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) Loncastuximab tesirine (diffuse large B-cell lymphoma and high-grade B-cell lymphoma, after ≥ 2 prior therapies)

of 2 November 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient loncastuximab tesirine on 15 May 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 12 May 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 August 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 loncastuximab tesirine 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 loncastuximab tesirine.

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

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

2.1.1 Approved therapeutic indication of Loncastuximab tesirine (Zynlonta) according to the product information

Zynlonta as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 02.11.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

Appropriate comparator therapy:

Therapy according to doctor's instructions under consideration of

- Tisagenlecleucel,
- axicabtagene ciloleucel,
- an induction therapy with
  - R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin and carboplatin) *or*
  - R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine) *or*
  - R-ICE (rituximab, ifosfamide, carboplatin, etoposide)

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

followed by high-dose therapy with **autologous** stem cell transplantation if there is a response to induction therapy,

- an induction therapy with
  - R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin and carboplatin) *or*
  - R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine) *or*
  - R-ICE (rituximab, ifosfamide, carboplatin, etoposide)

  followed by high-dose therapy with **allogeneic** stem cell transplantation if there is a response to induction therapy

b) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for CAR-T cell therapy or stem cell transplantation

Appropriate comparator therapy:

Therapy according to doctor's instructions under consideration of

- Polatuzumab vedotin + bendamustine + rituximab,
- tafasitamab + lenalidomide,
- pixantrone monotherapy,
- radiation

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 loncastuximab tesirine, the following active ingredients are approved for the present therapeutic indication:

Bleomycin, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, epcoritamab, glofitamab, ifosfamide, melphalan, methotrexate, methylprednisolone, mitoxantrone, pixantrone, polatuzumab vedotin, prednisolone, prednisone, tafasitamab, trofosfamide, vinblastine, vincristine, vindesine, rituximab, axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel.

Some of the medicinal products listed have a marketing authorisation for the superordinate therapeutic indication "non-Hodgkin lymphoma". The marketing authorisations are partly linked to (specified) concomitant active ingredients or do not fully cover the present therapeutic indication.

on 2. In principle, autologous or allogeneic stem cell transplantation can be considered as a non-medicinal treatment for relapsed or refractory DLBCL and HGBL. In addition, radiotherapy can be administered, for example, to treat localised residual manifestations of the lymphoma after completion of chemotherapy.

on 3. For this therapeutic indication, there are the following resolutions or guidelines of the G-BA for medicinal applications or non-medicinal treatments:

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

- Lisocabtagene maraleucel (resolution of 6 April 2023)
- Tafasitamab (resolution of 3 March 2022)
- Polatuzumab vedotin (resolution of 20 August 2020)
- Pixantrone (resolution of 16 May 2013)

- Axicabtagene ciloleucel (resolution of 3 November 2022)
- Tisagenlecleucel (resolution of 17 September 2020)

Guideline for Inpatient Treatment (last revised 7 December 2022: Allogeneic stem cell transplantation for aggressive B-non-Hodgkin lymphomas):

- 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.

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 care.

It should generally be noted that the HGBL was only listed as a definitive entity with the WHO classification[2] from June 2022 and has since been explicitly named by the EMA within the framework of the marketing authorisation. Prior to this update, HGBLs 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.

Overall, the evidence on treatment options for the present advanced treatment setting of relapsed or refractory DLBCL and HGBL after at least two lines of therapy is limited. The treatment recommendations basically show that the treatment of HGBL is based on the treatment of DLBCL, so that no differentiation of patient groups is made in this respect for the determination of the appropriate comparator therapy.

The present therapeutic indication generally refers to patients with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy and is not limited in terms of patient eligibility or ineligibility for an intensive therapeutic approach. According to the S3 guideline, there are distinct treatment

[2] Alaggio, R., Amador, C., Anagnostopoulos, I. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 36, 1720–1748 (2022). https://doi.org/10.1038/s41375-022-01620-2

recommendations for therapy with a primarily curative intention, such as CAR-T cell therapy and stem cell transplantation on the one hand, and therapy with a primarily palliative intention on the other. According to the scientific-medical societies, there is also a corresponding differentiation between curative and non-curative treatment options. In this regard, it also emerged from the statements submitted by clinical experts in the present benefit assessment procedure that in clinical practice, not only the suitability for high-dose therapy but also the suitability for CAR-T cell therapy are relevant parameters with regard to the treatment decision from the third line of therapy onwards. The G-BA therefore considers it appropriate to differentiate between two patient groups depending on their suitability for CAR-T cell therapy or stem cell transplantation when determining the appropriate comparator therapy.

