Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Polatuzumab vedotin (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: relapsed/ refractory diffuse large B-cell lymphoma)

of 20 June 2024

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

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

At its session on 20 August 2020, the G-BA decided on the benefit assessment of polatuzumab vedotin in the therapeutic indication "Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant." in accordance with Section 35a SGB V.

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

In a letter dated 2 February 2023, the pharmaceutical company was informed that the EUR 30 million turnover limit for polatuzumab vedotin had been exceeded within the period from December 2021 to November 2022. Likewise, by resolution of 2 February 2023 the procedure was suspended till 2 January 2024.

The pharmaceutical company has submitted the final dossier to the G-BA in due time 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 18 December 2023.

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

The G-BA came to a resolution on whether an additional benefit of polatuzumab vedotin compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of polatuzumab vedotin.

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

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

2.1.1 Approved therapeutic indication of Polatuzumab vedotin (Polivy) according to the product information

Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

Therapeutic indication of the resolution (resolution of 20.06.2024):

See the approved therapeutic indication.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

Appropriate comparator therapy for polatuzumab in combination with bendamustine and rituximab:

- Tafasitamab in combination with lenalidomide

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

Appropriate comparator therapy for polatuzumab in combination with bendamustine and rituximab:

- tisagenlecleucel
  or
- axicabtagene ciloleucel
  or
- lisocabtagene maraleucel

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

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

Therapy according to doctor's instructions under consideration of:

- tafasitamab in combination with lenalidomide,
- pixantrone monotherapy *and*
- radiation.

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

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

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

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

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

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

on 1. In addition to polatuzumab vedotin, medicinal products with the following active ingredients are approved as follows in the present 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 epcoritamab, glofitamab, loncastuximab tesirine, tafasitamab in combination with lenalidomide, rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel each have a marketing authorisation for the treatment of relapsed/ refractory diffuse large B-cell lymphoma (DLBCL).

Some of these marketing authorisations mentioned are linked to (specified) concomitant active ingredients and to certain numbers of previous lines of therapy.

on 2. A radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication. According to the available evidence, patients with a PET-positive residual tumour after second line of systemic therapy, for example, should receive consolidating radiotherapy.

Haematopoietic stem cell transplantation, on the other hand, is not an option, as the patients are ineligible for this according to the present therapeutic indication.

on 3. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- epcoritamab (resolution of 4 April 2024)
- tisagenlecleucel (resolution of 15 February 2024)
- glofitamab (resolution of 1 February 2024)
- axicabtagene ciloleucel (resolutions of 21 December 2023)
- lisocabtagene maraleucel (resolution of 16 November 2023)
- loncastuximab tesirine (resolution of 2 November 2023)
- lisocabtagene maraleucel (resolution of 06 April 2023)
- tafasitamab (resolution of 3 March 2022)
- pixantrone (resolution of 16 May 2013).

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.

The present therapeutic indication generally refers to patients with relapsed/ refractory DLBCL and is not restricted with regard to the number of previous lines of therapy. According to the available evidence, there are distinct treatment recommendations in this regard, depending on the number of previous lines of therapy. The G-BA therefore considers it appropriate to divide the therapeutic indication into patients after failure of one line of systemic therapy and patients after failure of two or more lines of systemic therapy. In this context, it is also assumed that patients in this therapeutic indication will generally continue to receive anti-neoplastic treatment, which is why best supportive care is not considered an appropriate comparator therapy.

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

In its recommendations for second-line therapy, the S3 guideline on DLBCL differentiates between patients who are eligible for a high dose and those who are not,

and makes differentiated therapy recommendations in each case. In this context, it is assumed that the adults who are ineligible for haematopoietic stem cell transplantation according to the present therapeutic indication are patients who are ineligible for a high dose. For these patients, the S3 guideline recommends therapy with a less intensive immunochemotherapy protocol such as the combination of rituximab, gemcitabine and oxaliplatin (R-GemOx) or the combination of tafasitamab and lenalidomide. However, the combination R-GemOx is not approved for this therapeutic indication. Nor can it be inferred from the available evidence that the off-label use of R-GemOx is generally preferable to approved medicinal products according to the generally recognised state of medical knowledge. R-GemOx is therefore not considered as an appropriate comparator therapy.

For the CD19-specific antibody tafasitamab, which is approved in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adults with relapsed/ refractory DLBCL who are not candidates for autologous stem cell transplant (ASCT), a hint for a non-quantifiable additional benefit was identified in the benefit assessment by resolution of 3 March 2022, since the scientific data did not allow quantification (based on a single-arm study).

