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 Polatuzumab Vedotin (new therapeutic indication: diffuse large B-cell lymphoma (DLBCL), combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP))

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

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

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

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

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient polatuzumab vedotin (Polivy) was listed for the first time on 15 February 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 24 May 2022, polatuzumab vedotin received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

Polatuzumab vedotin for the treatment of previously untreated diffuse large B-cell lymphoma (DLBCL) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

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

On 30 May 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient polatuzumab vedotin with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication)

"Polivy in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)".

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 1 September 2022 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 G22-22) 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 polatuzumab vedotin.

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 Polatuzumab Vedotin (Polivy) according to the product information

Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Therapeutic indication of the resolution (resolution of 1 December 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adults with previously untreated diffuse large B-cell lymphoma (DLBCL)

In summary, the additional benefit of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) is assessed as follows:

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

Justification:

The results of the multicentre, double-blind, placebo-controlled randomised POLARIX study comparing polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (Pola + R-CHP) versus rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) are available to assess the additional benefit of polatuzumab vedotin for the treatment of adults with previously untreated DLBCL.

The POLARIX study, ongoing since November 2017, is being conducted in a total of 211 study sites in 22 countries across Europe, North America, Asia and Australia.

In the dossier, the pharmaceutical company presents the results of the first data cut-off of the POLARIX study from 28 June 2021, which represents the primary analysis of progression-free survival (PFS). Another non-pre-specified interim analysis took place on 25 February 2022. As part of the written statement procedure, the pharmaceutical company submitted the results of the third data cut-off from 15 June 2022, including the final analysis of overall survival. This data cut-off is the basis of the benefit assessment. The end of the POLARIX study is defined as

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

the time when the last enrolled subject has reached the follow-up period of 3 years after the treatment completion visit.

A total of N = 879 subjects with previously untreated CD20-positive DLBCL with an International Prognostic Index (IPI) of 2 - 5 and an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 - 2 were enrolled in the study. 440 participants were randomised to the intervention arm (Pola + R-CHP) and 439 participants to the control arm (R-CHOP). Randomisation was stratified according to patients' IPI score (2 vs 3-5), bulky disease characteristic defined as lesion ≥ 7.5 cm (present vs absent) and geographical region (Western Europe, USA, Canada, Australia vs Asia vs other countries). Patient characteristics were comparable between the two study arms.

The subjects randomised to the intervention arm received 6 cycles of Pola + R-CHP followed by 2 cycles of rituximab. In the control arm, 6 cycles of R-CHOP followed by 2 cycles of rituximab were administered. In both study arms, patients received granulocyte colony-stimulating factor (G-CSF) for prevention of neutropenia.

The primary endpoint of the POLARIX study was PFS as assessed by the medical investigators.

Mortality

The endpoint of overall survival was defined in the POLARIX study as the time from randomisation to death from any cause. With regard to the endpoint of overall survival, there was no statistically significant difference between Pola + R-CHP and R-CHOP. Median duration of overall survival had not been reached in either study arm at the data cut-off from 15 June 2022.

Morbidity

Event-free survival (EFS)

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant. The significance of the endpoint depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

The endpoint "event-free survival" (EFS) in the POLARIX study was defined as the time between randomisation and the first occurrence of one of the following events:

- Disease progression or relapse,
- Initiation of a new anti-lymphoma therapy
  (An efficacy event as estimated by the medical investigator other than progression or relapse leading to initiation of Next Anti-Lymphoma Therapy (NALT) not specified in the protocol, e.g., confirmed or suspected residual disease),
- Biopsy after end of treatment demonstrating residual disease, whether or not NALT initiation has occurred; or
- death from any cause.

Recurrences were recorded using the Lugano response criteria for malignant lymphomas[2].

The prerequisite for curation is the achievement of a complete remission (CR). In order to depict the failure of the curative therapeutic approach, both a non-achievement of the CR by the therapy and a possible disease relapse after achieving the CR must therefore be recorded in the endpoint. Disease relapses are taken into account in the EFS via the events relapse and death. The disease progression component covers some of the patients who do not achieve a CR. However, against the background of the response criteria, disease progression does not represent all events of non-achievement of a CR, as partial remission (PR) and stable disease (SD) also represent events of non-achievement of a CR.

