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 (reassessment of an orphan drug > EUR 30 million turnover limit: diffuse large B-cell lymphoma (DLBCL), combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP), first-line)

of 20 June 2024

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 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.

Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) 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.

At its session on 1 December 2022, the G-BA decided on the benefit assessment of polatuzumab vedotin in the 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)" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Chapter 5 Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 2 January 2024, due to exceeding the € 30 million turnover limit within the period from December 2021 to November 2022. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO on 19 December 2023.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 April 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of polatuzumab vedotin compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 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 in relation to the appropriate comparator therapy

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 20.06.2024):

see the approved therapeutic indication

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for polatuzumab vedotin in combination with rituximab and CHP:

- Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In the therapeutic indication of previously untreated diffuse large B-cell lymphoma, in addition to polatuzumab vedotin, the chemotherapeutic agents bleomycin, busulfan, carmustine, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, mitoxantrone, vinblastine, vincristine, vindesine, the glucocorticoids dexamethasone, methylprednisolone, prednisolone and prednisone as well as the monoclonal antibody rituximab are generally approved.

on 2. Non-medicinal treatment includes stem cell transplantation and radiotherapy.

on 3. There are no resolutions on the benefit assessment of medicinal products with new active ingredients (Section 35a SGB V) in the therapeutic indication.

There is a resolution (16 January 2020) on the Directive on Inpatient Treatment Methods:

– Section 4 - Excluded methods: Allogeneic stem cell transplantation in adult patients with aggressive B-non-Hodgkin lymphoma who have not yet been treated with autologous stem cell transplantation

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy"). A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available.

The available evidence for patients with previously untreated DLBCL is categorised as limited overall.

According to current international guidelines and the written statement of the German Society for Haematology and Medical Oncology (DGHO), the immunochemotherapy R-CHOP, consisting of the components rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, is the preferred therapy standard for the first-line therapy of patients with DLBCL, including subjects at moderate-to-high or high risk. With regard to high-risk patients, other therapy regimens are also being discussed due to the poorer prognosis with R-CHOP compared to subjects without high-risk status.

According to the S3 guideline of the oncology guideline programme, the treatment alternatives doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) as well as rituximab in combination with cyclophosphamide, etoposide, doxorubicin, vincristine and prednisone (R-CHOEP) may also be considered for young patients (< 60 years) at increased risk. According to the product information, rituximab is approved in the therapeutic indication only in combination with a CHOP protocol.

It cannot be inferred from the available evidence and the written statement of the scientific-medical societies that, according to the generally recognised state of medical knowledge, the off-label use of R-ACVBP and R-CHOEP would be generally preferable to the combination therapy R-CHOP previously approved in the therapeutic indication or to the combination therapy R-CHOP previously approved in the therapeutic indication, for relevant patient groups or indication areas. R-ACVBP and R-CHOEP are therefore not determined as appropriate comparator therapy.

In addition, according to the S3 guideline and the written statements of the DGHO, substitution of vincristine in the R-CHOP protocol with the antibody-drug conjugate polatuzumab vedotin is a therapeutic alternative for subjects with DLBCL at a moderate-to-high or high risk.

For the benefit assessment according to Section 35a SGB V, a comparison with the active ingredient itself, specifically a comparison of identical therapies, is ruled out regarding the question of the benefit assessment. The subject of the present benefit assessment procedure is the active ingredient polatuzumab vedotin, which is therefore excluded from the appropriate comparator therapy. According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. Polatuzumab vedotin in combination with R-CHP is therefore not an appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

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. Recruitment took place in two phases: a global recruitment phase, in which recruitment of 875 patients was planned, and a subsequent continued recruitment phase in China until enrolment of additional 150 patients. The dossier presented evaluations of the entire study population, independent of the recruitment phase (N = 1,000 patients) 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. N = 500 patients each were randomised into the intervention arm (Pola + R-CHP) and 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.