In their written statement on the question of comparator therapy, the scientific-medical societies point out that there are patients who are not eligible for high-dose chemotherapy but are eligible for CAR-T cell therapy. In this context, the two CAR-T cell therapies axicabtagene ciloleucel and lisocabtagene maraleucel have been approved for the treatment of patients with DLBCL that has relapsed or is refractory to first-line chemoimmunotherapy within 12 months of completing it. However, the S3 guideline explicitly recommends these two therapy options only for patients who are eligible for a high dose and not for patients who are ineligible for a high dose. In the benefit assessments for lisocabtagene maraleucel and axicabtagene ciloleucel, no additional benefit was also identified for patients who are ineligible for high-dose therapy and who relapse or are refractory to first-line therapy within 12 months of completing it, compared with therapy according to doctor's instructions (resolutions of 16 November 2023 and 21 December 2023). Taking into account the guideline recommendations and the results of the benefit assessment, axicabtagene ciloleucel and lisocabtagene maraleucel cannot be considered as appropriate comparator therapies for the present patient population.

In the overall assessment, the G-BA therefore determined tafasitamab in combination with lenalidomide as an appropriate comparator therapy for adults with relapsed/ refractory DLBCL after failure of a line of systemic therapy who are not candidates for haematopoietic stem cell transplant.

Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for haematopoietic stem cell transplant

For the treatment setting after at least two lines of therapy, the S3 guideline includes 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. Although stem cell transplantation cannot be considered as an appropriate comparator therapy in the present case for the reasons mentioned, the scientific-medical societies have pointed out that there are patients who are unsuitable for high-dose chemotherapy but are eligible for CAR-T cell therapy. Against this background, the G-BA considers it appropriate to further

subdivide - according to the patients' suitability for CAR-T cell therapy - the patient population with relapsed/ refractory DLBCL after failure of two or more lines of systemic therapy who are not candidates for haematopoietic stem cell transplant.

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

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. In this regard, axicabtagene ciloleucel and lisocabtagene maraleucel are also approved for the treatment of relapsed/ refractory DLBCL after two or more lines of systemic therapy. Tisagenlecleucel is also approved in this treatment setting.

For tisagenlecleucel, a hint of a non-quantifiable additional benefit was identified in the benefit assessment by resolution of 15 February 2024, since the scientific data did not allow quantification (based on a single-arm study). In the benefit assessment of axicabtagene ciloleucel, no additional benefit could be identified by resolution of 21 December 2023, as no suitable data were available compared to the appropriate comparator therapy that would have enabled an assessment of the additional benefit. For lisocabtagene maraleucel, no additional benefit could be identified by resolution of 6 April 2023 either, as no suitable data were available compared to the appropriate comparator therapy that would have enabled an assessment of the additional benefit.

However, in the overall assessment, the available evidence does not indicate that one CAR-T cell therapeutic agent is generally preferable to the other. The G-BA therefore specifies tisagenlecleucel or axicabtagene ciloleucel or lisocabtagene maraleucel as the appropriate comparator therapy for adults with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant. The appropriate comparator therapy determined here includes several therapy options. These therapeutic alternatives are equally appropriate for the comparator therapy.

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

According to the available evidence and the statements of the scientific-medical societies, various chemotherapies or chemoimmunotherapies and targeted substances are therapy options after failure of two or more lines of systemic therapy for patients who are not candidates for either CAR-T cell therapy or haematopoietic stem cell transplant.

As already explained, tafasitamab is approved for the treatment of patients with relapsed/ refractory DLBCL who are not candidates for autologous stem cell transplant. By resolution of 3 March 2022, a hint for a non-quantifiable additional benefit was identified for tafasitamab since the scientific data did not allow quantification.

The active ingredient pixantrone has explicit marketing authorisation as monotherapy 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 therapy option for the treatment of multiple relapsed, aggressive B-cell lymphomas.

Due to the primary palliative treatment setting, palliative radiotherapy may also be a treatment option for patients who have undergone more than two prior systemic therapies.

In addition, epcoritamab, glofitamab and loncastuximab tesirine are three further approved treatment options after two or more lines of systemic therapy.

