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) Axicabtagene ciloleucel (new therapeutic indication: diffuse large B-cell lymphoma, high-grade B-cell lymphoma, after 1 prior therapy, relapsed within 12 months or refractory)

of 21 December 2023

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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 approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. 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

Axicabtagene ciloleucel (Yescarta) was listed for the first time on 1 December 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 14 October 2022, axicabtagene ciloleucel 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, sentence 7).

Yescarta for the treatment of diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

On 11 November 2022, the pharmaceutical company submitted the dossier to the G-BA for benefit assessment in accordance with Section 35a, paragraph 1, sentence 11 SGB V on time.

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 Section 5, paragraphs 1 to 6 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.

Yescarta exceeded the EUR 30 million turnover limit on 1 December 2023 and has not yet been assessed with evidence of medical benefit and additional medical benefit in relation to the appropriate comparator therapy. By resolution of 2 February 2023 the procedure was suspended for a limited period of time. In a letter dated 2 February 2023, the pharmaceutical company was requested to submit evidence in accordance with sentence 3 numbers 2 and 3 because of exceeding the 30 million euro turnover limit, and to provide evidence of the additional benefit in deviation from Section 35a, paragraph 1, sentence 11 SGB V.

The pharmaceutical company has submitted the final dossier to the G-BA in due time on 30 June 2023 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 the active ingredient axicabtagene ciloleucel with the new therapeutic indication*:* "Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 October 2023 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 axicabtagene ciloleucel 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, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 axicabtagene ciloleucel.

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:

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Axicabtagene ciloleucel (Yescarta) according to the product information

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Therapeutic indication of the resolution (resolution of 21.12.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy for axicabtagene ciloleucel:

Induction therapy with

- R-GDP (rituximab, gemcitabine, cisplatin, dexamethasone) *or*
- R-ICE (rituximab, ifosfamide, carboplatin, etoposide) *or*
- R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin)

followed by high-dose therapy with autologous or allogeneic stem cell transplantation if there is a response to induction therapy[2]

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy for axicabtagene ciloleucel:

Therapy according to doctor's instructions under consideration of

- polatuzumab in combination with bendamustine and rituximab *and*
- tafasitamab in combination with lenalidomide

[2] Taking into account the requirements of the Guideline for Inpatient Treatment Methods (last revised 18 October 2023): Section 4, paragraph 2, number 4

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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 addition to axicabtagene ciloleucel, the following active ingredients are approved for the lymphoma entities covered by this therapeutic indication:

The active ingredients bleomycin, carmustine, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, melphalan, methotrexate, methylprednisolone, mitoxantrone, pixantrone, prednisone, prednisolone, trofosfamide, vinblastine, vincristine and vindesine have the marketing authorisation for the superordinate therapeutic indication "non-Hodgkin lymphoma".

The active ingredients polatuzumab vedotin in combination with bendamustine and rituximab, tafasitamab in combination with lenalidomide, rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) and lisocabtagene maraleucel have the marketing authorisation for the treatment of diffuse large B-cell lymphoma (DLBCL) and high grade B-cell lymphoma (HGBCL) following first-line therapy.

The marketing authorisations mentioned are partly linked to (specified) concomitant active ingredients or do not fully cover the patient groups comprised by the present therapeutic indication.

on 2. In principle, autologous or allogeneic stem cell transplantation is considered as non-medicinal treatment in the present therapeutic indication. In addition, radiotherapy can be administered, for example, to treat localised residual manifestations of the lymphoma after completion of chemotherapy.

on 3. In the present therapeutic indication, the following resolutions or guidelines of the G-BA are available:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Lisocabtagene maraleucel (resolution of 16 November 2023)
- Tafasitamab (resolution of 3 March 2022)
- Polatuzumab vedotin (resolution of 20 August 2020)
- Pixantrone (resolution of 16 May 2013)

Guideline for Inpatient Treatment Methods (last revised 18 October 2023):

- 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 (exceptions: a) patients who have a very high risk of recurrence and who achieve a response at least in the sense of stable disease after salvage therapy; b) patients in whom sufficient stem cell harvesting for autologous stem cell transplantation was not possible and who achieve a response at least in the sense of stable disease after salvage therapy).

- Annex I: Methods required for hospital care: Allogeneic stem cell transplantation in adult patients with aggressive B-cell non-Hodgkin lymphomas who relapse after autologous stem cell transplantation and achieve a response at least in the sense of stable disease after salvage therapy.

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 therapeutic indication according to Section 35a, paragraph 7 SGB V. A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The present patient population consists of adults with early relapse or refractoriness to first-line therapy.

The evidence-based therapy recommendations of the current guidelines[3,4,5] basically indicate that the therapy of relapsed or refractory patients with HGBL, in case of eligibility for high-dose therapy, is based on the treatment of patients with relapsed or refractory DLBCL.

The present therapeutic indication generally refers to adults with DLBCL and HGBL who relapsed within 12 months from completion of, or are refractory to, first-line therapy, and is not restricted with regard to suitability or unsuitability for an intensive therapeutic approach. In the therapy recommendations relating to second-line therapy, the S3 guideline of the Oncology Guideline Programme[3] distinguishes between patients with early or late relapse who are eligible for high-dose therapy with the primary intention of curative treatment and second-line treatment of patients who are ineligible for high-dose therapy. This is also reflected in the present written statement from the German Society for Haematology and Medical Oncology. The S3 guideline also states that, in view of the availability of newer therapy options, the established categorisation into patients eligible for high-dose therapy and those ineligible for high-dose therapy is no longer expedient, but will continue to be used.

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[3] Guideline program in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies): Diagnostics, therapy and after-care for adult patients with diffuse large B-cell lymphoma and related entities; S3-guideline [online]. AWMF register number 018-038OL. Berlin (GER): Oncology guideline programme; 2022.

[4] National Institute for Health and Care Excellence (NICE). Non-Hodgkin's lymphoma: diagnosis and management [online]. 07.2021, last check 10.2021. London (GBR): NICE; 2016. (NICE Guideline; Band NG52).

[5] National Comprehensive Cancer Network (NCCN). B-Cell lymphomas; Vers. 05.2022 [online]. Fort Washington (USA): NCCN; 2022. (NCCN Clinical Practice Guidelines in Oncology).

The statement of the scientific-medical societies on the present benefit assessment procedure indicates that in medical treatment practice, the criterion of patients' eligibility for high-dose therapy is no longer relevant in the case of early relapses or refractoriness to first-line therapy due to the availability of CAR-T cell therapies. In the current clinical healthcare context, patients are categorised according to their eligibility for CAR-T cell therapy in accordance with the statements of the scientific-medical societies.

The presented assessment of the scientific-medical societies that the criterion of "eligibility for high-dose therapy" is no longer relevant for patients with early relapse or refractoriness to first-line therapy in the current healthcare context is largely based on the pivotal study evidence on lisocabtagene maraleucel and axicabtagene ciloleucel in the treatment setting under assessment. However, this assessment is currently not adequately reflected in the current guideline recommendations. It is therefore considered appropriate by the G-BA to differentiate the patient groups according to their suitability for high-dose therapy when determining the appropriate comparator therapy for the present resolution on axicabtagene ciloleucel in accordance with the currently valid guideline recommendations.

