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: Tafasitamab (diffuse large B-cell lymphoma (DLBCL), combination with lenalidomide)

of 3 March 2022

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, 1st 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 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 € 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 marketing authorisation 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 (German) market of the active ingredient tafasitamab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 September 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 August 2021.

Tafasitamab for the treatment of diffuse large B-cell lymphoma (DLBCL) is approved in combination with lenalidomide as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

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 marketing 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 2021 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 made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-26) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering 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 tafasitamab.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Tafasitamab (Minjuvi) according to product information

Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT).

Therapeutic indication of the resolution (resolution of 3 March 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT)

In summary, the additional benefit of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy is assessed as follows:

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

Justification:

The pharmaceutical company uses the results of the L-MIND study to demonstrate the extent of the additional benefit of tafasitamab for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults who are not eligible for autologous stem cell transplant (ASCT). Since no data from direct comparator studies are available, the pharmaceutical company also submits indirect comparisons with external control studies (RE-MIND and RE-MIND2) with the dossier.

About the L-MIND study

The L-MIND study is an ongoing multicentre, open-label, single-arm phase II study. The L-MIND study enrolled 81 patients with histologically confirmed, relapsed or refractory DLBCL who had already received CD20-targeted therapy and who were not eligible for autologous stem cell transplant (ASCT). Reasons for not being eligible for ASCT were advanced age (> 70 years; 46%), refractoriness to chemotherapy (22.5%), refusal of high-dose chemotherapy and/or ASCT (16 %), comorbidities (14%) or other reasons (1%).

The study population had a median age of 72 years and had received one (49%) or two (43%) prior systemic DLBCL therapies, and adults with up to 4 prior systemic DLBCL therapies were enrolled in the study. Patients had an Eastern Co-operative Oncology Group Performance Status (ECOG-PS) of 0 - 2 and about 60% had an International Prognostic Index (IPI) of 2 or 3. Although patients with primary refractoriness[2] were excluded based on the study criteria, 15

[2] Disease progression during first-line therapy according to the IWG response criteria (Cheson et al., 2007) and/or a response to first-line therapy lower than a partial response or a relapse/progression within 6 months of the end of first-line therapy

patients (18.5%) were primary refractory. In contrast, the relapse occurred in more than 75% of the patients in the L-MIND study after ≥ 12 months.

The study population was treated with tafasitamab (12 mg/kg) and lenalidomide (starting dose 25 mg) as combination therapy for up to 12 cycles of 28 days (depending, among other things, on occurring toxicity), followed by monotherapy with tafasitamab until disease progression in patients with at least one stable disease or beyond according to the medical investigator's risk/benefit assessment.

The study took place in a total of 10 EU countries as well as the UK and the USA and started in March 2016. The end of the study is planned for November 2022.

The primary endpoint of the study is the objective response rate; secondary endpoints include overall survival, progression-free survival and adverse events. Data are available from both the 1st data cut-off from 30 November 2018, as well as from the 2nd data cut-off from 30 November 2019 and the 3rd data cut-off from 30 October 2020. For the present benefit assessment, the data cut-off from 30 October 2020 is used, which was also submitted to the EMA in the marketing authorisation procedure.

Indirect comparisons

In the dossier, the pharmaceutical company presents an indirect comparison to derive an additional benefit of tafasitamab. For this indirect comparison, the pharmaceutical company presents the retrospective observational study RE-MIND2 in addition to the L-MIND study, in which patients with relapsed or refractory DLBCL were enrolled and given a patient-individual therapy.

In addition, the pharmaceutical company also submits the retrospective observational study RE-MIND, which was submitted with the dossier as part of the marketing authorisation procedure, but does not use it to derive an additional benefit. The RE-MIND study enrolled patients with relapsed or refractory DLBCL who were exclusively given lenalidomide monotherapy.

Propensity score matching was used for each of the two indirect comparisons to adjust for differences between the study populations. However, on the part of the pharmaceutical company, no systematic research was presented for the identification of potential confounders as well as for the operationalisation of the matching factors considered (e.g. to justify the choice of binary expressions) and an assessment based on this, so that other confounders or other operationalisations of the confounders considered may also be relevant.