In this regard, the present operationalisation of the EFS results in an ambiguity as to the extent to which the events of an SD or PR are fully recorded by the "initiation of next anti-lymphoma therapy" and "positive biopsy result after the end of treatment". However, in the POLARIX study, less than 10% of patients in the intervention and control arms had a PR and less than 1% had an SD at the end of treatment. Moreover, according to clinical experts at the oral hearing on the present benefit assessment, the operationalisation of the EFS used in the POLARIX study adequately reflects the reality of care. Against this background, there is still uncertainty about the significance of the EFS in the present operationalisation, which is estimated to be low.

The results for the EFS endpoint show a statistically significant difference in favour of Pola + R-CHP. The median EFS had not yet been reached in both the intervention and control arms of the POLARIX study at the time of the final data cut-off from 15 June 2022. The statistically significant difference is based on a hazard ratio (HR) of 0.785, an upper 95% confidence interval limit of 0.999 and a p value of 0.0484, indicating only a minimal statistically significant difference. It should be noted that the assessment of EFS events was not based on an independent central assessment, but was carried out by the local, but blinded, medical investigators.

In the overall assessment, the present minimal statistically significant difference in the EFS is not considered sufficiently reliable due to the low magnitude of the effect in connection with the existing limitations to be able to determine with sufficient certainty an improvement in the therapeutic benefit of Pola + R-CHP in relation to a failure of the potential cure by the present curative therapeutic approach.

Disease-free survival (DFS)

Disease-free survival was defined in the POLARIX study as the time from the first occurrence of a documented complete remission (CR) until the occurrence of a relapse or until death from any cause. The assessment of CR in the context of antineoplastic therapy as well as relapse

[2] Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-3068.

was performed by the medical investigators based on PET-CT and/or CT (with contrast agent) images using the Lugano criteria for malignant lymphomas[2].

Based on the curative therapeutic approach presented here, recurrences represent patient-relevant events. Recurrence means that the attempt at a cure by the curative therapeutic approach was unsuccessful.

The results for the DFS endpoint show a minimal statistically significant difference in favour of Pola + R-CHP with an HR of 0.72, an upper 95% confidence interval limit of 0.99 and a p value of 0.0397.

In accordance with the operationalisation of the DFS endpoint in the POLARIX study, only patients in whom a CR had been achieved as a result of the therapy in the intervention and comparator arm of the study were included in the evaluation. Thus, compared with the ITT population, this is an evaluation population which is selected by study treatment and is associated with a potential break in randomisation. There is a clear difference between the number of patients in the ITT population and the evaluation population for DFS. Moreover, more patients from the intervention arm than from the comparator arm are included in the analysis. Therefore, the outcome of the endpoint is assessed as being fraught with a high risk of bias per se.

Furthermore, the number of CR events in both treatment arms at the end of treatment is lower than the number of patients included in the DFS analysis. In addition to patients with CR after completion of first-line therapy, it is unclear as to the extent to which subjects, who had been diagnosed with CR in the meantime and a relapse has occurred in them before completion of therapy, were also considered for the DFS analysis. This ambiguity could not be completely resolved by the pharmaceutical company.

Due to the overall relevant uncertainties and taking into account the merely minimal statistically significant effect, the result for the DFS endpoint is not used in the present assessment to quantify the extent of the additional benefit.

Progression-free survival (PFS)

Progression-free survival (PFS) in the POLARIX study was defined as the time between randomisation and the first occurrence of disease progression, relapse or death from any cause, whichever occurred first.

PFS was statistically significantly prolonged with Pola + R-CHP compared to R-CHOP.

The endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The endpoint components disease progression and recurrence, among other endpoint components, are included in the endpoint of event-free survival (EFS).

Against the background of the curative therapeutic approach presented here, the significance of the PFS in the present operationalisation, also compared to the endpoints of event-free

survival (EFS) and disease-free survival (DFS), is assessed as unclear for the assessment of the extent of additional benefit. The PFS endpoint is not used to quantify the extent of additional benefit.