Taking into account the specific therapy recommendations for the lymphoma entities covered by this therapeutic indication, the following patient groups result:

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

If patients with an early relapse are eligible for high-dose therapy based on their general condition or comorbidity, CAR-T cell therapies are the main treatment strategy according to the available guidelines and statements of the scientific-medical societies. The CAR-T cell therapies axicabtagene ciloleucel or lisocabtagene maraleucel are recommended in the current guidelines.

The CAR-T cell therapies axicabtagene ciloleucel and lisocabtagene maraleucel are gene therapies. Autologous T cells are genetically modified by the introduction of a chimeric antigen receptor. The chimeric antigen receptor of axicabtagene ciloleucel and lisocabtagene maraleucel targets the same surface antigen, cluster of differentiation 19 (CD19).

The mode of action of CAR-T cells differs from the mode of action of the treatment options previously used in this therapeutic indication. As part of chemoimmunotherapy, cytostatic agents or anti-CD-20 antibodies are used for B-cell lymphoma, which do not constitute gene therapy. Although the subsequent stem cell transplantation is also based on a cellular or immunological mode of action, autologous or allogeneic stem cells, which have not been genetically modified and therefore do not act on a specific surface antigen, are infused to rebuild haematopoiesis. Therefore, chemoimmunotherapy is usually required to eliminate the malignant lymphoma cells before performing stem cell transplantation for B-cell lymphoma, whereas CAR-T cell therapy can also be used without prior chemoimmunotherapy.

Overall, it can be stated that the CAR-T cell therapy procedure shows relevant differences to the previous treatment standard with regard to the various therapy steps. In addition, suitability for high-dose therapy with autologous or allogeneic stem cell transplantation is not the same as patients' suitability for CAR-T cell therapy, which in principle represents a possible therapy option for a larger patient population.

While the product class of CAR-T cell therapies for the treatment of B-cell lymphomas has been established in healthcare for some time after at least two prior therapies, axicabtagene ciloleucel and lisocabtagene maraleucel were only recently approved for the second-line treatment of B-cell lymphomas in close proximity to each other. The benefit assessment procedure for lisocabtagene maraleucel was also only recently completed. A hint for a considerable additional benefit was identified here (resolution of 16 November 2023). For the therapeutic indication under assessment, the product class of CAR-T cell therapies is thus a new treatment option that should be compared with the same appropriate comparator therapy in accordance with Section 6 paragraph 3 AM-NutzenV in conjunction with Chapter 5 Section 6, paragraph 5, sentence 1 VerfO in order to ensure a standardised assessment.

According to Section 6, paragraph 2, sentence 2 AM-NutzenV, the determination of the appropriate comparator therapy must also be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. Effects on the medical treatment situation that only result from the addition of the new medicinal product must be disregarded.

In the overall assessment of the aspects presented, the G-BA considers it necessary for the determination of the appropriate comparator therapy in the present resolution on axicabtagene ciloleucel to disregard the effects on the medical treatment situation resulting overall from the addition of the product class of CAR-T cells, which includes both lisocabtagene maraleucel and axicabtagene ciloleucel.

In this particular case constellation, the G-BA considers it appropriate to base the determination of the appropriate comparator therapy for the considered patient group on the treatment standard that would result without the addition of the CAR-T cell therapies to be assessed.

According to the available guidelines, prior to the availability of CAR-T cell therapies, platinum-based induction chemotherapy, consolidated by high-dose therapy with autologous stem cell transplantation in case of response (complete remission (CR) or partial remission (PR)), was considered the therapy standard for all adults eligible for high-dose therapy with relapsed or refractory DLBCL, and HGBL following first-line therapy. In addition, allogeneic stem cell transplantation can be considered as consolidation in accordance with the Guideline for Inpatient Treatment Methods[6] , provided that the patient has achieved a response after salvage therapy that is at least equivalent to stable disease and the patient has a very high risk of relapse or it was not possible to harvest sufficient stem cells for autologous stem cell transplantation.

[6] Last revised 18 October 2023

According to the current guidelines, the treatment regimens GDP (gemcitabine, dexamethasone, cisplatin or carboplatin), DHAP (dexamethasone, cisplatin, cytarabine) and ICE (ifosfamide, carboplatin, etoposide), each in combination with rituximab, are specifically recommended as platinum-based induction chemotherapy. In accordance with the recommendations of the S3 guidelines, these treatment regimes were compared with each other in prospective randomised studies, whereby differences in toxicity were found with the same efficacy.[7,8] According to the scientific-medical societies, these three combination therapies represent the standard of care and have proven to be equivalent in the context of induction therapy. The protocols R-GDP, R-DHAP and R-ICE have already been used as standard protocols for induction therapy in this therapeutic indication as part of the G-BA's assessment of the "allogeneic stem cell transplantation for B-cell non-Hodgkin lymphomas" method.[9] Rituximab is approved in the present indication but only in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and individual components of the combination therapies mentioned (cisplatin, carboplatin, gemcitabine) are also not approved in the present indication.

Of the active ingredients approved for the treatment of non-Hodgkin lymphoma, only the platinum-free induction therapy MINE (mesna, ifosfamide, mitoxantrone, etoposide), which is mentioned in the American guideline of the National Comprehensive Cancer Network (NCCN) as another possible treatment regimen of lower priority, is available[5]. The statements of clinical experts in the present benefit assessment procedure indicate that MINE has no relevant significance in the present therapeutic indication and any sporadic use in the past was consolidated with a platinum-containing therapy. In agreement with the estimate of the clinical experts, all the available guidelines unanimously recommend platinum-containing induction therapy with R-GDP, R-ICE or R-DHAP, although it should be noted that the platinum-free induction therapy MINE is not mentioned at all in the S3 guideline relevant especially to the German healthcare context.

Taking into account the present evidence, the use of induction therapy with R-GDP, R-DHAP or R-ICE is generally preferable to induction therapy with MINE for the considered patient group in accordance with Section 6, paragraph 2, sentence 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The determination of CAR-T cell therapy in accordance with the guideline recommendations is not an option for the present resolution, taking into account Section 6, paragraph 2, sentence 2 SGB V. Therefore, it is appropriate to determine the off-label use of the above-mentioned combinations of medicinal products as the

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7 Gisselbrecht C, Glass B, Mounier N, Linch D, Gill D, Trneny M. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. 2009;27:15s

8 Crump M, Kuruvilla J, Couban S, MacDonald D, Kukreti V, Kouroukis C, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY12. J Clin Oncol. 2014;32:3490-6.

9 Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Guideline for Inpatient Treatment Methods: Allogeneic stem cell transplantation for aggressive B-cell non-Hodgkin lymphomas; 9 April 2020

appropriate comparator therapy for the present patient population. The other approved active ingredients listed under paragraph 1 do not correspond to the therapy recommendations for the indication in question and do not correspond to the therapy standard in the medical treatment situation according to Section 6, paragraph 2, sentence 2 AM-NutzenV as it would be without CAR-T cell therapies, as set out in the guidelines and in the statement of the scientific-medical societies.

In the overall assessment, induction therapy with R-GDP, R-ICE *or* R-DHAP followed by high-dose therapy with autologous or allogeneic stem cell transplantation is determined to be an appropriate comparator therapy for the present patient group if there is a response to induction therapy.

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

This patient group comprises adults with DLBCL and HGBL who are ineligible for high-dose therapy. According to the available guideline recommendations and the statements of the clinical experts in this benefit assessment procedure, adults with relapsed or refractory HGBCL are treated according to the relapsed or refractory DLBCL.