In the benefit assessments, a hint for a non-quantifiable additional benefit was identified for epcoritamab by resolution of 4 April 2024 and for glofitamab by resolution of 1 February 2024 respectively, since the scientific data did not allow quantification (based on a single-arm study in each case). It was identified that an additional benefit of loncastuximab tesirine is not proven, by resolution of 2 November 2023 on the patient group of adults with relapsed/ refractory DLBCL after two or more lines of systemic therapy who are not candidates for CAR-T cell therapy or stem cell transplant. Compared to the appropriate comparator therapy, no suitable data were available to allow an assessment of the additional benefit.

Epcoritamab, glofitamab and loncastuximab tesirine are relatively new treatment options. 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 for the patient group b2).

In the overall assessment, the G-BA determines a therapy according to doctor's instructions, taking into account tafasitamab in combination with lenalidomide, monotherapy with pixantrone and radiotherapy as an appropriate comparator therapy for adults with relapsed/ refractory DLBCL after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant. It is expected that a choice of several treatment options will be available to implement the therapy according to doctor's instructions.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

An additional benefit is not proven.

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

An additional benefit is not proven.

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

An additional benefit is not proven.

Justification:

In the dossier for the benefit assessment, the pharmaceutical company presented meta-analytically summarised data from the GO29365 and YO41543 studies. In doing so, it divides two populations according to the number of previous lines of therapy (after failure of one and after failure of at least two lines of systemic therapy).

GO29365 study

The GO29365 study is a completed, multicentre, open-label phase IB/II study comparing polatuzumab vedotin in combination with bendamustine and rituximab or bendamustine and obinutuzumab.

Adults with relapsed/ refractory DLBCL or follicular lymphoma (FL) after at least one systemic therapy who are not candidates for autologous haematopoietic stem cell transplant were enrolled. The study comprises a safety run-in phase Ib to determine the dose for phase II and a phase II, which were conducted consecutively and separately according to histology (DLBCL and FL). Study arms C and D comprise the randomised, controlled comparison of polatuzumab vedotin in combination with bendamustine and rituximab versus bendamustine in combination with rituximab in adults with relapsed/ refractory DLBCL, with a total of 80 patients enrolled and randomised in a 1:1 ratio.

YO41543 study

The YO41543 study is a completed, double-blind, randomised controlled trial comparing polatuzumab vedotin in combination with bendamustine and rituximab versus bendamustine in combination with rituximab. The study enrolled 42 adult Chinese patients with relapsed/ refractory DLBCL after at least one systemic therapy who were not candidates for autologous haematopoietic stem cell transplant. Randomisation took place in a 2:1 ratio to treatment with polatuzumab vedotin in combination with bendamustine and rituximab (N = 28) or the comparator therapy consisting of bendamustine in combination with rituximab (N = 14).

Assessment

In the comparator arm of both studies, bendamustine was used in combination with rituximab. However, bendamustine in combination with rituximab does not correspond to the appropriate comparator therapy for any of the three patient groups. The presented meta-analysis of the GO29365 and YO41543 studies therefore does not allow a comparison with the respective appropriate comparator therapy for any of the patient groups. As a result, no data are available for any of the patient groups to allow an assessment of the additional benefit.

An additional benefit of polatuzumab vedotin in combination with bendamustine and rituximab compared with the appropriate comparator therapy is therefore not proven for patient groups a), b1) and b2).

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the medicinal product Polivy with the active ingredient polatuzumab vedotin due to the exceeding of the € 30 million turnover limit in the therapeutic indication:

"Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant."

It was distinguished between the following three patient groups:

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

On patient group a)

Tafasitamab in combination with lenalidomide was determined to be the appropriate comparator therapy.

In the dossier for the benefit assessment, the pharmaceutical company presented meta-analytically summarised data from the GO29365 and YO41543 studies. In the comparator arm of both studies, bendamustine was used in combination with rituximab. The presented meta-analysis of the GO29365 and YO41543 studies therefore does not allow a comparison with the appropriate comparator therapy. As a result, no data are available to allow an assessment of the additional benefit. An additional benefit of polatuzumab vedotin in combination with bendamustine and rituximab is therefore not proven.

On patient group b1)

Tisagenlecleucel or axicabtagene ciloleucel or lisocabtagene maraleucel was determined as the appropriate comparator therapy.

In the dossier for the benefit assessment, the pharmaceutical company presented meta-analytically summarised data from the GO29365 and YO41543 studies. In the comparator arm of both studies, bendamustine was used in combination with rituximab. The presented meta-analysis of the GO29365 and YO41543 studies therefore does not allow a comparison with the appropriate comparator therapy. As a result, no data are available to allow an assessment of the additional benefit. An additional benefit of polatuzumab vedotin in combination with bendamustine and rituximab is therefore not proven.