Patient group a)

According to the S3 guideline, CAR-T cell therapy should be carried out from the second relapse onwards if it has not already been carried out in second-line therapy. The CAR-T cell therapies axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are available in this therapeutic indication. For axicabtagene ciloleucel (resolution of 3 November 2022) and tisagenlecleucel (resolution of 17 September 2020), a hint for a non-quantifiable additional benefit was identified within the scope of an orphan drug assessment because the scientific data did not allow quantification. The period of validity of the resolution on tisagenlecleucel was limited until 1 September 2023; the benefit assessment procedure is currently in progress after expiry of the deadline.

In addition, on 4 April 2022 the CAR-T cell therapy lisocabtagene maraleucel was approved for the treatment of relapsed or refractory DLBCL after at least 2 prior therapies. No additional benefit was identified for lisocabtagene maraleucel compared with the appropriate comparator therapy in the benefit assessment by resolution of 6 April 2023.
In Germany, lisocabtagene maraleucel was placed on the market for the first time 5 months post-authorisation on 1 September 2022. This CAR-T cell therapy has therefore been available for a relatively short time. In view of the fact that lisocabtagene maraleucel is still a relatively new therapy option, this CAR-T cell therapy is not designated as an appropriate comparator therapy for the present resolution.

According to the available guidelines and the statements of the scientific-medical societies, salvage chemoimmunotherapy including stem cell transplantation (autologous or allogeneic) is the therapy standard, especially after CAR-T cell therapy or for patients who are ineligible for such therapy. According to the guidelines[3,4], platinum-based chemoimmunotherapy is used as standard for induction therapy, with the platinum-containing combinations GDP (gemcitabine, dexamethasone, cisplatin or carboplatin), DHAP (dexamethasone, cisplatin, cytarabine) and ICE (ifosfamide, carboplatin, etoposide), each in combination with rituximab, being recommended as specific therapy regimens. In accordance with the S3 guidelines, these treatment regimens were compared with each other in prospective randomised studies, whereby

[3] Oncology L, DKG) DK, (DKH) DK, 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. [Accessed: 12.12.2022]. (NICE Guideline; Band NG52).

differences in toxicity were found with the same efficacy[5,6]. 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's lymphomas" method.[7] Rituximab is only approved in the present indication 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[8]. 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 to the German healthcare context.

In summary, if CAR-T cell therapy has already been carried out or is not an option for medical reasons, salvage chemoimmunotherapy consisting of R-GDP, R-DHAP or R-ICE should be accordingly carried out with the inclusion of stem cell transplantation. In these cases, the use of induction therapy with R-GDP, R-DHAP or R-ICE is generally preferable to induction therapy with MINE for this relevant patient group in accordance with Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). Therefore, it is appropriate to determine the off-label use of these combinations of medicinal products as the appropriate comparator therapy for this patient population. The other approved active ingredients listed under paragraph 1 do not correspond to the therapy recommendations for the present indication and to the therapy standard in the reality of care as set out in the guidelines and in the statement of the scientific-medical societies.

Overall, a therapy according to doctor's instructions is therefore determined as an appropriate comparator therapy, taking into account tisagenlecleucel, axicabtagene

[5] 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

[6] 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. URL: https://pubmed.ncbi.nlm.nih.gov/25267740/

[7] 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

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

ciloleucel, an induction therapy with R-GDP, R-DHAP or R-ICE followed by a high-dose therapy with autologous or allogeneic stem cell transplantation in response to the induction therapy.

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.

Patient group b)

For patients who are ineligible for CAR-T cell therapy or stem cell transplantation due to the course of their disease or their general condition, various chemo or chemo-immunotherapies as well as newer substances represent treatment options according to guidelines and statements by the scientific-medical societies.

The antibody-drug conjugate polatuzumab vedotin is approved in combination with bendamustine and rituximab (Pola-BR) for the treatment of adults with relapsed or refractory diffuse 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.

The active ingredient pixantrone has explicit marketing authorisation for the treatment setting of multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphoma (NHL). By resolution of the G-BA of 16 May 2013, it was determined that an additional benefit of pixantrone compared to the appropriate comparator therapy is not proven. Pixantrone is mentioned in the written statement of the scientific-medical societies as a therapeutic alternative to the treatment of multiple relapsed, aggressive B-cell lymphomas.