The more recent guidelines[3,5] unanimously recommend polatuzumab in combination with bendamustine and rituximab, tafasitamab in combination with lenalidomide and less intensive immunochemotherapy protocols, for example rituximab in combination with gemcitabine and oxaliplatin (R-GemOx), as therapy options.

The antibody-drug conjugate polatuzumab vedotin is approved in combination with bendamustine and rituximab for the treatment of adults with relapsed or refractory DLBCL if they are ineligible for haematopoietic stem cell transplantation. By resolution of 20 August 2020, a hint for a non-quantifiable additional benefit over bendamustine in combination with rituximab was identified for polatuzumab vedotin within the scope of an orphan drug assessment because the scientific data did not allow quantification.

The CD19-specific antibody tafasitamab is approved in combination with lenalidomide for the treatment of patients with relapsed or refractory DLBCL for who are ineligible for autologous stem cell transplantation. By resolution of 3 March 2022, a hint for a non-quantifiable additional benefit was identified for tafasitamab within the scope of an orphan drug assessment because the scientific data did not allow quantification.

With regard to less intensive immunochemotherapies, the available evidence mentions the combination therapy R-GemOx in particular as a further treatment option, but it is not approved for this indication. It cannot be inferred from the available evidence that, according to the generally recognised state of medical knowledge, the off-label use of R-GemOx is generally preferable to the medicinal products previously approved in the therapeutic indication or, for relevant patient groups or indication areas, to the medicinal products previously approved in the

therapeutic indication. R-GemOx is therefore not determined to be an appropriate comparator therapy.

Since October 2022, the CAR-T cell therapy lisocabtagene maraleucel has been another approved therapy option for patients with DLBCL and HGBCL who are ineligible for high-dose therapy. The benefit assessment procedure for lisocabtagene maraleucel in the second-line treatment in case of early relapses or refractoriness was only recently completed. No additional benefit was identified for the patient group ineligible for high-dose therapy, as no data were available for this patient group. According to the statements of the scientific-medical societies, CAR-T cells are also a relevant therapy option for patients who are ineligible for high-dose therapy. However, the German S3 guideline does not include a recommendation for the use of lisocabtagene maraleucel in the second-line treatment of patients who are ineligible for high-dose therapy. In addition, reference is made to the above statements on patient group a), according to which it is necessary for the determination of the appropriate comparator therapy in the present resolution on axicabtagene ciloleucel to disregard the effects on the medical treatment situation resulting overall from the addition of the product class of CAR-T cells, which includes both axicabtagene ciloleucel and lisocabtagene maraleucel. Lisocabtagene maraleucel is therefore not determined to be an appropriate comparator therapy.

The available evidence shows that the therapy options polatuzumab in combination with bendamustine and rituximab as well as tafasitamab in combination with lenalidomide cannot be considered equally suitable for all patients included in the therapeutic indication, taking into account comorbidities and, if applicable, previous therapy and the further course of therapy. Therefore, in the overall assessment, a therapy according to doctor's instructions, taking into account polatuzumab in combination with bendamustine and rituximab and tafasitamab in combination with lenalidomide, is determined as the appropriate comparator therapy for adults with DLBCL and HGBCL who are ineligible for high-dose therapy.

It should be noted here that the HGBL was only listed as a definitive entity with the WHO classification from June 2022 and has since been explicitly named by the EMA within the framework of the marketing authorisation.[10] Prior to this update, HGBCLs were subsumed under DLBCLs. The G-BA therefore considers it appropriate to consider treatment options that were approved before the WHO classification was updated in June 2022 when determining the appropriate comparator therapy for both DLBCL and HGBL.

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

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

[10] Alaggio, R., Amador, C., Anagnostopoulos, I. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukaemia 36; 1720-1748 (2022)

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.

Change of the appropriate comparator therapy

The appropriate comparator therapy was originally determined as follows:

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy for axicabtagene ciloleucel:

- Induction therapy with MINE (mesna, ifosfamide, mitoxantrone, etoposide) followed by high-dose therapy with autologous or allogeneic stem cell transplantation if there is a response to induction therapy

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy for axicabtagene ciloleucel:

Therapy according to doctor's instructions under consideration of

- Pola-BR (polatuzumab in combination with bendamustine and rituximab)
- Tafasitamab + lenalidomide

This appropriate comparator therapy was determined for the present benefit assessment procedure on axicabtagene ciloleucel under the effects of the ruling of the Federal Social Court (FSC) of 22 February 2023. According to the FSC's comments on this ruling (file ref.: B 3 KR 14/21 R), medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

Within the scope of this provision, it was to be noted that medicinal therapies not approved for the treatment of DLBCL and HGBL who relapse within 12 months from completion of, or are refractory to, first-line therapy are mentioned in the current guidelines or by scientific-medical societies and/or the AkdÄ (Drugs Commission of the German Medical Association) according to Section 35a, paragraph 7, sentence 4 SGB V.

With the entry into force of the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) on 27 July 2023, the G-BA can exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

In view of the fact that for the present benefit assessment of axicabtagene ciloleucel, off-label use of medicinal products can be considered as an appropriate comparator therapy, also taking into account the statements of scientific-medical societies in the present procedure, a review of the appropriate comparator therapy under the regulations after the entry into force of the ALBVVG was necessary. In the course of this, the appropriate comparator therapy was changed for the present resolution.

This change means that the results of the ZUMA-7 study submitted by the pharmaceutical company in the dossier can be used for the present assessment for patient group a). The ZUMA-7 study was the basis of the IQWiG's dossier assessment. In addition, the results of the ZUMA-7 study were the subject of the statements, which is why the change in the appropriate comparator therapy does not necessitate a renewed conduct of the benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

   Hint for a non-quantifiable additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submits results of the ZUMA-7 study. In the ongoing, open-label phase III ZUMA-7 study, axicabtagene ciloleucel is being compared with induction therapy with R-ICE, R-DHAP, R-ESHAP and R-GDP followed by high-dose chemotherapy (HDCT) with autologous stem cell transplantation (SCT). The study has been conducted in 77 study sites in Australia, Asia, Europe and North America since January 2018.

Adults with DLBCL and HGBL with refractory or relapsed disease within 12 months of completing first-line therapy consisting of rituximab and anthracycline-based chemoimmunotherapy were enrolled in the study. In addition, the aim had to be to continue with HDCT and autologous SCT if the patients responded to induction therapy, were in good general condition (ECOG-PS 0-1), had adequate organ function and radiologically documented disease.

A total of 359 patients were enrolled - stratified by response to first-line therapy (primary refractory vs relapse ≤ 6 months vs relapse > 6 and ≤ 12 months after first-line therapy) and by secondary age-adjusted international prognostic index (sAAIPI) (0 or 1 vs 2 or 3) - randomised in a 1:1 ratio to either treatment with axicabtagene ciloleucel (N = 180) or induction + HDCT + autologous SCT (N = 179).

The treatment with axicabtagene ciloleucel was carried out according to the requirements in the product information. In the period between leukapheresis and lymphodepletion, patients could receive bridge therapy with corticosteroids as required by the principal investigator. Bridge therapy in the form of chemoimmunotherapy was not permitted in the ZUMA-7 study.