Patient-reported endpoints:

For the patient-reported endpoints on morbidity, responder analyses were provided by the pharmaceutical company on the percentage of subjects with deterioration in the cancer-specific EORTC QLQ-C30 questionnaire, the Functional Assessment of Cancer Therapy/ Gynaecologic Oncology Group - Neurotoxicity (FACT/GOG-NTX) questionnaire and the European Quality of Life 5 Dimension visual analogue scale (EQ-5D-VAS). In addition, a pre-specified time-to-event analysis was presented for time to deterioration in the fatigue score of the EORTC QLQ-C30 by ≥ 10 points. Furthermore, MMRM analyses of change compared to baseline were presented.

Against the background of the handling of missing values (exclusion from the analysis population) and the return rates achieved, the responder analyses are not used for the benefit assessment. The MMRM analyses are considered for the present assessment. In addition, the pre-specified time-to-event analysis for time to deterioration in the fatigue score of the EORTC QLQ-C30 by ≥ 10 points is used for morbidity.

Disease symptomatology

Based on the results for the EORTC QLQ-C30 symptom scales, there was no statistically significant difference between the treatment arms for any symptom scale in the MMRM analyses at the end of treatment.

Chemotherapy-induced neurotoxicity

Chemotherapy-induced neurotoxicity was assessed using the FACT/GOG-NTX. There was a statistically significant advantage of Pola + R-CHP over R-CHOP at the end of treatment in the MMRM analyses.

However, no evaluations of standardised irrelevance thresholds (e.g., Hegdes` g) for the mean differences (MD) were submitted by the pharmaceutical company. The clinical relevance of this effect therefore remains unclear.

General health status

Based on the results for the EQ-5D-VAS, there was no statistically significant difference between the treatment arms in the MMRM analyses.

<u>Quality of life</u>

For the patient-reported endpoints on quality of life, responder analyses were provided by the pharmaceutical company on the percentage of subjects with deterioration in the cancer-specific questionnaire EORTC QLQ-C30 as well as in the questionnaire Functional Assessment of Cancer Therapy-Lymphoma (FACT-LymS). In addition, a pre-specified time-to-event analysis

was presented for time to deterioration in the physical functioning scale of the EORTC QLQ-C30 by ≥ 10 points. Furthermore, MMRM analyses of change compared to baseline were presented.

Against the background of the handling of missing values (exclusion from the analysis population) and the return rates achieved, the responder analyses are not used for the benefit assessment. The MMRM analyses are considered for the present assessment. In addition, the pre-specified time-to-event analysis for time to deterioration in the physical functioning scale of the EORTC QLQ-C30 by ≥ 10 points is used.

Based on the results of the MMRM analyses on the EORTC QLQ-C30 scales and the FACT-LymS, as well as the time to deterioration in the physical functioning scale of the EORTC QLQ-C30 by ≥ 10 points, no statistically significant difference was observed between the treatment groups.

Thus, neither an advantage nor a disadvantage for Pola + R-CHP can be determined with regard to quality of life.

Side effects

Adverse events (AEs) were recorded in the POLARIX study from the first dose of study medication up to 90 days after the last dose or until the start of subsequent therapy. There was no statistically significant difference in the occurrence of AEs, serious AEs (SAEs) or severe AEs, or in therapy discontinuations due to AEs.

In detail, Pola + R-CHP showed a statistically significant disadvantage of AEs of the system organ class (SOC) infections and infestations. In addition, there was an increase in febrile neutropenia and diarrhoea with Pola + R-CHP. There was also a disadvantage of Pola + R-CHP with regard to severe febrile neutropenia. However, there was a statistically significant advantage of Pola + R-CHP for the SOC cardiac disorders. There was no statistically significant difference for SAEs or AEs of special interest.

Overall, no advantage or disadvantage of Pola + R-CHP over R-CHOP can be derived from the results on side effects.

Overall assessment

For the benefit assessment of polatuzumab vedotin for the treatment of adults with previously untreated DLBCL, the results of the double-blind, randomised POLARIX study comparing Pola + R-CHP versus R-CHOP are available.

For the endpoint of overall survival, there were no statistically significant differences between the treatment arms in the POLARIX study.

In the endpoint category of morbidity, the endpoint of event-free survival (EFS) showed a minimal statistically significant difference in favour of Pola + R-CHP, which due to the low magnitude of the effect in connection with the existing limitations is not considered

sufficiently reliable to be able to determine with sufficient certainty an improvement in the therapeutic benefit of Pola + R-CHP in this respect.

