mogamulizumab was compared with vorinostat.

Vorinostat is not approved in Germany; however, according to the written statements received, it is used in Germany in individual cases. In accordance with the statements of the clinical experts in the written statement procedure, in the present therapeutic indication, several therapeutic options, including approved medicinal products, are used in clinical practice against the background of a heterogeneous patient collective. Overall, it can be assumed that the comparator vorinostat used in the study does not reflect the standard of care in Germany.

For overall survival as well as for the endpoint category morbidity and health-related quality of life, neither advantages nor disadvantages of treatment with mogamulizumab compared with vorinostat can be determined in the overall assessment.

With regard to side effects, there is a relevant, but no more than minor, advantage of mogamulizumab compared with vorinostat in terms of severe adverse events (CTCAE grade ≥ 3) and therapy discontinuations because of adverse events.

Because of the limitations in the significance of the present study for the reality of care in Germany, from the perspective of the G-BA, there are major uncertainties in the interpretation of the study results. These are estimated to be so significant that, despite the relevant advantages with respect to side effects, they do not allow a quantification of the extent of the additional benefit overall.

Furthermore, there are still uncertainties in the interpretation of the patient-reported endpoints because of the open study design and the short observation period as a result of low return rates.

In the overall view, there is a hint for a non-quantifiable additional benefit of mogamulizumab compared with vorinostat because the scientific data basis does not allow quantification.

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

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

The resolution will be based on the information from the dossier of the pharmaceutical company. However, it should be considered that the range of patient numbers presented tends to be an overestimation. This is mainly due to the fact that the derivation for all prevalent cases with MF and SS is not restricted to patients who have received at least one previous systemic therapy.

Overall, patient numbers are subject to uncertainty and tend to be overestimated.

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 Poteligeo (active ingredient: mogamulizumab) at the following publicly accessible link (last access: 26 October 2020):

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

Treatment with mogamulizumab may be initiated and monitored only by specialists in internal medicine, haematology, and oncology, specialists in skin and venereal diseases, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with mycosis fungoides or Sézary syndrome.

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 November 2020).

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 different for each individual patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", the time between individual treatments, and 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				
Mogamulizumab	Cyclical (every 28 days) 1st cycle: Day 1, 8, 15, and 22; 2nd – 13th cycle: Day 1 and 15:	13	2–4	28

Usage and consumption:

The active ingredient mogamulizumab is dosed depending on body weight. For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017– Questions about Health – body measurements of the population" were used as a basis (average body weight): 77.0 kg)[3].

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annually consumption by potency
Medicinal product to be assessed					
Mogamulizumab	1 mg/kg = 77 mg	77 mg	4 × 20 mg	28	112 × 20 mg

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

Costs:

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

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

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Mogamulizumab 20 mg	5 ml CII	€ 1,890.78	€ 1.77	€ 110.19	€ 1,778.82
Abbreviations: CII = concentrate for the preparation of an injection or infusion solution					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 November 2020

Costs for additionally required SHI services:

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

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

No additionally required SHI services are taken into account in calculating costs.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the 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 *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the *Hilfstaxe*. The cost representation is based on the pharmacy sales 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 according to the regulations in Annex 3 of the *Hilfstaxe*.

3. Bureaucratic costs

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

4. Process sequence

On 11 June 2020, the pharmaceutical company submitted a dossier for the benefit assessment of mogamulizumab to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2.

The benefit assessment of the G-BA was published on 15 September 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 October 2020.

The oral hearing was held on 27 October 2020.

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

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

At its session on 3 December 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 September 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	13 October 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 October 2020	Conduct of the oral hearing
Working group Section 35a	3 November 2020 17 November 2020	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 on Medicinal Products	24 November 2020	Concluding discussion of the draft resolution

Plenum	3 December 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 3 December 2020

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

Prof. Hecken