Patients with disease progression after a previous response on day 50 could again be administered lymphodepletion and treated with axicabtagene ciloleucel.

In the comparator arm, patients initially received induction therapy with 2 to 3 cycles of R-ICE, R-DHAP, R-ESHAP or R-GDP at the principal investigator's discretion. Patients who achieved a partial or complete response to therapy according to the Lugano classification (Cheson et al.; 2014) after 2 to 3 cycles of induction therapy (around day 50) subsequently received HDCT and autologous SCT.

Subsequent antineoplastic therapies were at the discretion of the principal investigator in both study arms and were possible without limitation. Overall, 49% of patients in the intervention arm and 72% in the comparator arm received at least 1 subsequent therapy at the 2nd data cut-off, including chemo(immuno)therapy (81%) and high-dose therapy followed by autologous SCT (15%) in the intervention arm and autologous CD19-CAR-T therapy (77%) in the comparator arm.

The primary endpoint of the ZUMA-7 study is event-free survival (EFS). Results are also available for other endpoints in the categories of mortality, morbidity, health-related quality of life and side effects.

Two data cut-offs have been carried out so far. The data cut-off from 18.03.2021 is the primary EFS analysis and 1st interim analysis for overall survival. The data cut-off from 25.01.2023 was the final analysis of overall survival.

Implementation of the appropriate comparator therapy

In the comparator arm of the ZUMA-7 study, R-DHAP, R-ICE, R-ESHAP or R-GDP was used with subsequent HDCT and SCT. The R-ESHAP regimen administered in the ZUMA-7 study is not explicitly mentioned in the S3 guideline, but was only used in 3% of patients in the study. Overall, the appropriate comparator therapy, which was determined with amendments for the present resolution, is assessed as implemented.

On the implementation of the ZUMA-7 study

In the European Public Assessment Report (EPAR) for axicabtagene ciloleucel in the present therapeutic indication, the European Medicines Agency (EMA) points out that it was not ensured during the course of the study that the conduct and monitoring of the study were shielded from each other, although the integrity of the ZUMA-7 study is not called into question by the EMA[11]. IQWiG identified a high risk of bias across endpoints in this regard. Thus, it is not certain whether the protocol changes in Amendment 5, which reduced the triggers for the primary EFS analysis from 270 to 250 EFS events and for the first OS analysis from 140 to 110 deaths, were made without knowledge of the data. The pharmaceutical company explains that the protocol changes in Amendment 5 were triggered based on the available pooled and blinded data and justified by a plateau in observed EFS events across both study arms. This explanation seems plausible. It was found that only very few EFS events additionally occurred between the primary EFS analysis (1st data cut-off) and the 2nd data

[11] European Medicines Agency. Yescarta; Assessment report [online]. 2022 [accessed: 18.08.2023]. https://www.ema.europa.eu/documents/variation-report/yescarta-h-c-004480-ii-0046-epar-assessment-report-variation_en.pdf.

cut-off. Although the uncertainty described by IQWiG is included in the present assessment, no high risk of bias is derived for all study endpoints based on this alone.

In addition, only the administration of corticosteroids as a bridge therapy between leukapheresis and axicabtagene ciloleucel infusion was permitted in the ZUMA-7 study. This approach in the ZUMA-7 study is considered acceptable for the benefit assessment against the background of the explanations by the clinical assessment experts. The clinical experts explained in their statements that the question of bridge therapy is currently being addressed. The recommendation of the S3 guideline in favour of bridge therapy with platinum-containing chemoimmunotherapy is based on consensus and not on evidence, and relates exclusively to third-line therapy. Even the evidence now available for second-line treatment from the ZUMA-7, TRANSFORM and BELINDA studies cannot conclusively demonstrate any advantages of a specific bridge therapy. Therefore, the omission of platinum-based chemoimmunotherapy as a bridge therapy cannot be considered a deviation from the standard of care. There is no increased uncertainty for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

The overall survival was operationalised in the ZUMA-7 study as the time from randomisation to death from any cause.

Within the framework of the written statement procedure, the pharmaceutical company submits information on the subsequent therapies. The subsequent therapies used are generally considered appropriate.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of axicabtagene ciloleucel. The extent of the prolongation of survival time is assessed as a minor improvement.

Morbidity

Failure of the curative therapeutic approach

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 event-free survival (EFS) endpoint could be used as an approximation to illustrate the failure of the curative therapeutic approach.

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.

The percentage of patients with an event as well as the time to event occurrence are potentially relevant for the assessment.

In the ZUMA-7 study, EFS was defined as the time from randomisation to the first occurrence of one of the following events:

- Death from any cause
- Disease progression
- Stable disease (SD) as best response until study day 150 post randomisation
- Start of a new lymphoma therapy

In the dossier, the pharmaceutical company presents results for the EFS endpoint according to the blinded centralised assessment only for the 1st data cut-off. Results for the EFS endpoint as assessed by the principal investigator are submitted for the 1st and 2nd data cut-offs. The data submitted by the pharmaceutical company as part of the written statement procedure clarify that the EFS was no longer collected according to the blinded centralised assessment at the 2nd data cut-off. For this endpoint, the results of the 1st data cut-off thus cover the longest available observation period.

For the endpoint "initiation of new lymphoma therapy", it was not clear from the pharmaceutical company's dossier whether this per se represents a failure of the curative therapeutic approach. As part of the written statement procedure, information on the reasons for the events in the endpoint "initiation of new lymphoma therapy" in the comparator arm was presented according to the blinded centralised assessment.

As part of the written statement procedure, the pharmaceutical company submits a sensitivity analysis for the EFS endpoint according to blinded centralised assessment. In this sensitivity analysis, only the initiation of new lymphoma therapy due to efficacy concerns was considered a qualifying event for the EFS endpoint instead of the initiation of new lymphoma therapy for any reason, according to the pharmaceutical company. The pharmaceutical company defines EFS in the context of this sensitivity analysis as disease progression, death from any cause or residual disease leading to the initiation of new lymphoma therapy.

The assessment of the endpoint of failure of the curative therapeutic approach is based on the evaluations of the EFS according to the centralised assessment (data cut-off from 18.03.2021), the sensitivity analysis taking into account the initiation of new lymphoma therapy due to efficacy concerns as a qualifying event (data cut-off from 18.03.2021) as well as the sensitivity analyses of IQWiG.

With regard to the question of the extent to which the EFS endpoint can reflect the failure of the curative therapeutic approach, the present operationalisation of the EFS endpoint is subject to uncertainties. IQWiG stated that for a relevant percentage of patients who had achieved a CR or PR in the comparator arm after induction therapy, it was unclear why they did not subsequently receive stem cell transplantation. In particular, uncertainties remained for the event "initiation of new lymphoma therapy" as to whether some of the patients in the comparator arm had reasons that did not necessarily represent a failure of the curative therapeutic approach. The representatives of the clinical scientific-medical societies explained in the written statement procedure that the decision as to whether high-dose therapy with stem cell transplantation can be carried out after induction therapy is based not only on the achievement of CR or PR, but also on the general condition of the patients, who are usually older and very burdened by the toxic induction therapies, as well as other laboratory parameters (LDH) and clinical symptoms that may occur after imaging. The percentage of

patients who did not receive SCT in the comparator arm corresponds to that of previous studies in the therapeutic indication (e.g. TRANSFORM study).