In the dossier, the pharmaceutical company submits the results of the 3rd data cut-off of the POLARIX study from 15 June 2022, which represents 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 the time when the last subject enrolled during the global recruitment phase has reached the follow-up period of 3 years after the treatment completion visit.

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 progression-free survival (PFS) assessed by the medical investigators. Other endpoints were collected in the categories of mortality, morbidity, health-related quality of life and side effects.

Extent and probability of the additional benefit

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

Progression-free survival (PFS)

Progression-free survival (PFS) in the POLARIX study was operationalised as the time between randomisation and the first occurrence of one of the following events: (1) progression or recurrence, (2) death from any cause. The assessment of PFS by the medical investigators was based on PET-CT and/or CT (with contrast agent) images using the Lugano criteria for malignant lymphomas.

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

The endpoint is a composite endpoint composed of the 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 of 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 EFS endpoint, is assessed as unclear for the assessment of the extent of additional benefit. The PFS endpoint is not used for the benefit assessment of polatuzumab vedotin.

Failure of the curative therapeutic approach (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 EFS 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.

In the dossier, the pharmaceutical company presented evaluations on various pre-specified operationalisations of the EFS endpoint as well as on the operationalisation of the EFS end-of-treatment (EFS-EOT) defined *post hoc*.
The EFS-EOT was defined as the time from randomisation to the first occurrence of one of the following events:

- death from any cause,
- progression or recurrence, or
- failure to achieve a complete remission (CR) at the end of treatment.

The principal investigator's assessment of the response to treatment was based on clinical examinations and imaging procedures (PET/CT and/or CT [with contrast agent] images) using the Lugano criteria for malignant lymphomas[2].

2 Cheson BD, Fisher RI, Barrington SF 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.

The operationalisation of the EFS-EOT is suitable for reflecting the failure of the curative therapeutic approach and is therefore used for the benefit assessment of polatuzumab vedotin.

For the EFS-EOT endpoint, the time-to-event analysis showed a statistically significant difference to the advantage of Pola + R-CHP over R-CHOP. The median EFS-EOT 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 0.80, an upper 95% confidence interval limit of 0.98 and a p value of 0.030, indicating only a minor extent of the effect. This effect was not reflected in the event rate, for which there was no statistically significant difference between the treatment groups.

In the subgroup analysis for the sex characteristic, an effect modification was found for both the event rate and the EFS-EOT. In each case, there was a statistically significant advantage of Pola + R-CHP for men and no statistically significant difference for women. In the overall analysis of the available results from the POLARIX study, this effect modification by the sex characteristic is considered insufficient to derive corresponding separate statements on the additional benefit in the overall assessment.

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, the G-BA assumes uncertainty with regard to the transferability of the results for the EFS endpoint to the German healthcare context.

In the overall assessment the present statistically significant difference in the EFS-EOT 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.

Recurrences (disease-free survival, DFS)

For the recurrences endpoint, the pharmaceutical company presented evaluations of the operationalisation of disease-free survival at the end-of-treatment (DFS-EOT) defined *post hoc* in its dossier.

The DFS-EOT was defined as the time from a documented complete remission (CR) to the end of treatment, 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 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].

Only patients who achieved a CR at the end of treatment in the intervention or comparator arm were included in the evaluations of the DFS-EOT. These are 381 out of 500 (76%) vs 364 out of 500 (73%) patients in the intervention arm vs the comparator arm.

Thus, compared with the ITT population, this is an evaluation population which is selected by study treatment and is associated with an interruption in randomisation.

The DFS-EOT is therefore unsuitable for the benefit assessment of polatuzumab vedotin. The occurrence of relapses is depicted via the operationalisation of the EFS-EOT endpoint (failure of the curative therapeutic approach).