The reporting quality of the submitted study documents basically shows numerous limitations.

About the RE-MIND2 study

The RE-MIND2 study enrolled patients with relapsed and refractory DLBCL who were given patient-individual therapy according to doctor's instructions in line with the study protocol. In the view of the G-BA, the majority of the treatment options carried out in the RE-MIND2 study correspond to the treatment standard considered generally accepted in Germany.

The underlying information was retrospectively extracted from patient records. In doing so, similarity in terms of the geographical origin of the patients between the studies was taken into account. Propensity score matching between the L-MIND and RE-MIND2 studies was done at a ratio of 1:1, despite an originally planned ratio of up to 1:4. Confounders included age, Ann Arbor Stage, refractoriness to the last line of therapy, number of prior therapies,

primary refractoriness, prior ASCT, elevated LDH levels, neutropenia and anaemia. In contrast, the ECOG-PS was not included in the matching presented as a primary analysis. However, a sensitivity analysis presented with the inclusion of the ECOG-PS as part of the written statement procedure represents a partially or completely different matching population. The criteria considered appear to be relevant in principle for the adjustment in the present therapeutic indication, but no systematic research is available in this regard, as already described. There was also no examination of multivariable imbalances between the patient characteristics considered in the matching.

The most relevant prognostic criterion in the therapeutic indication is the "time between initial diagnosis of DLBCL and first relapse", according to the clinical experts' statements as part of the written statement procedure. The clinical experts justified this by stating that DLBCL patients who are refractory or have an early relapse respond significantly worse to already established therapy options than patients with a late relapse. According to the clinical experts, due to the high percentage of patients with a late relapse in the L-MIND study, it can be assumed that the population was selected with regard to risk, since only very few patients with refractoriness or an early relapse and thus, poor risk, were included. No information is available for the RE-MIND2 study in this regard, so it is unclear whether the study populations of the L-MIND and RE-MIND2 studies are sufficiently comparable with regard to this relevant prognostic criterion "time between initial DLBCL diagnosis and first relapse". For the propensity score matching, the primary refractoriness was taken into account in binary form in the matching, but in the view of the G-BA, the operationalisation is not sufficient to adequately represent the criterion "time between initial diagnosis of DLBCL and first relapse" in the present therapeutic indication.

In addition, only limited information on the operationalisation of patient-relevant endpoints is available from the RE-MIND2 study, so that there are also uncertainties in the comparability of the L-MIND and RE-MIND studies in this respect.

Overall, the indirect comparison between the L-MIND and RE-MIND2 studies is thus based on major uncertainties, which result in particular from the question of sufficient comparability of the study populations with regard to the relevant prognostic factor "time between initial DLBCL diagnosis and first relapse". In addition, there is no assessment and systematic research to identify potential confounders in the therapeutic indication.

In the overall analysis, the RE-MIND2 study is therefore not used for an indirect comparison to derive an additional benefit of tafasitamab.

About the RE-MIND study

The external control study RE-MIND was submitted for the calculation of an indirect comparison with the L-MIND study as part of the marketing authorisation procedure. The underlying information was extracted retrospectively from patient records, with the enrolled patients given lenalidomide monotherapy. In the view of the G-BA, this therapy is a suitable treatment option for some of the patients in the therapeutic indication.

For propensity score matching, the confounders age, Ann Arbor stage, refractoriness to the last line of therapy, number of prior therapies, primary refractoriness, prior ASCT, elevated LDH levels, neutropenia and anaemia were also considered. In contrast, the ECOG-PS was not included in the matching presented as a primary analysis. In contrast, a sensitivity analysis presented with the inclusion of the ECOG-PS represents a partially or completely different matching population. As already explained in the section "About the RE-MIND2 study", the factors taken into account for propensity score matching appear to be relevant in principle for the adjustment in the present therapeutic indication, but no systematic research is available

in this regard. A check for multivariable imbalances between the patient characteristics considered in the matching is also not available.