A more detailed list of the reasons for the failure of this curative therapeutic approach would have been desirable in order to finally clarify the question of why patients with CR or PR did not receive SCT after induction therapy in the comparator arm. In addition, in order to more comprehensively illustrate the failure of the curative therapeutic approach, it is also necessary to record the failure to achieve a CR after completion of treatment as a qualifying event in its own right. This information is unavailable.

Overall, despite existing uncertainties, the results on EFS are therefore assessed to be sufficiently significant in almost all available analyses to make an assessment regarding the failure of the curative therapeutic approach, even against the background of large effects. In this case, the result on overall survival is also included in the further assessment, which shows a statistically significant difference to the advantage of axicabtagene ciloleucel. In view of the uncertainties and taking into account the sensitivity analyses, an overall advantage of axicabtagene ciloleucel over induction + HDCT + autologous SCT was identified, the extent of which cannot be quantified.

Symptomatology (EORTC QLQ-C30) and health status (EQ-5D VAS)

In the dossier, the pharmaceutical company submits evaluations of symptomatology assessed using the symptom scales of the EORTC-QLQ-C30 questionnaire and the health status assessed using the EQ-5D VAS at the 1st data cut-off from 18.03.2021. In the dossier, no data on the relevant 2nd data cut-off were submitted.

As part of the written statement procedure, the pharmaceutical company presents additional evaluations.

Overall, there are uncertainties regarding the data quality and evaluability of the patient-reported endpoints collected in the ZUMA-7 study:

The percentage of missing values increases sharply over the course of the study, so that by the time of the survey on day 100, only < 50% of the randomised patients in the comparator arm are included in the evaluations. In addition, there is a high differential percentage of patients missing from the evaluation.

For these reasons, the results on the endpoints on symptomatology and health status are not used for the benefit assessment.

Health-related quality of life

Quality of life was assessed in the ZUMA-7 study using the functional scales of the EORTC-QLQ-C30 questionnaire.

Reference is made to the above statements on the symptomatology endpoint. The results on health-related quality of life are not used for the benefit assessment.

Side effects

In the ZUMA-7 study, adverse events (AEs) were collected until study day 150 or until switching to another lymphoma therapy, whichever occurred first.

The analysis population presented is the safety analysis set, which only includes patients in the intervention arm who received an infusion of axicabtagene ciloleucel. AEs in these patients that occurred during the preparatory processes, i.e. leukapheresis, bridge therapy and lymphodepletion, are not included in the evaluation. In contrast, all patients who received a dose of induction chemotherapy were included in the evaluations in the comparator arm.

This is problematic, as evaluations are necessary for the benefit assessment in which AEs are taken into account during the preparatory processes and waiting time until the infusion of axicabtagene ciloleucel. This is therefore an incomplete analysis population.

The evaluations presented by the pharmaceutical company on endpoints in the endpoint category of side effects are therefore unsuitable for the benefit assessment.

It is therefore not possible to perform a benefit-risk assessment for axicabtagene ciloleucel on the basis of the data presented.

Overall assessment/ conclusion

For the benefit assessment of axicabtagene ciloleucel, data are available from the open-label, randomised phase III ZUMA-7 study on mortality, morbidity, quality of life and side effects compared to induction therapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation.

For the overall survival, there is a statistically significant difference in favour of axicabtagene ciloleucel. The extent of the prolongation of survival time is assessed as a minor improvement.

In the morbidity endpoint category, an advantage of axicabtagene ciloleucel was identified based on the results for the event-free survival (EFS) endpoint with regard to failure of the curative therapeutic approach. However, the extent of this advantage cannot be quantified due to relevant uncertainties.

No suitable data is available on symptomatology (assessed using the EORTC-QLQ-C30) and health status (assessed using the EQ-5D-VAS) due to an excessively high percentage of missing values and the high differential percentage of patients missing from the evaluation. This also applies to the data on health-related quality of life (collected using EORTC-QLQ-C30).

The available evaluations for the endpoints on side effects are unsuitable for the benefit assessment. It is therefore not possible to perform a benefit-risk assessment for axicabtagene ciloleucel on the basis of the data presented.

In the overall assessment, a non-quantifiable additional benefit was therefore identified for axicabtagene ciloleucel for the treatment of DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, compared with induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing open-label, randomised, phase III ZUMA-7 study.

The risk of bias at the study level is rated as low.

The endpoint-specific risk of bias for the endpoint of overall survival is assessed as low.

Limitations result from the fact that no suitable data are available for the patient-reported endpoints on symptomatology, assessed with the EORTC QLQ-C30, and health status, assessed with the EQ-5D VAS, as well as on health-related quality of life.

In the overall assessment of the described limitations, the reliability of data for the additional benefit determined is classified in the hint category.

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company presented data from the single-arm ALYCANTE study, in which 62 patients with relapsed or refractory DLBCL who were ineligible for autologous stem cell transplantation were treated with axicabtagene ciloleucel after first-line therapy. Since this is not a comparison with the appropriate comparator therapy, the ALYCANTE study is unsuitable for the benefit assessment.

Overall, there are therefore no suitable data for the assessment of the additional benefit of axicabtagene ciloleucel compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of axicabtagene ciloleucel finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

The evaluations on adverse events from the pivotal ZUMA-7 study presented by the pharmaceutical company were unsuitable for the benefit assessment, which is why it was not possible to make the benefit-risk assessment of axicabtagene ciloleucel on the basis of the data presented in the present assessment.

This is based in particular on the fact that the pharmaceutical company used an inappropriate evaluation population for the presented results on side effects, in which data on adverse events from the intervention arm of the ZUMA-7 study were not taken into account.

Conditions of the limitation

For the new benefit assessment after the expiry of the limitation, evaluations of all endpoints on adverse events in the ZUMA-7 study must be presented based on an analysis population that not only includes patients in the intervention arm who received an infusion with axicabtagene ciloleucel, but also includes adverse events during the preparatory processes, i.e. leukapheresis, bridge therapy and lymphodepletion. According to the study protocol and the information provided by the pharmaceutical company in Module 4 of the dossier, adverse events were also recorded in the ZUMA-7 study during the preparatory processes or since randomisation.

Time-to-event analyses must also be presented for these evaluations.

Furthermore, the results on all patient-relevant endpoints from the ZUMA-7 study that are used to demonstrate an additional benefit must be presented in the dossier for the new benefit assessment after the expiry of the limitation.

For this purpose, the G-BA considers a limitation for the resolution until 1 July 2024 to be appropriate.

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

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 7 VerfO, the procedure for the benefit assessment of the medicinal product axicabtagene ciloleucel recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of axicabtagene ciloleucel in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product axicabtagene ciloleucel can be carried out at an earlier point in time due to other reasons (cf. Chapter 5 Section 1, paragraph 2, Nos. 2 to 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient axicabtagene ciloleucel.

The therapeutic indication assessed here is as follows: "Treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy."

In the therapeutic indication under consideration, a distinction was made between two patient groups with regard to their suitability for high-dose therapy.

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Data from the phase III ZUMA-7 study for comparing axicabtagene ciloleucel with induction therapy (R-ICE, R-DHAP, R-ESHAP or R-GDP) + HDT + autologous SCT are available for this patient group.

For the overall survival, there is a statistically significant difference in favour of axicabtagene ciloleucel. The extent of the prolongation of survival time is assessed as a minor improvement.