On patient group b2)

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions under consideration of tafasitamab in combination with lenalidomide, pixantrone monotherapy and radiotherapy.

In the dossier for the benefit assessment, the pharmaceutical company presented meta-analytically summarised data from the GO29365 and YO41543 studies. In the comparator arm of both studies, bendamustine was used in combination with rituximab. The presented meta-analysis of the GO29365 and YO41543 studies therefore does not allow a comparison with the appropriate comparator therapy. As a result, no data are available to allow an assessment of the additional benefit. An additional benefit of polatuzumab vedotin in combination with bendamustine and rituximab 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 patient numbers stated by the pharmaceutical company in the dossier, taking into account the mean value of the percentage ranges for patient groups b1) and b2) from the pharmaceutical company's written statement. The pharmaceutical company's approach is mathematically comprehensible but fraught with uncertainties. These arise in particular from the unclear transferability of many of the percentage values used in the individual calculation steps and the questionable suitability of some of the sources used. A significant uncertainty also arises from the fact that the pharmaceutical company assumes in its derivation that the ratio of the percentage of patients with a stem cell transplant to the percentage of patients with basic suitability for such a therapy in the third line corresponds to the analogous ratio from the second line. In the overall assessment, it is assumed that the information on patient group a) is largely plausible and that the information on patient groups b1) and b2) is uncertain.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Polivy (active ingredient: polatuzumab vedotin) at the following publicly accessible link (last access: 2 May 2024):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 June 2024).

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

For the cost representation, one year is assumed for all medicinal products.

CAR-T cell therapies (patient group b1)

Axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel 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.

Axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are listed on LAUER-TAXE®, but are only dispensed to appropriately qualified inpatient treatment facilities. 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, tisagenlecleucel and lisocabtagene maraleucel are administered as a single intravenous infusion according to the requirements in the underlying product information.

Treatment period:

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Polatuzumab vedotin in combination with bendamustine and rituximab				
Polatuzumab vedotin	on day 1 of a 21-day cycle	6	1	6
Bendamustine	on day 1 + 2 of a 21-day cycle	6	2	12
Rituximab	on day 1 of a 21-day cycle	6	1	6
Appropriate comparator therapy				
Tafasitamab in combination with lenalidomide				
Tafasitamab	Combination therapy 28-day cycle; Cycle 1: day 1, 4, 8, 15 and 22 Cycle 2+3: day 1, 8, 15 and 22 Cycle 4–12: day 1 and 15	12.0	Cycle 1: 5 Cycle 2+3: 4 Cycle 4–12: 2	31.0
	Monotherapy 28-day cycle; day 1 and 15	1.0	2	2.0
Lenalidomide	on day 1-21 of a 28-day cycle	12	21	252

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Polatuzumab vedotin in combination with bendamustine and rituximab				
Polatuzumab vedotin	on day 1 of a 21-day cycle	6	1	6
Bendamustine	on day 1 + 2 of a 21-day cycle	6	2	12
Rituximab	on day 1 of a 21-day cycle	6	1	6
Appropriate comparator therapy				
Tisagenlecleucel	Single dose	1	1	1
Axicabtagene ciloleucel	Single dose	1	1	1
Lisocabtagene maraleucel	Single dose	1	1	1

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Polatuzumab vedotin in combination with bendamustine and rituximab				
Polatuzumab vedotin	on day 1 of a 21-day cycle	6	1	6
Bendamustine	on day 1 + 2 of a 21-day cycle	6	2	12
Rituximab	on day 1 of a 21-day cycle	6	1	6
Appropriate comparator therapy				
Tafasitamab in combination with lenalidomide				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Tafasitamab	Combination therapy 28-day cycle; Cycle 1: day 1, 4, 8, 15 and 22 Cycle 2+3: day 1, 8, 15 and 22 Cycle 4–12: day 1 and 15	12.0	Cycle 1: 5 Cycle 2+3: 4 Cycle 4–12: 2	31.0
	Monotherapy 28-day cycle; day 1 and 15	1.0	2	2.0
Lenalidomide	on day 1-21 of a 28-day cycle	12	21	252
Pixantrone monotherapy				
Pixantrone	Day 1, 8, 15 of a 28-day cycle	1 – 6	3	3 - 18
Radiation				
Radiation	Different from patient to patient			

Consumption:

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

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[2]

For the appropriate comparator therapies on patient group b1) tisagenlecleucel, lisocabtagene maraleucel as well as 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, lisocabtagene maraleucel and axicabtagene ciloleucel are independent of the specific number of vials or infusion bags used.