The results for the endpoint of disease-free survival (DFS) are not used to quantify the extent of the additional benefit due to the overall relevant uncertainties caused by the break in randomisation and the present operationalisation of DFS and taking into account the merely minimal statistically significant effect.

With regard to the patient-reported endpoints of disease symptomatology and general health status, there were no statistically significant differences between the study arms, so that neither an advantage nor a disadvantage of Pola + R-CHP can be identified. The clinical relevance of the statistically significant effect in the endpoint chemotherapy-induced neurotoxicity is unclear.

In terms of quality of life, the results on the EORTC QLQ-C30 and FACT-LymS showed no statistically significant differences, which is why neither an advantage nor a disadvantage of Pola + R-CHP can be identified with regard to quality of life.

The endpoints on side effects show no relevant difference overall between Pola + R-CHP compared to R-CHOP, which is why neither an advantage nor a disadvantage of Pola + R-CHP can be identified.

In the overall assessment, the G-BA classifies the extent of the additional benefit of Pola + R-CHP as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

For the assessment of the additional benefit of polatuzumab vedotin, results of the double-blind, randomised POLARIX study comparing Pola + R-CHP versus R-CHOP were presented.

The risk of bias at the study level is estimated to be low. For the endpoints, the risk of bias is partly low, partly high and unclear for the patient-reported endpoints.

Uncertainties arise from the close follow-up carried out in the POLARIX study by means of PET-CT and CT examinations in all study participants. This was also done for asymptomatic subjects every 6 months for 2 years and then every 12 months for the following years.

This approach deviates from clinical practice, according to the statement of the clinical experts at the oral hearing. Against the background of high false-positive rates of PET-CT and CT examinations[3], the G-BA assumes uncertainty with regard to the transferability of the results for the EFS endpoint to the German healthcare context.

The overall significance of the results for the observed non-quantified additional benefit is low, which is why the significance of the evidence is classified as a "hint".

[3] Tokola S, Kuitunen H, Turpeenniemi-Hujanen T, Kuittinen O. Interim and end-of-treatment PET-CT suffers from high false-positive rates in DLBCL: Biopsy is needed prior to treatment decisions. Cancer Med. 2021 May;10(9):3035-3044. doi: 10.1002/cam4.3867. Epub 2021 Mar 31. PMID: 33792190; PMCID: PMC8085947.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient polatuzumab vedotin. Polivy was approved as an orphan drug under "special conditions".

The therapeutic indication assessed here is as follows: "Polivy in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)."

For the benefit assessment of polatuzumab vedotin for the treatment of adults with previously untreated DLBCL, the results of the double-blind, randomised POLARIX study comparing polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (Pola + R-CHP) versus rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) are available.

For the endpoint of overall survival, there is no statistically significant difference between the treatment arms in the POLARIX study.

In the endpoint category of morbidity, the endpoint of event-free survival (EFS) showed a minimal statistically significant difference in favour of Pola + R-CHP, which due to the low magnitude of the effect in connection with the existing limitations is not considered sufficiently reliable to be able to determine with sufficient certainty an improvement in the therapeutic benefit of Pola + R-CHP.

The results for the endpoint of disease-free survival (DFS) are not used to quantify the extent of the additional benefit due to the overall relevant uncertainties and taking into account the merely minimal statistically significant effect.

There were no statistically significant differences in the patient-reported endpoints of disease symptomatology and general health status. The clinical relevance of the statistically significant effect in the endpoint chemotherapy-induced neurotoxicity is unclear.

There were no statistically significant differences with regard to quality of life and side effects.

In the overall assessment, a hint for a non-quantifiable additional benefit of Pola + R-CHP is identified since the scientific data does not allow quantification.

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

Adults with previously untreated diffuse large B-cell lymphoma (DLBCL)

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The range of patients in the SHI target population stated by the pharmaceutical company is plausible in terms of magnitude. Uncertainties arise in particular

from estimating the percentage of subjects with previously untreated DLBCL who start first-line therapy. The proportionate value of 90% assumed to form the lower limit is based on a joint analysis that included European countries other than Germany and whose transferability to the German healthcare context is therefore uncertain.