The combination chemotherapies CEOP (cyclophosphamide, etoposide, vincristine, prednisone) and EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) are also approved for this indication. From the statements of the clinical experts in the present benefit assessment procedure, it emerged that the combination chemotherapies mentioned have no relevant significance in the present treatment setting - especially as the combination therapies mentioned or the active ingredients contained in these combination therapies have already been used previously within the therapeutic sequence. The combination therapies mentioned are not designated as an appropriate comparator therapy.

Due to the predominantly palliative treatment setting, palliative radiotherapy may also be a treatment option for patients who have undergone more than two prior systemic therapies. In view of the fact that, according to the clinical experts, treatment with best

supportive care alone can only be considered for very few patients - primarily patients of very advanced age - in the present therapeutic indication, best supportive care alone is not determined to be an appropriate comparator therapy.

The active ingredients glofitamab and epcoritamab are treatment options in the present therapeutic indication. These active ingredients were only recently approved (marketing authorisation on 07.07.2023 and 22.09.2023). Based on the generally accepted state of medical knowledge, glofitamab and epcoritamab are not determined to be an appropriate comparator therapy for the present resolution.

Against this background, a therapy according to doctor's instructions is determined as appropriate comparator therapy for patient group b), taking into account pola-BR, tafasitamab + lenalidomide, pixantrone and radiotherapy.

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

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

Change of the appropriate comparator therapy

Originally, the appropriate comparator therapy was determined as follows:

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for a high-dose therapy

Appropriate comparator therapy for loncastuximab tesirine:

Therapy according to doctor's instructions under consideration of

- Tisagenlecleucel,
- axicabtagene ciloleucel,
- induction therapy with MINE (mesna, ifosfamide, mitoxantrone, etoposide) followed by high-dose therapy with **autologous** stem cell transplantation if there is a response to induction therapy

  and

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

b) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for a high-dose therapy

Appropriate comparator therapy for loncastuximab tesirine

Therapy according to doctor's instructions under consideration of

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone),
- dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone),
- Polatuzumab vedotin + bendamustine + rituximab,
- tafasitamab + lenalidomide,
- pixantrone monotherapy,
- radiation,
- and best supportive care

This appropriate comparator therapy was determined for the present benefit assessment procedure on loncastuximab tesirine 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 relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy are mentioned in the present 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 loncastuximab tesirine, 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 addition, the statements submitted by clinical experts in the present benefit assessment procedure showed that, with regard to the treatment decision from the third line of therapy onwards, not only the suitability for high-dose therapy but also the suitability for CAR-T cell therapy are relevant parameters; in this respect, according to the S3 guideline, there are distinct treatment recommendations for therapy with a primarily curative intention, such as CAR-T cell therapy and stem cell transplantation on the one hand, and therapy with a primarily palliative intention on the other.

Against this background, the appropriate comparator therapy was changed for the present resolution.

This does not affect the present assessment of the additional benefit of loncastuximab tesirine.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

An additional benefit is not proven.

b) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for CAR-T cell therapy or stem cell transplantation

An additional benefit is not proven.

Justification:

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

and

b) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for CAR-T cell therapy or stem cell transplantation

For the benefit assessment of loncastuximab tesirine for the treatment of adults with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy, the pharmaceutical company submitted the single-arm phase II LOTIS-2 study.

LOTIS-2 study

The single-arm phase II LOTIS-2 study investigated the efficacy and safety of loncastuximab tesirine in adults with relapsed or refractory, not otherwise specified (NOS) DLBCL, HGBL with MYC and BCL2 and/or BCL6 rearrangements and primary mediastinal large B-cell lymphoma (PMBCL). Patients had to have already received at least two lines of systemic therapy.

A total of 145 patients were enrolled, including 127 (87.6%) with DLBCL, 11 (7.6%) with HGBL and 7 (4.8%) with PMBCL.

The study was conducted from August 2018 to September 2022 in a total of 28 study sites across Europe and North America.

For the LOTIS-2 study, 5 data cut-offs were performed. For the individual endpoints, the results of the 1st data cut-off from 06.04.2020 and the 3rd data cut-off from 01.03.2021 were submitted. For the overall survival endpoint, the results of the 5th data cut-off from 15.09.2022 (final analysis of overall survival) were submitted.

Overall assessment

The results of the single-arm LOTIS-2 study are available for the assessment of the additional benefit of loncastuximab tesirine.

The results of the single-arm LOTIS-2 study presented are unsuitable for assessment of the additional benefit as they do not allow a comparison with the appropriate comparator therapy. Therefore, an additional benefit of loncastuximab tesirine as monotherapy in adults with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Zynlonta" with the active ingredient loncastuximab tesirine.