Complete remission (CR) at month 24

As part of the written statement procedure, the pharmaceutical company submitted pre-specified evaluations on the percentage of patients with a cure at 24 months after randomisation (CR at month 24 after randomisation). The principal investigator's finding of a cure was made on a visit 24 months (± 3 months) after randomisation. At this point, patients who received one or more subsequent therapies and only achieved a CR during the subsequent therapies were potentially included. It is unclear how many of the patients included in the CR endpoint at month 24 only achieved a CR with subsequent therapy. Depicting a cure with Pola + R-CHP would require evaluations in which only patients with a CR achieved under the initial study therapy and persisting at month 24 are included as an event. The pharmaceutical company did not submit such evaluations. The evaluations presented on the CR endpoint at month 24 are unsuitable for the benefit assessment of polatuzumab vedotin.

Symptomatology (EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS)

Disease-specific symptomatology was surveyed in the POLARIX study using the questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy - Lymphoma Subscale (FACT-LymS) and Functional Assessment of Cancer Therapy / Gynaecologic Oncology Group - Neurotoxicity Subscale (FACT/GOG-NtxS).

For the endpoints of fatigue, nausea and vomiting, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea (assessed using the EORTC QLQ-C30) and for the FACT-LymS and FACT/GOG-NtxS, the evaluations based on mean value differences showed no statistically significant difference between the treatment groups.

For the pain endpoint (assessed using the EORTC QLQ-C30), the evaluation based on mean differences showed a statistically significant difference to the disadvantage of Pola + R-CHP compared to R-CHOP. However, the clinical relevance of this difference is unclear.

B symptoms

The B symptomatology (fever, night sweats, weight loss) was surveyed using both the FACT-LymS questionnaire and the electronic case report form (eCRF). There was also no statistically significant difference between the treatment arms for the B symptoms endpoint (surveyed using eCRF).

Health status (EQ-5D VAS)

Health status was surveyed in the POLARIX study using the visual analogue scale of the EQ-5D questionnaire (EQ-5D VAS). Based on the mean differences, there was no statistically significant difference between the treatment groups.

In the overall analysis of the results, neither an advantage nor a disadvantage was found for Pola + R-CHP compared to R-CHOP in terms of morbidity.

Health-related quality of life

For the assessment of health-related quality of life, the pharmaceutical company submitted evaluations on the EORTC QLQ-C30. There was no statistically significant difference between the treatment arms for the endpoints of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning.

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

Side effects

Adverse events (AEs) were surveyed 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), severe AEs, or in therapy discontinuations due to AEs.

In detail, the specific AEs "febrile neutropenia" (PT, severe AEs) and "diarrhoea" (PT, severe AEs) each showed a statistically significant difference to the disadvantage of Pola + R-CHP. The subgroup analysis showed an effect modification in the endpoint "diarrhoea" by the IPI score characteristic. For patients with an IPI score of 3 – 5, there was a statistically significant difference to the disadvantage of Pola + R-CHP, while there was no statistically significant difference for patients with an IPI score of 1 – 2.

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.

For the endpoint of failure of the curative therapeutic approach, operationalised as event-free survival - end of treatment (EFS-EOT), the time-to-event analysis showed a statistically significant difference with a minor extent of the effect in favour of Pola + R-CHP, which was not reflected in the event rate. Due to the minor extent of the effect, it is considered insufficiently reliable with regard to the existing limitations to be able to determine a relevant improvement in the therapeutic benefit of Pola + R-CHP with sufficient certainty.

With regard to the disease symptomatology, surveyed using the EORTC QLQ-C30, there was a statistically significant difference to the disadvantage of Pola + R-CHP in the pain endpoint, the clinical relevance of which is unclear. There were no statistically significant differences

between the study arms in the other results on disease symptomatology and general health status based on the results of the EORTC QLQ-C30, FACT-LymS, FACT/GOG-NtxS and EQ-5D VAS questionnaires. There was also no statistically significant difference for the B symptoms surveyed, so that neither an advantage nor a disadvantage for Pola + R-CHP can be identified.