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 Polivy (active ingredient: polatuzumab vedotin) at the following publicly accessible link (last access: 22 August 2022):

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

Treatment with polatuzumab vedotin 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).

Data on the safety and efficacy of polatuzumab vedotin are not available for patients with an International Prognostic Index (IPI) of 0-1.

This medicinal product was authorised 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 November 2022).

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.

Combination therapy with polatuzumab vedotin is given on day 1 of a 21-day cycle over a period of 6 cycles. Rituximab is administered as combination therapy in cycles 1 - 6, followed by monotherapy in cycles 7 and 8.

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				
Polatuzumab vedotin	on day 1 of a 21-day cycle	6	1	6
In combination with cyclophosphamide + doxorubicin + prednisone + rituximab (R-CHP)				
Cyclophosphamide	on day 1 of a 21-day cycle	6	1	6
Doxorubicin	on day 1 of a 21-day cycle	6	1	6
Prednisone	on day 1 - 5 of a 21-day cycle	6	5	30
Rituximab	on day 1 of a 21-day cycle	8	1	8

Consumption:

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average body height: 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).

The dosages of the R - CHP regime were taken from the POLARIX clinical study. The dosages for R - CHP were accordingly considered as follows: Rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m² and oral prednisone 100 mg/day.

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					
Polatuzumab vedotin	1.8 mg/kg BW = 138.6 mg	138.6 mg	1 x 140 mg	6	6 x 140 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	6	6 x 1,000 mg + 6 x 500 mg
Doxorubicin	50 mg/m² = 95 mg	95 mg	2 x 50 mg	6	12 x 50 mg
Prednisone	100 mg	100 mg	2 x 50 mg	30	60 x 50 mg
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Polatuzumab vedotin 140 mg	1 PIC	€ 11,906.03	€ 1.77	€ 0.00	€ 11,904.26
Cyclophosphamide 1,000 mg	6 PSI	€ 127.41	€ 1.77	€ 6.43	€ 119.21
Cyclophosphamide 500 mg	6 PSI	€ 84.41	€ 1.77	€ 9.25	€ 73.39
Doxorubicin 50 mg[4]	5 SFI	€ 682.12	€ 1.77	€ 53.06	€ 627.29
Doxorubicin 50 mg[4]	1 SFI	€ 151.23	€ 1.77	€ 11.07	€ 138.39
Prednisone 50 mg[4]	50 TAB	€ 68.02	€ 1.77	€ 4.49	€ 61.76
Prednisone 50 mg[4]	10 TAB	€ 23.16	€ 1.77	€ 0.94	€ 20.45
Rituximab 500 mg	1 CIS	€ 1,777.30	€ 1.77	€ 84.18	€ 1,691.35
Rituximab 100 mg	2 CIS	€ 717.18	€ 1.77	€ 33.50	€ 681.91
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets					

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<u>Costs for additionally required SHI services:</u>

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations

[4] Fixed reimbursement rate

(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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

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	Treatment days/ year	Costs/ patient/ year
Polatuzumab vedotin in combination with rituximab							
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 SFI	€ 23.67	€ 1.77	€ 5.58	€ 16.32	8	€ 65.28
Paracetamol 500 - 1,000 mg	10 TAB each 500 mg	€ 1.06[4]	0.05	0.04	€ 0.97	8	€ 0.97
	10 TAB each 1,000 mg	€ 1.06[4]	0.05	0.04	€ 0.97	8	€ 0.97
Rituximab							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1	€ 5.50
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	Treatment days/ year	Costs/ patient/ year

Hepatitis B antibody status (GOP number 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Abbreviations: SFI = solution for injection; TAB = tablets							

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Polatuzumab Vedotin

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

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review

based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 May 2022 the pharmaceutical company submitted a dossier for the benefit assessment of polatuzumab vedotin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

The benefit assessment of the G-BA was published on 1 September 2022 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 22 September 2022.

The oral hearing was held on 10 October 2022.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 8 November 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 November 2022, and the proposed resolution was approved.

At its session on 1 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 August 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	4 October 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 October 2022	Conduct of the oral hearing
Working group Section 35a	18 October 2022 1 November 2022 15 November 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 products	22 November 2022	Concluding discussion of the draft resolution
Plenum	1 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 December 2022

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

Prof. Hecken