Zynlonta received a conditional marketing authorisation.

Loncastuximab tesirine is approved as monotherapy in adults for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) after two or more lines of systemic therapy.
In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adults with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy who are eligible for CAR-T cell therapy or stem cell transplantation

b) Adults with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy who are ineligible for CAR-T cell therapy or stem cell transplantation

<u>About patient group a)</u>

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions, taking into account the CAR-T cell therapies tisagenlecleucel and axicabtagene ciloleucel as well as induction therapy with R-GDP, R-DHAP or R-ICE followed by high-dose therapy with autologous or allogeneic stem cell transplantation in response to the induction therapy.
To demonstrate the additional benefit of loncastuximab tesirine compared to the appropriate comparator therapy, the pharmaceutical company submits the single-arm LOTIS-2 study. The data presented are unsuitable for comparison with the appropriate comparator therapy.

An additional benefit of loncastuximab tesirine as monotherapy in adults with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy who are eligible for CAR-T cell therapy or stem cell transplantation is therefore not proven.

<u>About patient group b)</u>

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions, taking into account polatuzumab vedotin + bendamustine + rituximab, tafasitamab + lenalidomide, pixantrone and radiotherapy.

To demonstrate the additional benefit of loncastuximab tesirine compared to the appropriate comparator therapy, the pharmaceutical company submits the single-arm LOTIS-2 study. The data presented are unsuitable for comparison with the appropriate comparator therapy.

An additional benefit of loncastuximab tesirine as monotherapy in adults with relapsed or refractory DLBCL and HGBL after two or more lines of systemic therapy who are ineligible for CAR-T cell therapy or stem cell transplantation is therefore 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 G-BA bases its resolution on the information from the written statement of the pharmaceutical company. It must be taken into account that the patient numbers presented for the patient groups a) and b) are subject to uncertainties. With regard to the lower limit for patient group a) and the upper limit for patient group b), this results from the fact that the information originate from a review addressing second-line therapy, i.e. a previous line of therapy. The upper limit for patient group a) and the lower limit for patient group b) were based on information on patient access to CAR-T cell therapies in Austria. This percentage may be an underestimate as correspondingly higher percentages were calculated for Germany. Furthermore, the HGBL is not taken into account when determining the percentages.

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 Zynlonta (active ingredient: loncastuximab tesirine) at the following publicly accessible link (last access: 19 July 2023):

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

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

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the EMA's requirements for additional risk minimisation measures, the pharmaceutical company must ensure that all healthcare professionals who may prescribe loncastuximab tesirine and each subject treated with loncastuximab tesirine receive a patient pass containing safety information on the risks of photosensitivity reactions and a warning for the healthcare professional treating the person. Patients should carry their patient pass with them at all times.

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: 15 October 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.

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.

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[9]. Furthermore, for the treatment regimens and dosages in relation to the combination therapy R-GDP, the study by Crump et al. (2014)[10] 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)[11] are taken into account.

CAR-T cell therapies

Axicabtagene ciloleucel and tisagenlecleucel are 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 appropriate comparator therapy.

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

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

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.

Treatment period:

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

[9] https://register.awmf.org/assets/guidelines/018-038OLl_Diagnostik-Therapie-Nachsorge-erwachsene-PatientIinnen-diffusen-grosszelligen-B-Zell-Lymphom-verwandten-Entitaeten-DLBC-2022-10.pdf

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Loncastuximab tesirine	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
CAR-T cell therapies				
Axicabtagene ciloleucel	Single dose	1	1	1
Tisagenlecleucel	Single dose	1	1	1
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) [10]				
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) [11]				
Rituximab	1 x per 21-day cycle (before day – 1)	2 – 3	1	2 – 3
Ifosfamide	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3
Mesna	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3

[10] 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

[11] 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

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)[11]				
Rituximab	1 x per 21-day cycle (before day – 1)	2 – 3	1	2 – 3
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 – 3	4	8 – 12
Cytarabine	2 x per 21-day cycle (2 x on day 2)	2 – 3	1	4 – 6
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)[10]				
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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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)[11]				
Rituximab	1 x per 21-day cycle (before day – 1)	2 – 3	1	2 – 3
Ifosfamide	1 x per 21-day cycle (day 2)	2 – 3	1	2 – 3
Mesna	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)[11]				
Rituximab	1 x per 21-day cycle (before day – 1)	2 – 3	1	2 – 3
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 – 3	4	8 - 12
Cytarabine	2 x per 21-day cycle (2 x on day 2)	2 – 3	1	4 – 6
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	35.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
			(average length of stay)	

b) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for CAR-T cell therapy or stem cell transplantation

