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
Glofitamab (diffuse large B-cell lymphoma, after ≥ 2 prior therapies)

of 1 February 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.

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

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

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

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

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and 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 glofitamab on 1 August 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 28 July 2023.

Glofitamab for the treatment of diffuse large B-cell lymphoma (DLBCL), after ≥ 2 prior therapies, is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 November 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-17) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of glofitamab.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Glofitamab (Columvi) in accordance with the product information

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

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

Therapeutic indication of the resolution (resolution of 1 February 2024):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

Justification:

For the assessment of the additional benefit of glofitamab in patients with relapsed or refractory DLBCL, the pharmaceutical company presented data from the pivotal, single-arm phase I/II NP30179 study.

NP30179 study

The NP30179 study is a single-arm, ongoing phase I/II dose escalation and dose expansion study in subjects with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma. The study is designed in three parts and consists of a dose escalation phase (part 1 and part 2) and a dose expansion phase (part 3) to investigate the safety, efficacy, tolerability and pharmacokinetics of glofitamab.

The NP30179 study has been conducted since February 2017 at a total of 41 study sites in Spain, France, the USA, Australia, Belgium, Italy, Poland, Denmark, Taiwan, Canada, the Czech Republic, Finland and New Zealand.

Study participants had to have a histologically confirmed haematological malignancy with assumed CD20 expression according to the criteria defined in the study. In addition, depending on the part of the study, they had to have a recurrence after at least one prior therapy or a lack of response to at least one prior therapy. In addition, patients should not have any available treatment options that would prolong survival (e.g. standard chemotherapy or autologous stem cell transplantation).

The study included 17 different cohorts with various disease entities in subjects with relapsed/ refractory (R/R) B-cell non-Hodgkin lymphoma, of which the subjects included in cohorts D2 (excluding subcohort 2), D3 and D5 for the present benefit assessment comprise the present therapeutic indication with relapsed or refractory DLBCL after ≥ 2 prior therapies.

Cohort D2 [Sub.2] was part of the dose escalation phase (Part 1 and Part 2 of the study), while cohorts D3 and D5 were part of the dose expansion phase (Part 3 of the study). The prerequisite for the dose expansion phase was a relapse or lack of response to at least 2 prior lines of systemic therapy (including at least one therapy with anthracyclines and anti-CD20 antibodies).

The patients from D2 (sub 2), D3 and D5 form the sub-population relevant for the benefit assessment and were treated according to the product information and thus received the corresponding dosage regimen of glofitamab, pretreatment with obinutuzumab as well as premedication and prophylaxis for cytokine release syndrome (CRS). A total of 508 patients were enrolled in the study. A total of 155 patients from the cohorts D2 (Sub 2) (7 subjects), D3 (108 subjects) and D5 (40 subjects) relevant for the benefit assessment received glofitamab

treatment in line with the product information. Unless otherwise identified, the data refer to the cohorts relevant for the benefit assessment (D2 (Sub.2), D3 and D5).

The primary endpoint of the NP30179 study was tumour response (CR rate), secondary endpoints included overall survival (OS) and endpoints in the categories of morbidity, health-related quality of life (only for cohorts D3 and D5) and side effects.

For the study, a total of three data cut-offs were performed:

- 14 September 2021
- 15 June 2022 (data cut-off relevant for the marketing authorisation)
- 10 October 2022 (FDA 3-month safety update)

For the benefit assessment of glofitamab, the data cut-off from 15.06.2022 is used. In addition, the safety endpoints of the data cut-off from 10.10.2022 are considered.

On the results of the pivotal NP30179 study:

Mortality

For the benefit assessment, the NP30179 study evaluation of overall survival for the ITT population of the pooled cohorts D2 [Sub.2] and D3 of the NP30179 study was used, as many subjects in cohort D5 were already censored before month 12.

Of 115 subjects in the ITT population, 65 subjects (56.5%) had died by the evaluation date of 15.06.2022.

An interpretation and assessment of the data on mortality is not possible due to the missing control group. Therefore, no statements on the extent of additional benefit can be derived for the mortality category.

Morbidity

Progression-free survival (PFS)

In the NP30179 study, PFS was collected as a secondary endpoint. PFS was defined as the time from the first dose of study medication to disease progression (PD, progressive disease) or death from any cause, whichever occurred first. PFS was assessed by an independent review committee (IRC) in accordance with the Lugano criteria 2014.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The "mortality" endpoint component was assessed as an independent endpoint in the present study via the "overall survival" endpoint. The morbidity component was not assessed on the basis of symptoms according to the operationalisation, but exclusively using imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected by this, as there is no control group, and no statement on the extent of the additional benefit can be derived. The PFS endpoint is presented additionally.

Tumour response (CR)

The primary efficacy endpoint "complete response (CR)" is defined as the percentage of subjects whose best overall response (BOR) is a CR, based on the IRC assessment of PET-CT scans according to the Lugano criteria. Subjects for whom no response assessment (regardless of reason) was available were assumed to be non-responders.