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

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Polatuzumab vedotin in combination with bendamustine and rituximab					
Polatuzumab vedotin	1.8 mg/kg BW = 139.9 mg	139.9 mg	1 x 140 mg	6	6 x 140 mg
Bendamustine	90 mg/m^2 = 171.9 mg	171.9 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg + 36 x 25 mg
Rituximab	375 mg/m^2 = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	6	6 x 500 mg + 18 x 100 mg
Appropriate comparator therapy					
Tafasitamab in combination with lenalidomide					
Tafasitamab	12 mg/kg = 932.4 mg	932.4 mg	5 x 200 mg	33.0	165.0 x 200 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	252	252 x 25 mg

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Polatuzumab vedotin in combination with bendamustine and rituximab					
Polatuzumab vedotin	1.8 mg/kg BW = 139.9 mg	139.9 mg	1 x 140 mg	6	6 x 140 mg
Bendamustine	90 mg/m^2 = 171.9 mg	171.9 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg + 36 x 25 mg
Rituximab	375 mg/m^2 = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	6	6 x 500 mg + 18 x 100 mg
Appropriate comparator therapy					
Tisagenlecleucel	0.6 - 6 × 10^8	0.6 - 6 × 10^8	1	1	1

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	CAR-positive viable T cells	CAR-positive T cells	single infusion bag		single infusion bag
Axicabtagene ciloleucel	1 - 2 x 10^6 CAR-positive viable T cells per kg	1 - 2 x 10^6/kg CAR-positive T cells	1 single infusion bag	1	1 single infusion bag
Lisocabtagene maraleucel	100 × 10^6 CAR-positive viable T cells	100 × 10^6 CAR-positive viable T cells	1 single infusion bag	1	1 single infusion bag

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Polatuzumab vedotin in combination with bendamustine and rituximab					
Polatuzumab vedotin	1.8 mg/kg BW = 139.9 mg	139.9 mg	1 x 140 mg	6	6 x 140 mg
Bendamustine	90 mg/m^2 = 171.9 mg	171.9 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg + 36 x 25 mg
Rituximab	375 mg/m^2 = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	6	6 x 500 mg + 18 x 100 mg
Appropriate comparator therapy					
Tafasitamab in combination with lenalidomide					
Tafasitamab	12 mg/kg = 932.4 mg	932.4 mg	5 x 200 mg	33.0	165.0 x 200 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	252	252 x 25 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
Pixantrone monotherapy					
Pixantrone	50 mg/m² = 95.5 mg	95.5 mg	4 x 29 mg	3 - 18	12 x 29 mg – 72 x 29 mg
Radiation					
Radiation	Different 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.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Polatuzumab vedotin in combination with bendamustine and rituximab					
Polatuzumab vedotin 140 mg	1 PIC	€ 10,680.39	€ 2.00	€ 0.00	€ 10,678.39
Bendamustine 100 mg	5 PIC	€ 1,620.96	€ 2.00	€ 204.04	€ 1,414.89
Bendamustine 100 mg	1 PIC	€ 331.03	€ 2.00	€ 40.46	€ 288.57
Bendamustine 25 mg	5 PIC	€ 414.43	€ 2.00	€ 51.01	€ 361.42
Bendamustine 25 mg	1 PIC	€ 99.39	€ 2.00	€ 11.15	€ 86.24
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 2.00	€ 84.18	€ 1,691.16
Rituximab 100 mg	2 CIS	€ 717.21	€ 2.00	€ 33.50	€ 681.71
Appropriate comparator therapy					
Tafasitamab in combination with lenalidomide					
Tafasitamab 200 mg	1 PCI	€ 654.48	€ 2.00	€ 35.61	€ 616.87
Lenalidomide 25 mg[3]	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Pixantrone monotherapy					
Pixantrone 29 mg	1 PIC	€ 485.44	€ 2.00	€ 0.00	€ 483.44

3 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

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Tisagenlecleucel	1 single infusion bag	€ 239,000.00	€ 0[4]	€ 239,000.00
Axicabtagene ciloleucel	1 single infusion bag	€ 272,000.00	€ 0[4]	€ 272,000.00
Lisocabtagene maraleucel	1 single infusion bag	€ 345,000.00	€ 0[4]	€ 345,000.00
Abbreviations: HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, PIC = powder for the preparation of an infusion solution concentrate				

LAUER-TAXE® last revised: 1 June 2024

Costs for additionally required SHI services:

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

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

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 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Prophylactic premedication

Antipyretic and antihistamine premedication is only recommended in the product information of lisocabtagene maraleucel, tisagenlecleucel and axicabtagene ciloleucel.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

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

For axicabtagene ciloleucel, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (500 mg/m² = 955 mg) and fludarabine (30 mg/m² = 57.3 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/m² = 477.5 mg) and fludarabine (25 mg/m² = 47.75 mg) is given daily for 3 days, with infusion administered 2 to 14 days after the start of lymphocyte depletion.