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Loncastuximab tesirine	1 x per 21-day cycle	17.4	1	17.4
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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pixantrone monotherapy				
Pixantrone	Day 1, 8, 15 (28-day cycle)	1.0 – 6.0	3	3.0 – 18.0
radiation				
radiation	varies from patient to patient			

Consumption:

For dosages depending on body weight or body surface, 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).[12]

For the appropriate comparator therapy options tisagenlecleucel and axicabtagene ciloleucel, the consumption of vials or infusion bags is presented 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 tisagenlecleucel and axicabtagene ciloleucel are independent of the specific number of vials or infusion bags used.

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

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					
Loncastuximab tesirine	Cycle 1 + 2: 0.15 mg/kg = 11.55 mg (21-day cycle)	Cycle 1 + 2: 11.55 mg	Cycle 1 + 2: 2 x 10 mg	17.4	19.4 x 10 mg

[12] 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
	From cycle 3 up to disease progression: 0.075 mg/kg = 5.78 mg (21-day cycle)	From cycle 3 up to disease progression: 5.78 mg	From cycle 3 onwards: 1 x 10 mg		
Appropriate comparator therapy					
CAR-T cells					
Axicabtagene ciloleucel	< 100 kg: 1 - 2 x 10^6 viable CAR+ T cells per 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			
Tisagenlecleucel	0.6 - 6 x 10^8 viable CAR+ T cells (regardless of body weight)	0.6 - 6 x 10^8 viable CAR+ T cells	1 single infusion bag	1	1 single infusion bag
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)[10]					
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 –

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					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)					
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 – 3.0 x 500 mg + 9.0 x 100 mg
Ifosfamide	5,000 mg/m² = 9,500 mg	9,500 mg	2 x 5000 mg	2 – 3	4.0 x 5000 mg – 6.0 x 5000 mg
Mesna	1,000 mg/m² = 1,900 mg	1,900 mg	3 x 5 x 400 mg	2 – 3	30 x 400 mg – 45 x 400 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)					

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 – 3.0 x 500 mg + 9.0 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	2,000 mg/m² = 3,800 mg	3,800 mg	2 x 2,000 mg	4 – 6	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
Induction chemotherapy followed by high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy					
Induction chemotherapy					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[10]					
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 – 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)					
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 – 3.0 x 500 mg + 9.0 x 100 mg

Ifosfamide	5,000 mg/m² = 9,500 mg	9,500 mg	2 x 5000 mg	2 – 3	4.0 x 5000 mg – 6.0 x 5000 mg
Mesna	1,000 mg/m² = 1,900 mg	1,900 mg	3 x 5 x 400 mg	2 – 3	30 x 400 mg – 45 x 400 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)					
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 – 3.0 x 500 mg + 9.0 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	2,000 mg/m² = 3,800 mg	3,800 mg	2 x 2,000 mg	4 – 6	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 relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for CAR-T cell therapy or stem cell transplantation

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					
Loncastuximab tesirine	Cycle 1+2: 0.15 mg/kg = 11.55 mg (21-day cycle)	Cycle 1+2: 11.55 mg	Cycle 1 + 2: 2 x 10 mg	17.4	19.4 x 10 mg
	From cycle 3 up to disease progression: 0.075 mg/kg = 5.78 mg (21-day cycle)	From cycle 3 up to disease progression: 5.78 mg	From cycle 3 onwards: 10 mg		
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/m² = 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/m² = 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
Pixantrone monotherapy					
Pixantrone	50 mg/m² = 95 mg	95 mg	4 x 29 mg	3.0 – 18.0	12.0 x 29 mg – 72.0 x 29 mg
radiation					
radiation	varies from patient to patient				

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	€ 5,291.26
2023	A04E	35.0	9.226	€ 4,000.71	1.9083	€ 230	€ 36,910.55	€ 15,362	€ 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	€ 10,741.71
2023	A15C	23.4	5.380	€ 4,000.71	1.2260	€ 230	€ 21,523.82	€ 6,598	€ 28,122.15

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Loncastuximab tesirine 10 mg	1 PCI	€ 24,403.18	€ 2.00	€ 2,383.51	€ 22,017.67
Appropriate comparator therapy					
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 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
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					