The assessment of the response is not based on symptoms, but mainly on imaging procedures as part of the Lugano classification. For this reason, the above-mentioned endpoints are classified as not patient-relevant.

With regard to the therapeutic indication, the endpoint of complete response is an important prognostic factor and relevant for the treatment decision. A complete response associated with a noticeable reduction in disease symptoms for the subject is generally patient-relevant for the benefit assessment. However, the operationalisation presented here is primarily based on imaging procedures. No further information on physical examinations can be found in the study documents and is not included in the Lugano classification. Complete response is not a validated surrogate of a patient-relevant endpoint in the present population covered by the therapeutic indication. Overall, the "complete response" endpoint is therefore assessed as not patient-relevant.

Regardless of this, the results of the NP30179 study for the tumour response endpoint do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group. The endpoint of tumour response is presented additionally.

Symptomatology

Health status was assessed in the NP30179 study using the symptom scales of the EORTC QLQ-C30 and the FACT-LymS in cohorts D3 and D5.

A priori, according to SAP, the evaluation should take place in the PRO evaluable population. This includes all subjects for whom both a baseline and a post-baseline value are available. According to the information in the study report, this is a total of 128 subjects for the analysable PRO evaluable population. However, no results could be identified for this population in the study documents.

The dossier for the benefit assessment presented results for the EORTC QLQ-C30 and the FACT-LymS for a population of 147 subjects. It is not clear why the sample sizes differ between the study report and the dossier. The return rates calculated by the pharmaceutical company (Module 4 Annex) are also not comprehensible and do not refer to the ITT or PRO evaluable population, but to the number of subjects still in the study at the respective cycle. This is assessed as improper. Apparently, the required return rates of (≥ 70%) have only been achieved up to cycle 2.

In addition, a responder analysis for the deterioration by 10 points is presented for the EORTC QLQ-C30 in the dossier documents. The reference population is 127 subjects. On the one hand, the specification of the reference population and, on the other, the time period for the responder analysis is unclear. The same applies to the FACT-LymS. A responder analysis for the deterioration by 9 points was presented here. The reference population is 124 subjects. The sample size in the reference population and the time period for the responder analysis are also unclear here.

In addition, 47 subjects (30.5%) reported a lack of PRO assessment at the planned survey time points as the most frequent protocol violation. It is not possible to conclusively assess whether and, if so, at what intervals from the planned data collection time point it was caught up with the PRO assessments.

Due to the mentioned inconsistencies between study documents and dossier documents as well as the addressed discrepancies regarding the different reference population, the return rates incorrectly calculated by the pharmaceutical company and the responder analysis presented, the results of the symptomatology using EORTC QLQ-C30 and FACT-LymS are not presented.

Regardless of this, the results of the NP30179 study for symptomatology do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

Quality of life

Quality of life data were assessed in the NP30179 study using the EORTC QLQ-C30. There are the same points of criticism as described for the EORTC QLQ-C30 under the category of morbidity under symptomatology.

Due to the mentioned inconsistencies between study documents and dossier documents as well as the addressed discrepancies regarding the different reference population, the return rates incorrectly calculated by the pharmaceutical company and the responder analysis presented, the results of the quality of life using EORTC QLQ-C30 and are not presented.

Regardless of this, the results of the NP30179 study for quality of life do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

Side effects

The evaluations of side effects refer to adverse events (AEs) that occurred from the administration of the study medication until 90 days after the last dose in the safety population (N = 154).

Total adverse events (AEs)

An adverse event occurred in almost all adults of the ITT population (152 out of 154 patients (98.7%)). These are only presented additionally.

Serious adverse events (SAEs)

75 out of 154 patients (48.7%) had at least one serious adverse event.

Severe adverse events (CTCAE grade ≥ 3)

At least one severe AE with CTCAE grade ≥ 3 occurred in 99 out of 154 patients of the ITT population (64.3%).

Therapy discontinuation due to adverse events

In 14 patients (9.1%), an adverse event occurred that led to the discontinuation of the study medication.

Specific AEs

Serious adverse events with an incidence ≥ 5% of patients by system organ class (SOC) were immune system disorders (22.1%), infections and infestations (18.2%), blood and lymphatic system disorders (6.5%) and benign, malignant and non-specific neoplasms (including cysts and polyps) (5.2%).

Severe adverse events with CTCAE grade ≥ 3 with an incidence ≥ 5% of patients by system organ class (SOC) were blood and lymphatic system disorders (35.1%), infections and infestations (16.9%), investigations (11.7 %) and metabolism and nutrition disorders (11.0%).

In summary, no conclusions can be drawn on the extent of the additional benefit for the side effects category due to the absence of a control group.