With regard to the patient characteristic "time between initial DLBCL diagnosis and first relapse" already discussed in the section "About the RE-MIND2 study", no information is available for the RE-MIND study, so that it is also unclear for this indirect comparison whether the L-MIND and RE-MIND studies are sufficiently comparable with regard to the criterion "time between initial DLBCL diagnosis and first relapse".

Finally, only limited information on the operationalisation of patient-relevant endpoints is available from the RE-MIND study, so that there are also uncertainties in the comparability of the L-MIND and RE-MIND studies in this respect.

Overall, the indirect comparison between the L-MIND and RE-MIND studies is therefore based on major uncertainties, which result in particular from the question of sufficient comparability of the study populations with regard to the relevant prognostic factor "time between initial DLBCL diagnosis and first relapse". In addition, there is no assessment and systematic research to identify potential confounders in the therapeutic indication.

In the overall analysis, the G-BA follows the pharmaceutical company and does not use the RE-MIND study for an indirect comparison to derive an additional benefit of tafasitamab.

Thus, no suitable comparator data are available for the assessment of tafasitamab for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults who are not eligible for autologous stem cell transplant.

About the results of the L-MIND study

Mortality

In the L-MIND study, 41 (51.3%) deaths were observed, with a median survival time of 33.5 months.

No conclusions on the extent of the additional benefit could be derived due to the absence of comparator data.

Morbidity

Progression-free survival (PFS)

PFS was assessed as a secondary endpoint in the L-MIND study and defined as the time from initial administration of the study medication until the occurrence of disease progression or death from any cause, whichever occurs first. In doing so, the endpoint component of disease progression was recorded according to the revised response criteria for malignant lymphomas according to Cheson et al. (2007). However, it is not clear from the study documents whether only disease progression or also relapses were recorded under disease progression.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The "mortality" endpoint component was assessed as an independent endpoint in the present study via the "overall survival" endpoint.

The morbidity component was not assessed on the basis of symptoms according to the operationalisation, but exclusively using imaging 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 extent of the additional benefit remains unaffected.

Notwithstanding that, the results of the L-MIND study for the PFS endpoint do not allow a statement to be made on the extent of the additional benefit due to the absence of suitable comparator data. The PFS endpoint is presented additionally.

Objective response rate (ORR)

Objective response rate was assessed as the primary endpoint in the L-MIND study and is defined as the percentage of patients with a complete response (CR) or partial response (PR) up to disease progression based on key radiological and clinical assessments. In addition, as a further component of response, the pharmaceutical company submits the duration of response (up to a CR or PR), which is defined as the time interval between the initial point of time of a tumour response (CR or PR, whichever occurs first) and the first point of time of a documented disease progression or relapse.

The endpoint of complete response (CR) is an important prognostic factor and relevant for the treatment decision. A CR associated with a noticeable reduction in disease symptoms for the patient is generally relevant for the benefit assessment.

In the L-MIND study, the ORR endpoint was assessed using imaging procedures on the basis of the response criteria of the International Working Group (IWG, Cheson et al., 2007). Thus, the endpoint was not assessed based on symptoms but on asymptomatic findings. In addition, there are relevant uncertainties regarding the operationalisation of the endpoint. The objective response rate is assessed as being not directly patient-relevant in the present operationalisation.

B-symptomatology

B-symptomatology was not defined as a separate endpoint in the L-MIND study, but the symptoms encompassed by B-symptomatology were assessed at the beginning of each treatment cycle. These are:

- unintentional weight loss of more than 10% within the past 6 months,
- fever (> 38°C) on all of the past 3 days in the absence of an infection and
- night sweats in the absence of an infection.

At baseline, less than 10% of patients showed lymphoma-associated B symptomatology. After 4 cycles, B-symptoms were still reported for one study participant (1.3%).

A decrease in B-symptomatology represents a patient-relevant effect. However, the operationalisation, in particular the assessment is not fully comprehensible in the L-MIND study. Further information, for example on the duration of the response, is also not available due to low return rates.