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
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 5 g	1 CIS	€ 177.77	€ 2.00	€ 7.90	€ 167.87
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 200 mg	1 CIS	€ 81.90	€ 2.00	€ 3.35	€ 76.55
Cytarabine 2,000 mg	1 ILL	€ 77.06	€ 2.00	€ 3.12	€ 71.94
Polatuzumab vedotin 140 mg	1 PCI	€ 10,680.39	€ 2.00	€ 433.33	€ 10,245.06
Bendamustine 25 mg	5 PCI	€ 374.81	€ 2.00	€ 17.25	€ 355.56
Bendamustine 100 mg	5 PCI	€ 1,465.28	€ 2.00	€ 69.00	€ 1,394.28
Tafasitamab 500 mg	1 PCI	€ 654.48	€ 2.00	€ 61.05	€ 591.43
Lenalidomide 25 mg	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.92
Pixantrone 29 mg	1 PCI	€ 485.44	€ 2.00	€ 18.75	€ 464.69
Mesna 400 mg	50 AMP	€ 148.19	€ 2.00	€ 17.33	€ 128.86
CAR-T cells					
Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)		Costs of the medicinal product
Axicabtagene ciloleucel	1 single infusion bag	€ 420,000.00	€ 0 [13]		€ 272,000.00
Tisagenlecleucel	1 single infusion bag	€ 239,000.00	€ 0 [13]		€ 239,000.00
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; CAP = capsules; PCI = powder for a concentrate for the preparation of an infusion solution; ILL = injection/infusion solution					

LAUER-TAXE® last revised: 15 October 2023

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

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

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

During therapy with loncastuximab tesirine, 4 mg dexamethasone is administered twice daily for 3 days (perorally or intravenously), starting the day before or at least 2 hours before the administration of loncastuximab tesirine, to mitigate pyrrolobenzodiazepine-related toxic effects.

As antipyretic and antihistamine premedication is only recommended in the product information for axicabtagene ciloleucel and tisagenlecleucel and no specific dosage recommendations are given for polatuzumab vedotin, these costs are indicated as non-quantifiable.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Axicabtagene ciloleucel and tisagenlecleucel are autologous cell products 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 the medicinal product to be assessed and the mentioned active ingredients of the appropriate comparator therapy.

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.

For tisagenlecleucel, provided the white blood cell count is not below ≤ 1,000 cells/µl one week prior to infusion, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (250 mg/m^2 = 475 mg) and fludarabine (25 mg/m^2 = 47.5 mg) is given daily for 3 days, with infusion administered 2 to 14 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 or tisagenlecleucel. This examination is not required for all comparators in the context of patient-individual 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
Appropriate comparator therapy:							
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
Tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 250 mg/m² = 475 mg	1 PSI at 500 mg	€ 23.50	€ 2.00	€ 1.54	€ 19.96	3.0	€ 59.88
Fludarabine 25 mg/m² = 47.5 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 334.35
Screening for HBV, HCV and HIV							
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Hepatitis 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
Induction chemotherapy prior to autologous or allogeneic stem cell transplantation (R-GDP, R-DHAP, R-ICE)							
Rituximab (R-GDP, R-DHAP, R-ICE)							
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Premedication							
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 [14] (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 – 3.0	€ 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.							

[14] 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
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		
Polatuzumab vedotin + bendamustine + rituximab							
Bendamustine and rituximab							
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 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 [14] (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	6.0	€ 2.68 – € 3.01
Polatuzumab vedotin							
Premedication							
Antihistamine	Incalculable						
Antipyretic	Incalculable						
Abbreviations: SFI = solution for injection; TAB = tablets; DSS = dry substance without solvent; PSI = powder for solution for injection							

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.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called undetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

Concomitant active ingredient:

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

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

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

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

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

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

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

Designation

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

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy, who are **not** eligible for CAR-T cell therapy or stem cell transplantation

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 26 July 2022, 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 12 May 2023, the pharmaceutical company submitted a dossier for the benefit assessment of loncastuximab tesirine to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 May 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 loncastuximab tesirine.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 August 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 August 2023. The deadline for submitting statements was 5 September 2023.

The oral hearing was held on 25 September 2023.

By letter dated 26 September 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 12 October 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 24 October 2023, and the proposed resolution was approved.

At its session on 2 November 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 July 2022	Determination of the appropriate comparator therapy
Plenum	1 June 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	20 September 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 September 2023	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	5 October 2023 18 October 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	24 October 2023	Concluding discussion of the draft resolution
Plenum	2 November 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 2 November 2023

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

Prof. Hecken