In the morbidity endpoint category, an advantage of axicabtagene ciloleucel was identified based on the results for the event-free survival (EFS) endpoint with regard to failure of the curative therapeutic approach. However, the extent of this advantage cannot be quantified due to relevant uncertainties.

No suitable data are available on symptomatology (assessed using the EORTC-QLQ-C30) and health status (assessed using the EQ-5D-VAS). This also applies to the data on health-related quality of life (collected using EORTC-QLQ-C30).

The available evaluations for the endpoints on side effects are unsuitable for the benefit assessment. It is therefore not possible to perform a benefit-risk assessment for axicabtagene ciloleucel on the basis of the data presented.

In the overall assessment, a non-quantifiable additional benefit was identified for axicabtagene ciloleucel compared with induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation.

In the overall assessment of the present limitations, the reliability of data for the additional benefit determined is classified in the hint category.

The period of validity of the resolution is limited until 1 July 2024 because additional evaluations of side effects are considered necessary

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

For the benefit assessment, the pharmaceutical company submitted the results from the single-arm ALYCANTE study. As this is not a comparison with the appropriate comparator therapy, the ALYCANTE study is unsuitable for the benefit assessment.

Overall, there are therefore no suitable data for the assessment of the additional benefit of axicabtagene ciloleucel compared to the appropriate comparator therapy. Thus, an additional benefit of axicabtagene ciloleucel over the appropriate comparator therapy is not proven.

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

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

The dossier submitted by the pharmaceutical company underestimates the incidence of DLBCL and HGBL used as a baseline and restricts the target population beyond the therapeutic indication stated in the product information.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of lisocabtagene maraleucel (resolution of 16 November 2023)[12]. A more valid estimate of the number of patients in the SHI target population is available here; this can be used despite continuing uncertainties.

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 Yescarta (active ingredient: axicabtagene ciloleucel) at the following publicly accessible link (last access: 20 September 2023):

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient pass. Training material for all healthcare professionals who will prescribe, dispense, and administer axicabtagene ciloleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of 1 dose of tocilizumab at the point of treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

The patient training programme should explain the risks of cytokine release syndrome and serious neurologic side effects, the need to report symptoms immediately to the treating physician, to remain close to the treatment facility for at least 4 weeks after infusion of axicabtagene ciloleucel, and to carry the patient emergency card at all times.

Axicabtagene ciloleucel must be used in a qualified treatment facility. For the infusion of axicabtagene ciloleucel in the present therapeutic indication, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2023).

For the presentation of the costs, one year is assumed for all medicinal products.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

[12] Benefit assessment procedure D-951 of lisocabtagene maraleucel

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

CAR-T cell therapies

Axicabtagene ciloleucel concerns genetically modified, patient's own (autologous) T cells, which are usually obtained by leukapheresis. Since leukapheresis is part of the manufacture of the medicinal product according to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for these active ingredients as treatment options of the medicinal product to be assessed.

Axicabtagene ciloleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment facilities, and administered there. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Axicabtagene ciloleucel is administered as a single intravenous infusion according to the requirements in the underlying product information.

Induction chemotherapy before stem cell transplantation

The induction chemotherapies R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin), R-ICE (rituximab + ifosfamide + carboplatin + etoposide) and R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin) do not have a marketing authorisation in the present therapeutic indication. In accordance with the recommendation of the S3 guideline, the G-BA uses 2 - 3 cycles as the basis for calculating costs in the context of off-label use of these combination therapies[3]. Furthermore, for the treatment regimens and dosages in relation to the combination therapy R-GDP, the study by Crump et al. (2014)[8] referenced in the S3 guideline and, in relation to the combination therapies R-ICE and R-DHAP, the study by Gisselbrecht et al. referenced in the S3 guideline (2010)[13] are taken into account.

Inpatient treatments

Some treatment options of the appropriate comparator therapy are carried out on an inpatient basis. The inpatient costs are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG (Diagnosis Related Group) multiplied by the federal base rate value of 2023 (€ 4,000.71). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee according to Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (from 1 January 2023: € 230) and the treatment-specific nursing revenue valuation ratio.

13 Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28 (27):4184-90

Treatment period:

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Axicabtagene ciloleucel	Single dose	1	1	1
Appropriate comparator therapy				
Induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation if there is a response to induction chemotherapy				
Induction chemotherapy				
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]				
Rituximab	1 x per 21-day cycle (day 1)	2 – 3	1	2 – 3
Gemcitabine	2 x per 21-day cycle (day 1 + 8)	2 – 3	2	4 – 6
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 – 3	4	8 – 12
Cisplatin	1 x per 21-day cycle (day 1)	2 – 3	1	2 – 3
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[13]				
Rituximab	1 x per 21-day cycle (day 1, additionally once on the day before the first cycle)	2 – 3	1	3 – 4
Ifosfamide	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3
Carboplatin	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3
Etoposide	3 x per 21-day cycle (day 1 - 3)	2 – 3	3	6 – 9
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,13]				
Rituximab	1 x per 21-day cycle (day 1; additionally once **optionally** on	2 – 3	1	2 – 4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	the day before the first cycle)			
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 – 3	4	8 – 12
Cytarabine	2 x on day 2 of a 21-day cycle	2 – 3	1	2 – 3
Cisplatin	1 x per 21-day cycle (day 1)	2 – 3	1	2 – 3
High-dose chemotherapy with autologous stem cell transplantation				
Stem cell collection from autologous donors with chemotherapy or with most severe complications or comorbidities (CC), age > 15 years	once		15.9 (average length of stay)	15.9
Autologous stem cell transfusion	once		23.4 (average length of stay)	23.4
Induction chemotherapy followed by high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy				
Induction therapy				
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]				
Rituximab	1 x per 21-day cycle (day -1)	2 – 3	1	2 – 3
Gemcitabine	2 x per 21-day cycle (day 1 + 8)	2 – 3	2	4 – 6
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 – 3	4	8 – 12
Cisplatin	1 x per 21-day cycle (day 1)	2 – 3	1	2 – 3
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[13]				
Rituximab	1 x per 21-day cycle (day 1; additionally once on the day before the first cycle)	2 – 3	1	3 – 4
Ifosfamide	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Carboplatin	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3
Etoposide	3 x per 21-day cycle (day 1 - 3)	2 – 3	3	6 – 9
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,13]				
Rituximab	1 x per 21-day cycle (day 1; additionally once **optionally** on the day before the first cycle)	2 – 3	1	2 – 4
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 – 3	4	8 – 12
Cytarabine	2 x on day 2 of a 21-day cycle	2 – 3	1	2 – 3
Cisplatin	1 x per 21-day cycle (day 1)	2 – 3	1	2 – 3
High-dose chemotherapy with allogeneic stem cell transplantation				
Highly complex and intensive block chemotherapy	once		7.5 (average length of stay)	7.5
Allogeneic stem cell transfusion	once		35.0 (average length of stay)	35.0

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Axicabtagene ciloleucel	Single dose	1	1	1
Appropriate comparator therapy				
Polatuzumab vedotin + bendamustine + rituximab				
Polatuzumab vedotin	1 x per 21-day cycle	6.0	1	6.0
Bendamustine	2 x per 21-day cycle	6.0	2	12.0
Rituximab	1 x per 21-day cycle	6.0	1	6.0
Tafasitamab + lenalidomide				
Tafasitamab	Cycle 1: Day 1, 4, 8, 15 and 22 (28-day cycle)	13.0	Cycle 1: 5	33.0
	Cycle 2 + 3: Day 1, 8, 15, 22 (28-day cycle)		Cycle 2 + 3: 4	
	Cycle 4 up to disease progression: Day 1 and 15 (28-day cycle)		From cycle 4 onwards: 2	
Lenalidomide	Day 1 – 21 of a 28-day cycle	12.0	21	252.0

Consumption:

For dosages depending on body weight (bw) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" 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).[14]

The consumption of vials and infusion bags is presented for the medicinal product to be assessed, axicabtagene ciloleucel, according to the requirements in the product information. These are administered to the patient in a single infusion depending on the number of cells per vial or infusion bag. The annual treatment costs of axicabtagene ciloleucel are independent of the specific number of vials or infusion bags used.