In terms of quality of life, the results on the EORTC QLQ-C30 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 showed no relevant differences 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, there were no relevant differences for the benefit assessment of polatuzumab vedotin. The additional benefit of Pola + R-CHP compared to R-CHOP for the treatment of adults with previously untreated DLBCL is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient polatuzumab vedotin due to the exceeding of the € 30 million turnover limit. Polatuzumab vedotin was approved as an orphan drug.

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 adults with previously untreated DLBCL, rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) was determined to be an appropriate comparator therapy.

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

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

For the endpoint of failure of the curative therapeutic approach, operationalised as event-free survival - end of treatment (EFS-EOT), the time-to-event analysis showed a statistically significant difference with a minor extent of the effect in favour of Pola + R-CHP, which was not reflected in the event rate. Due to the minor extent of the effect, it is considered insufficiently reliable with regard to the existing limitations to be able to determine a relevant improvement in the therapeutic benefit of Pola + R-CHP with sufficient certainty.

With regard to the disease symptomatology, there was a statistically significant difference to the disadvantage of Pola + R-CHP in the pain endpoint, the clinical relevance of which is unclear. There were no statistically significant differences in the other results on disease symptomatology or the general health status.

With regard to quality of life and side effects, there were no relevant differences between the treatment arms for the benefit assessment of polatuzumab vedotin.

In the overall assessment, there were no relevant advantages or disadvantages of Pola + R-CHP compared to R-CHOP for the benefit assessment. An additional benefit is therefore not proven.

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 percentage value of 90% assumed to form the lower limit is based on an analysis whose representativeness for the German healthcare context is 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: 26 April 2024):

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.

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: 1 June 2024).

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

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.

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 BSA, cyclophosphamide 750 mg/m² BSA, doxorubicin 50 mg/m² BSA and oral prednisone 100 mg/day.

According to the product information, rituximab should be used in combination with CHOP for eight cycles. In the control arm of the POLARIX study, six cycles of R-CHOP followed by two cycles of rituximab were administered. According to the healthcare context in Germany, an administration of six cycles of rituximab is the standard therapy in the therapeutic indication. An administration of six to eight cycles is possible according to the generally recognised state of medical knowledge. For the presentation of treatment costs, the dosages and treatment duration (8 cycles) of the R - CHOP regimen were taken from the product information for rituximab (sections 4.2 and 5.1). The dosages for R - CHOP were accordingly considered as follows: Rituximab 375 mg/m² BSA, cyclophosphamide 750 mg/m² BSA, doxorubicin 50 mg/m² BSA, prednisone 40 mg/m² BSA and vincristine 1.4 mg/m² BSA.

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.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dosage strengths as well as the scalability of the respective dosage form.

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 from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[3].

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)				

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
Appropriate comparator therapy				
Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)				
Cyclophosphamide	on day 1 of a 21-day cycle	8	1	8
Doxorubicin	on day 1 of a 21-day cycle	8	1	8
Prednisone	on day 1 - 5 of a 21-day cycle	8	5	40
Rituximab	on day 1 of a 21-day cycle	8	1	8
Vincristine	on day 1 of a 21-day cycle	8	1	8

Consumption:

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 = 139.9 mg	139.9 mg	1 x 140 mg	6	6 x 140 mg
In combination with rituximab + cyclophosphamide + doxorubicin + prednisone (R-CHP)					
Cyclophosphamide	750 mg/m² BSA = 1,432.5 mg	1,432.5 mg	1 x 1,000 mg + 1 x 500 mg	6	6 x 1,000 mg + 6 x 500 mg
Doxorubicin	50 mg/m² BSA= 95.5 mg	95.5 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 BSA = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg
Appropriate comparator therapy					
Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)					
Cyclophosphamide	750 mg/m² BSA = 1,432.5 mg	1,432.5 mg	1 x 1,000 mg + 1 x 500 mg	8	8 x 1,000 mg + 8 x 500 mg
Doxorubicin	50 mg/m² BSA= 95.5 mg	95.5 mg	2 x 50 mg	8	16 x 50 mg
Prednisone	40 mg/m² BSA= 76.4 mg	76.4 mg	1 x 50 mg + 1 x 20 mg + 1 x 5 mg	40	40 x 50 mg + 40 x 20 mg + 40 x 5 mg
Rituximab	375 mg/m² BSA = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Vincristine[4]	1.4 mg/m² BSA	2 mg	1 x 2 mg	8	8 x 2 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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	€ 10,680.39	€ 2.00	€ 0.00	€ 10,678.39
Cyclophosphamide 500 mg	6 PSI	€ 84.44	€ 2.00	€ 9.25	€ 73.19
Cyclophosphamide 1000 mg	6 PSI	€ 127.45	€ 2.00	€ 6.43	€ 119.02
Doxorubicin 50 mg[5]	1 INF	€ 151.26	€ 2.00	€ 11.07	€ 138.19
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 2.00	€ 84.18	€ 1,691.16
Rituximab 100 mg	2 CIS	€ 717.21	€ 2.00	€ 33.50	€ 681.71
Prednisone 50 mg[5]	50 TAB	€ 68.06	€ 2.00	€ 4.49	€ 61.57
Prednisone 50 mg[5]	10 TAB	€ 23.19	€ 2.00	€ 0.94	€ 20.25
Appropriate comparator therapy					
Cyclophosphamide 500 mg	6 PSI	€ 84.44	€ 2.00	€ 9.25	€ 73.19
Cyclophosphamide 500 mg	1 PSI	€ 23.50	€ 2.00	€ 1.54	€ 19.96
Cyclophosphamide 1,000 mg	6 PSI	€ 127.45	€ 2.00	€ 6.43	€ 119.02
Cyclophosphamide 1,000 mg	1 PSI	€ 30.68	€ 2.00	€ 1.07	€ 27.61
Doxorubicin 50 mg	1 INF	€ 151.26	€ 2.00	€ 11.07	€ 138.19
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 2.00	€ 84.18	€ 1,691.16

[4] The single dose should not exceed 2 mg according to the product information of vincristine.
[5] Fixed reimbursement rate

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
Rituximab 100 mg	2 CIS	€ 717.21	€ 2.00	€ 33.50	€ 681.71
Prednisone 50 mg[5]	50 TAB	€ 68.06	€ 2.00	€ 4.49	€ 61.57
Prednisone 20 mg[5]	50 TAB	€ 20.91	€ 2.00	€ 0.76	€ 18.15
Prednisone 5 mg[5]	50 TAB	€ 14.18	€ 2.00	€ 0.23	€ 11.95
Vincristine 2 mg	1 SFI	€ 37.66	€ 2.00	€ 1.25	€ 34.41
Abbreviations: PIC = powder for the preparation of an infusion solution concentrate; PSI = powder for solution for injection; INF = infusion solution; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 1 June 2024

Costs for additionally required SHI services:

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

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

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

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 1.10.2009 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 agents 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 do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing

of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

Basic principles of the assessed medicinal product

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

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

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

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for polatuzumab vedotin (Polivy); Roche - Polivy; last revised: May 2022

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

At its session on 23 June 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 December 2023.

On 19 December 2023 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 6 VerfO.

By letter dated 21 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient polatuzumab vedotin.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 April 2024. The deadline for submitting statements was 23 April 2024.

The oral hearing was held on 6 May 2024.

By letter dated 7 May 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 31 May 2024.

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 11 June 2024, and the proposed resolution was approved.

At its session on 20 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 June 2020	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	12 December 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	30 April 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 May 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 May 2024 5 June 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	11 June 2024	Concluding discussion of the draft resolution
Plenum	20 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 June 2024

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

Prof. Hecken