According to the statements of the clinical experts in the written statement procedure, B-symptoms are characteristic of DLBCL, but not predictive, since the observed symptoms in relapsed or refractory DLBCL are not exclusively lymphoma-related.

Notwithstanding that, the results of the L-MIND study for the B-symptomatology endpoint do not allow a statement to be made on the extent of the additional benefit due to the absence of suitable comparator data.

In the overall analysis of the results on morbidity, no statements on the extent of additional benefit can be derived due to the absence of suitable comparator data.

Quality of life

Quality of life was not recorded in the L-MIND study.

Side effects

Total adverse events (AEs)

One adverse event occurred in all patients enrolled in the study. The results are presented additionally.

Serious adverse events (SAEs)

43 out of 81 patients (53.1%) had at least one serious adverse event (SAE). The most frequent SAEs are "Infections and infestations".

Severe adverse events (CTCAE grade ≥ 3)

63 out of 81 study participants (77.8%) had at least one severe AE with CTCAE grade ≥ 3. The most frequent AEs with a severity grade ≥ 3 were "Blood and lymphatic system disorders" and "Infections and infestations".

Therapy discontinuation due to adverse events

In 20 patients (24.7%), an adverse event occurred that led to the discontinuation of at least one active ingredient component of the study medication.

AE of special interest

In 37% of the study participants, "skin rash" occurred as a post-hoc adverse event of special interest. In addition, "diseases of the urinary tract" should be mentioned as another post-hoc AE of special interest.

In the overall analysis of the results on side effects, no statements can be made on the extent of additional benefit due to the absence of suitable comparator data.

Overall assessment / conclusion

For the benefit assessment of tafasitamab in combination with lenalidomide followed by tafasitamab for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT), results from the single-arm, pivotal phase II L-MIND study on overall survival, morbidity and side effects are available.

In addition, the pharmaceutical company presents an indirect comparison with the RE-MIND2 external control study. Another indirect comparison with the RE-MIND external control study is also submitted with the dossier, but is not used by the pharmaceutical company to derive an additional benefit. Overall, the indirect comparisons between the studies are based on large uncertainties, which result in particular from the question of sufficient comparability of the study populations with regard to the relevant prognostic factor "time between initial DLBCL diagnosis and first relapse". Furthermore, there is also no assessment and systematic research to identify potential confounders in the therapeutic indication.

Due to these uncertainties, the indirect comparisons are not suitable for making statements about the extent of additional benefit and are not used for the benefit assessment. Thus, quantification of the additional benefit is not possible on the basis of the data presented.

In the overall assessment, a non-quantifiable additional benefit is determined for tafasitamab in combination with lenalidomide followed by tafasitamab for the treatment of relapsed or refractory DLBCL in adults who are not eligible for autologous stem cell transplant since the scientific data does not allow quantification.

Significance of the evidence

The L-MIND study is a single-arm study, so there are no direct comparator data for a control group. The indirect comparisons with external control studies submitted by the pharmaceutical company are inappropriate. Overall, the available data do not allow a comparative assessment.

The result is a hint for an additional benefit with regard to significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Minjuvi with the active ingredient tafasitamab.

Tafasitamab was approved as an orphan drug under special conditions for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults who are not eligible for autologous stem cell transplant (ASCT).

The benefit assessment of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy is based on the pivotal, ongoing, single-arm, phase II L-MIND study.

In addition, the pharmaceutical company presents an indirect comparison with the RE-MIND2 external control study. Another indirect comparison with the RE-MIND external control study is also submitted with the dossier, but is not used by the pharmaceutical company to derive an additional benefit. Overall, the indirect comparisons between the studies are based on large uncertainties, which result in particular from the question of sufficient comparability of the study populations with regard to the relevant prognostic factor "time between initial DLBCL diagnosis and first relapse". Furthermore, there is also no assessment and systematic research to identify potential confounders in the therapeutic indication.

Due to these uncertainties, the indirect comparisons are not suitable for making statements about the extent of additional benefit and are not used for the benefit assessment. Thus, quantification of the additional benefit is not possible on the basis of the data presented.