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

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					
Axicabtagene ciloleucel	< 100 kg: 1 - 2 x 10^6 viable CAR+ T cells/kg	1 - 2 x 10^6/kg CAR+ T cells	1 single infusion bag	1	1 single infusion bag
	≥ 100 kg: 2 x 10^8 Viable CAR+ T cells (from 100 kg regardless of body weight)	2 x 10^8 CAR+ T cells			
Appropriate comparator therapy					
Induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation if there is a response to induction chemotherapy					
Induction chemotherapy					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 – 3	2.0 x 500 mg + 6.0 x 100 mg –

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					3.0 x 500 mg + 9.0 x 100 mg
Gemcitabine	1,000 mg/m² = 1,900 mg	1,900 mg	1 x 2,000 mg	4 – 6	4.0 x 2,000 mg – 6.0 x 2,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	8 – 12	8.0 x 40 mg – 12.0 x 40 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	2 – 3	2.0 x 100 mg + 2.0 x 50 mg – 3.0 x 100 mg + 3.0 x 50 mg
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[13]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	3 – 4	3.0 x 500 mg + 9.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg
Ifosfamide	5,000 mg/m² = 9,500 mg	9,500 mg	2 x 5,000 mg	2 – 3	4.0 x 5,000 mg – 6.0 x 5,000 mg
Carboplatin	AUC = 5 (= 641.4 mg); max. 800 mg	641.4 mg – 800 mg	1 x 600 mg + 1 x 50 mg – 1 x 600 mg + 4 x 50 mg	2 – 3	2.0 x 600 mg + 2.0 x 50 mg - 3.0 x 600 mg + 3.0 x 50 mg – 2.0 x 600 mg + 8.0 x 50 mg - 3.0 x 600 mg + 12.0 x 50 mg
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	6 – 9	6.0 x 200 mg – 9.0 x 200 mg
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,13]					
Rituximab	375 mg/m2 = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 – 4	2.0 x 500 mg + 6.0 x 100 mg – 4.0 x 500 mg + 12.0 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
Dexamethasone	40 mg	40 mg	1 x 40 mg	8 – 12	8.0 x 40 mg – 12.0 x 40 mg
Cytarabine	2 x daily 2,000 mg/m2 = 2 x 3,800 mg	7,600 mg	4 x 2,000 mg	2 – 3	8.0 x 2,000 mg – 12.0 x 2,000 mg
Cisplatin	100 mg/m^2 = 190 mg	190 mg	2 x 100 mg	2 – 3	4.0 x 100 mg – 6.0 x 100 mg
Induction chemotherapy followed by high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy					
Induction therapy					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]					
Rituximab	375 mg/m^2 = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 – 3	2.0 x 500 mg + 6.0 x 100 mg – 3.0 x 500 mg + 9.0 x 100 mg
Gemcitabine	1,000 mg/m^2 = 1,900 mg	1,900 mg	1 x 2,000 mg	4 – 6	4.0 x 2,000 mg – 6.0 x 2,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	8 - 12	8.0 x 40 mg – 12.0 x 40 mg
Cisplatin	75 mg/m^2 = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	2 – 3	2.0 x 100 mg + 2.0 x 50 mg – 3.0 x 100 mg + 3.0 x 50 mg
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[13]					
Rituximab	375 mg/m^2 = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	3 – 4	3.0 x 500 mg + 9.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg
Ifosfamide	5,000 mg/m^2 = 9,500 mg	9,500 mg	2 x 5,000 mg	2 – 3	4.0 x 5,000 mg – 6.0 x 5,000 mg
Carboplatin	AUC = 5	641.4 mg –	1 x 600 mg + 1 x 50 mg	2 – 3	2.0 x 600 mg + 2.0 x 50 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
	(= 641.4 mg); max. 800 mg	800 mg	– 1 x 600 mg + 4 x 50 mg		- 3.0 x 600 mg + 3.0 x 50 mg – 2.0 x 600 mg + 8.0 x 50 mg - 3.0 x 600 mg + 12.0 x 50 mg
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	6 – 9	6.0 x 200 mg – 9.0 x 200 mg
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,13]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 – 4	2.0 x 500 mg + 6.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	8 - 12	8.0 x 40 mg – 12.0 x 40 mg
Cytarabine	2 x daily 2,000 mg/m² = 2 x 3,800 mg	7,600 mg	4 x 2,000 mg	2 – 3	8.0 x 2,000 mg – 12.0 x 2,000 mg
Cisplatin	100 mg/m² = 190 mg	190 mg	2 x 100 mg	2 – 3	4.0 x 100 mg – 6.0 x 100 mg

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

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					
Axicabtagene ciloleucel	< 100 kg: 1 - 2 x 10^6 viable CAR+ T cells/kg	1 - 2 x 10^6/kg CAR+ T cells	1 single infusion bag	1	1 single infusion bag
	≥ 100 kg: 2 x 10^8 Viable CAR+ T cells (from 100 kg regardless of body weight)	2 x 10^8 CAR+ T cells			
Appropriate comparator therapy					
Polatuzumab vedotin + bendamustine + rituximab					
Polatuzumab vedotin	1.8 mg/kg = 138.6 mg	138.6 mg	1 x 140 mg	6.0	6.0 x 140 mg
Bendamustine	90 mg/m^2 = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12.0	12.0 x 100 mg + 36.0 x 25 mg
Rituximab	375 mg/m^2 = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	6.0	6.0 x 500 mg + 18.0 x 100 mg
Tafasitamab + lenalidomide					
Tafasitamab	12 mg/kg = 924 mg	924 mg	5 x 200 mg	33.0	165.0 x 200 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	252.0	252.0 x 25 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Inpatient treatments:

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Appropriate comparator therapy									
High-dose chemotherapy with allogeneic stem cell transplantation									
2023	R61G	7.5	0.992	€ 4,000.71	0.7667	€ 230	€ 3,968.70	€ 1,323.56	€ 5,291.26
2023	A04E	35.0	9.226	€ 4,000.71	1.9083	€ 230	€ 36,910.55	€ 15,362.82	€ 52,272.37
High-dose chemotherapy with autologous stem cell transplantation									
2023	A42A	15.9	1.979	€ 4,000.71	0.7723	€ 230	€ 7,917.41	€ 2,824.30	€ 10,741.71
2023	A15C	23.4	5.380	€ 4,000.71	1.2260	€ 230	€ 21,523.82	€ 6,598.33	€ 28,122.15

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Axicabtagene ciloleucel	1 single infusion bag	€ 272,000	€ 0[15]	€ 272,000

[15] The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.