For lisocabtagene maraleucel, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (300 mg/m² = 573 mg) and fludarabine (30 mg/m² = 57.3 mg), is given daily for 3 days, with infusion administered 2 to 7 days after the start of lymphocyte depletion.

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)

Patients should be tested for hepatitis B infection prior to starting treatment with rituximab. In the case of tisagenlecleucel, axicabtagene ciloleucel and lisocabtagene maraleucel therapy, patients must be tested for the presence of hepatitis B, hepatitis C and HIV infection before the respective treatment is initiated.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations.[5]

Diagnostics to rule out hepatitis C requires sensibly coordinated steps. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-RNA detection to confirm the diagnosis of an HCV infection.[6]

These examinations are 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.

5 S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

6 S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf

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							
Polatuzumab vedotin in combination with bendamustine and rituximab							
Rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI 4 mg each	€ 23.72	€ 2.00	€ 5.29	€ 16.43	6	€ 49.29
Paracetamol 500 – 1,000 mg	10 TAB 500 mg each 10 TAB each 1,000 mg	€ 2.96 € 3.32	€ 0.15 € 0.17	€ 0.13 € 0.14	€ 2.68 € 3.01	6	€ 2.68 - € 3.01
HBV diagnostics							
Hepatitis B Surface antigen status (GOP: 32781)	-	-	-	-	€ 5.50	1	€ 5.50
Hepatitis B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1	€ 5.90
Appropriate comparator therapy:							
Tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Fludarabine 25 mg/m² = 47.75 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3	€ 334.35
Cyclophosphamide 250 mg/m² = 477.50 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 2.85	€ 57.95	3	€ 57.95
Screening for HBV, HCV and HIV							
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	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1	€ 9.80
HIV HIV-1 and HIV-2	-	-	-	-	€ 4.45	1	€ 4.45

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
antibody status (GOP: 32575)							
Axicabtagene ciloleucel							
Conditioning chemotherapy for lymphocyte depletion							
Fludarabine 30 mg/m² = 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3	€ 668.70
Cyclophosphamide 500 mg/² = 950 mg	6 PSI at 500 mg	€ 84.44	€ 2.00	€ 9.25	€ 73.19	3	€ 73.19
Screening for HBV, HCV and HIV							
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	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1	€ 4.45
Lisocabtagene maraleucel							
Conditioning chemotherapy for lymphocyte depletion							
Fludarabine 30 mg/m² = 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3	€ 668.70
Cyclophosphamide 300 mg/m² = 570 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 2.85	€ 57.95	3	€ 57.95
Screening for HBV, HCV and HIV							
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	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1	€ 4.45

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
Abbreviations: SFI = solution for injection, CII = concentrate for injection or infusion solution, PSI = powder for solution for injection, TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

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

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

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

Basic principles of the assessed medicinal product

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

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered

due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

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

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

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

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

Concomitant active ingredient

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

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

assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

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

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

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

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section

35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

a) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of one line of systemic therapy who are not candidates for haematopoietic stem cell transplant

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

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

b1) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are candidates for CAR-T cell therapy and are not candidates for haematopoietic stem cell transplant

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 polatuzumab vedotin (Polivy); Polivy®; last revised: May 2022

b2) Adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after failure of two or more lines of systemic therapy who are not candidates for CAR-T cell therapy and haematopoietic stem cell transplant

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 polatuzumab vedotin (Polivy); Polivy®; last revised: May 2022

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 12 December 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 18 December 2023 the pharmaceutical company submitted a dossier for the benefit assessment of polatuzumab vedotin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 21 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient polatuzumab vedotin.

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

The oral hearing was held on 6 May 2024.

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

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 11 June 2024, and the proposed resolution was approved.

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

Chronological course of consultation

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

Berlin, 20 June 2024

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

Prof. Hecken