In the overall assessment, a hint for a non-quantifiable additional benefit is determined for tafasitamab in combination with lenalidomide since the scientific data does not allow quantification.

The significance of the evidence gives a hint for the additional benefit determined.

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

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT)

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

In the present therapeutic indication, it is a heterogeneous patient population consisting of patients with different numbers of prior therapies and different forms of DLBCL. The information provided by the pharmaceutical company in the dossier is mathematically comprehensible, but there are methodological limitations and the transferability of the proportion values used is questionable at several points. In particular, the upper limit calculated in the present dossier tends to be an overestimate. In the absence of better data basis and in order to enable a consistent consideration of the patient numbers, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication, the G-BA considers it appropriate to use the patient numbers cited in the resolution on polatuzumab vedotin of 20 August 2020.

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 Minjuvi (active ingredient: tafasitamab) at the following publicly accessible link (last access: 16 December 2021):
https://www.ema.europa.eu/documents/product-information/minjuvi-epar-product-information_en.pdf

Treatment with tafasitamab should only be initiated and monitored by specialists in internal medicine, haematology and oncology, experienced in the treatment of patients with diffuse large B-cell lymphoma (DLBCL).

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

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant (ASCT)

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 February 2022).

In the present therapeutic indication, the product information for tafasitamab specifies a combination with lenalidomide over 12 cycles. The recommended dose of tafasitamab is 12 mg/ kg body weight. For lenalidomide, the recommended initial dose is 25 mg. Combination therapy is followed by the administration of tafasitamab as a single agent until disease progression or unacceptable toxicity.

For the presentation of the costs, one year is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued prematurely due to non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tafasitamab	Combination therapy 28-day cycle; Cycle 1: Day 1.4, 8.15 and 22 Cycle 2+3: Day 1, 8, 15 and 22 Cycle 4–12: Day 1 and 15	12	Cycle 1: 5 Cycle 2+3: 4 Cycle 4–12: 2	31
	Monotherapy: 28-day cycle; Day 1 and 15	1	2	2
Lenalidomide	on day 1-21 of a 28-day cycle	12	21	252

Consumption:

The average body measurements were applied for dosages depending on body weight (BW) or body surface area (BSA), (average body height of adults: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916). 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).[3]

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					
Tafasitamab	12 mg/kg = 924 mg	924 mg	5 x 200 mg	33	165 x 200 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	252	252 x 25 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					
Tafasitamab 200 mg	1 SFI	€ 999.97	1.77	€ 54.74	€ 943.46
Lenalidomide 25 mg	21 HC	€ 8,331.13	1.77	€ 475.20	€ 7,854.16
Abbreviations: HC = hard capsules; SFI = solution for injection					

LAUER-TAXE® last revised: 15.02.2022

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

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

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.

According to the product information for tafasitamab (Minjuvi), patients should be pretreated with premedication, which may include antipyretics, antihistamines or corticosteroids, prior to administration of tafasitamab. This premedication is recommended during the first 3 infusions and is optional for subsequent infusions. The product information does not provide any specific information why the necessary costs cannot be quantified for the premedication.

Patients receiving therapy with lenalidomide should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[4]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

Overall, additionally required SHI services are required for the diagnosis of suspected chronic hepatitis B, which are taken into account in the resolution.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed: *Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy*				
Lenalidomide	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)	1	€ 89.50	€ 89.50

Other SHI services:

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

[4] "Update of the S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

On 30 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of tafasitamab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 December 2021 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 2022.

The oral hearing was held on 24 January 2022.

An amendment to the benefit assessment with a supplementary assessment from data submitted in the written statement procedure was submitted on 11 February 2022.

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 22 February 2022, and the proposed resolution was approved.

At its session on 3 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation

Subcommittee Medicinal product	7 December 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	11 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 January 2022	Conduct of the oral hearing
Working group Section 35a	2 February 2022 16 February 2022	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 product	22 February 2022	Concluding discussion of the draft resolution
Plenum	3 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 March 2022

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

Prof. Hecken