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
Appropriate comparator therapy					
Rituximab					
Rituximab 500 mg	2 CIS	€ 3,639.53	€ 2.00	€ 350.68	€ 3,286.85
Rituximab 500 mg	1 CIS	€ 1,819.93	€ 2.00	€ 172.53	€ 1,645.40
Rituximab 100 mg	2 CIS	€ 748.12	€ 2.00	€ 69.93	€ 676.19
Gemcitabine					
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Dexamethasone					
Dexamethasone 40 mg	10 TAB	€ 46.29	€ 2.00	€ 0	€ 44.29
Dexamethasone 40 mg	20 TAB	€ 81.59	€ 2.00	€ 0	€ 79.59
Cisplatin 142.5 mg					
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Cisplatin 190 mg					
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Ifosfamide					
Ifosfamide 5 g	1 CIS	€ 177.77	€ 2.00	€ 7.90	€ 167.87
Carboplatin					
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 50 mg	1 CIS	€ 34.66	€ 2.00	€ 1.11	€ 31.55
Etoposide					
Etoposide 200 mg	1 CIS	€ 81.90	€ 2.00	€ 3.35	€ 76.55
Cytarabine					
Cytarabine 2,000 mg	1 ILL	€ 77.06	€ 2.00	€ 3.12	€ 71.94
Bendamustine					
Bendamustine 25 mg	5 PCI	€ 414.43	€ 2.00	€ 51.01	€ 361.42
Bendamustine 25 mg	1 PCI	€ 99.39	€ 2.00	€ 11.15	€ 86.24
Bendamustine 100 mg	5 PCI	€ 1,620.96	€ 2.00	€ 204.07	€ 1,414.89
Bendamustine 100 mg	1 PCI	€ 331.03	€ 2.00	€ 40.46	€ 288.57
Other medicinal products					
Polatuzumab vedotin 140 mg	1 PIC	€ 10,680.39	€ 2.00	€ 433.33	€ 10,245.06
Tafasitamab 500 mg	1 PCI	€ 654.48	€ 2.00	€ 61.05	€ 591.43
Lenalidomide 25 mg	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Abbreviations: AMP = ampoules; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; ILL = solution for injection/ infusion; TAB = tablets; PIC = powder for the preparation of an infusion solution concentrate; PCI = powder for a concentrate for the preparation of an infusion solution					

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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.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of 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.

Prophylactic premedication

Antipyretic and antihistamine premedication is only recommended in the product information of axicabtagene ciloleucel. These costs cannot be quantified as no specific dosage recommendations are given in the product information of polatuzumab vedotin.

Mesna is given in combination with ifosfamide for the prophylaxis of haemorrhagic cystitis.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Axicabtagene ciloleucel is an autologous cell product produced from the patient's own T cells. Therefore, a leukapheresis is usually necessary to obtain the cell material. Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for axicabtagene ciloleucel.

For axicabtagene ciloleucel, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (500 mg/m^2 = 950 mg) and fludarabine (30 mg/m^2 = 57 mg), is given daily for 3 days, with infusion administered 3 to 5 days after the start of lymphocyte depletion.

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) under CAR-T cell therapy

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with axicabtagene ciloleucel. This test is not required for all therapy options of the appropriate comparator therapy. Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, hepatitis C and HIV, the costs of additionally required SHI services are presented in the resolution.

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
Medicinal product to be assessed							
Axicabtagene ciloleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 500 mg/m² = 950 mg	6 PSI at 500 mg	€ 84.44	€ 2.00	€ 9.25	€ 73.19	3.0	€ 73.19
Fludarabine 30 mg/m² = 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 668.70
Screening for HBV, HCV and HIV							
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Appropriate comparator therapy							
Induction chemotherapy (R-GDP, R-DHAP, R-ICE) prior to autologous or allogeneic stem cell transplantation							
Rituximab (R-GDP, R-DHAP, R-ICE)							
HBV diagnostics							
HBV test Hepatitis B Surface antigen status (GOP: 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Premedication (R-GDP)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	2.0 – 3.0	€ 16.19 – € 32.38
Paracetamol[16] (500 mg - 1,000 mg, PO)	10 TAB 500 mg –	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	2.0 – 3.0	€ 2.68 – € 3.01

[16] 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	Treatment days/ year	Costs/ patient/ year
	10 TAB 1000 mg						
Premedication (R-DHAP)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	2.0 – 4.0	€ 16.19 – € 32.38
Paracetamol[16] (500 mg - 1,000 mg, PO)	10 TAB 500 mg – 10 TAB 1000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	2.0 – 4.0	€ 2.68 – € 3.01
Premedication (R-ICE)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	3.0 – 4.0	€ 32.38
Paracetamol[16] (500 mg - 1,000 mg, PO)	10 TAB 500 mg – 10 TAB 1000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	3.0 – 4.0	€ 2.68 – € 3.01
Cisplatin (R-GDP, R-DHAP)							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	2.0 – 3.0	91.10
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	2.0 – 3.0	€ 21.79 – € 54.37
	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58		
Mesna (R-ICE)							
Mesna (Bolus with 1,900 mg mesna (= 20% of the ifosfamide dose), followed by 24-hour continuous infusion with at least 1,900 mg up to 9,500 mg	Bolus with 1,900 mg followed by 24-hour continuous infusion with 1,900 mg						
	10 SFI 400 mg	€ 32.26	€ 2.00	€ 0.99	€ 29.27	2 - 3	€ 58.54 - € 87.81
	Bolus of 1,900 mg followed by 24-hour continuous infusion of 9,500 mg followed by subsequent infusion of 4,750 mg						

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
(= 20% - 100% of the ifosfamide dose), followed by subsequent infusion with up to 4,750 mg mesna (= 0% - 50% of the ifosfamide dose) for 6 - 12 hours	50 AMP 400 mg	€ 148.19	€ 2.00	€ 17.33	€ 128.86	2-3	€ 257.72 - € 386.58
Polatuzumab vedotin + bendamustine + rituximab							
Bendamustine and rituximab							
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP: 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Rituximab							
Premedication							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	6.0	€ 48.57
Paracetamol[16] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	6.0	€ 2.68 – € 3.01
Abbreviations: AMP = ampoules; SFI = solution for injection; INF = infusion solution; CII = concentrate for injection or infusion solution; TAB = tablets; PSI = powder for solution for injection							

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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 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 special agreement on contractual unit costs of retail pharmacist services (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 SGBV.

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:

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

   - 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 axicabtagene ciloleucel (Yescarta); product information for Yescarta; last revised: July 2023

b) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are ineligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

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

   References:

   Product information for axicabtagene ciloleucel (Yescarta); product information for Yescarta; last revised: July 2023

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 7 March 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The plenum newly determined the appropriate comparator therapy at its session on 1 June 2023.

On 30 June 2023, the pharmaceutical company submitted a dossier for the benefit assessment of axicabtagene ciloleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 3 July 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 axicabtagene ciloleucel.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 October 2023. The deadline for submitting statements was 23 October 2023.

The oral hearing was held on 6 November 2023.

By letter dated 7 November 2023, 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 1 December 2023.

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 12 December 2023, and the proposed resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 March 2023	Determination of the appropriate comparator therapy
Plenum	1 June 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	31 October 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	6 November 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 November 2023 6 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 December 2023

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

Prof. Hecken