Overall assessment/ conclusion

The data from the label-enabling, single-arm NP30179 study are available for the benefit assessment. No other data on this or indirect comparison thereof is available.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

In summary, the extent of the available results is classified as non-quantifiable because the scientific data basis does not permit quantification.

Significance of the evidence

As the study NP30179 study is a phase I/II study without a control arm, a high risk of bias at study and endpoint level is assumed.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Columvi with the active ingredient glofitamab.

Glofitamab received a conditional marketing authorisation for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

For the benefit assessment, the pharmaceutical company submits data from the label-enabling, single-arm NP30179 study. No other data on this or indirect comparison thereof is available.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

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).

In order to allow consistent consideration of the patient numbers taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication, the patient numbers of loncastuximab tesirine (resolution of 2 November 2023) are used. In this regard, the resolution on the benefit assessment of loncastuximab tesirine (resolution of 2 November 2023) stated a patient number of approx. 680 - 1,200 (patients eligible for CAR-T cell therapy or stem cell transplantation) and approx. 680 - 700 (patients not eligible for CAR-T cell therapy or stem cell transplantation) for correspondingly subdivided patient groups, with a total number of approx. 1,360 - 1,900 patients. In contrast, the patient numbers determined in the pharmaceutical company's dossier is of a comparable order of magnitude (1,350 to 1,790 patients). This is mathematically plausible, but is subject to methodological uncertainty overall and is not considered to be a clearly better estimate of patient numbers than the most recent resolutions.

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 Columvi (active ingredient: glofitamab) at the following publicly accessible link (last access: 21 December 2023):

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

Treatment with glofitamab 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).

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 European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about the cytokine release syndrome.

In the pivotal study NP30179, only patients for whom no available treatment options that would prolong survival were available at the time the study was conducted were enrolled.

Obinutuzumab is not approved for pretreatment prior to starting therapy with glofitamab. The application for marketing authorisation was withdrawn. Obinutuzumab is not reimbursable for this indication.

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 January 2024).

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.

According to the product information, all patients are pretreated with a single dose of obinutuzumab (1,000 mg) on day 1, cycle 1[2]. Glofitamab is administered with a dose escalation regimen: In cycle 1 2.5 mg glofitamab is administered on day 8 , 10 mg glofitamab is infused on day 15. In cycles 2 to 12, 30 mg glofitamab is infused in each case. The product information states that all patients should receive premedication with an antipyretic and an antihistamine (all cycles). In cycles 1 to 3, a glucocorticoid is also administered before all glofitamab infusions.

[2] Obinutuzumab is not approved for pretreatment prior to therapy with glofitamab. The application for marketing authorisation was withdrawn. Obinutuzumab is not reimbursable for this indication, which is why the necessary costs cannot be quantified.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Glofitamab	Cycle 1: 2 x per 21-day cycle Cycle 2 - 12: 1 x per 21-day cycle	13	1	13

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Glofitamab	Cycle 1: Day 8: 2.5 mg	Cycle 1: Day 8: 2.5 mg	1 x 2.5 mg	13	1 x 2.5 mg 34 x 10 mg
	Cycle 1: Day 15: 10 mg	Cycle 1: Day 15: 10 mg	1 x 10 mg		
	Cycle 2 – 12: 30 mg	Cycle 2 – 12: 30 mg	3 x 10 mg		

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Glofitamab 2.5 mg	1 CIS	€ 1,272.47	€ 2.00	€ 69.83	€ 1,200.64
Glofitamab 10 mg	1 CIS	€ 4,948.20	€ 2.00	€ 279.30	€ 4,666.90
CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 January 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 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient or year
Medicinal product to be assessed							
Glofitamab							
Premedication							
Dexamethasone [3] 20 mg, IV	10 x 4 mg SFI	€ 16.92	€ 2.00	€ 0.45	€ 14.47	4	€ 28.94

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	Treatment days/ year	Costs/ patient or year
Diphenhydramine[3] 50 mg	20 TAB 50 mg each	€ 4.38	€ 0.22	€ 0.19	€ 3.97	13	€ 3.97
Paracetamol[3] 500 mg – 1,000 mg	20 TAB 500 mg each	€ 3.47	€ 0.17	€ 0.15	€ 3.15	13	€ 3.15 - € 6.02
	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01		
Abbreviations: SFI = solution for injection; TAB = tablets							

Other SHI services:

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

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

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

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

Basic principles of the assessed medicinal product

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

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

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

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

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

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

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

Concomitant active ingredient:

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy

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.

References:

Product information for glofitamab (Columvi); Columvi; last revised: July 2023

3. Bureaucratic costs calculation

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

4. Process sequence

On 28 July 2023, the pharmaceutical company submitted a dossier for the benefit assessment of glofitamab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 November 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 22 November 2023.

The oral hearing was held on 11 December 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 October 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	5 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 December 2023	Conduct of the oral hearing
Working group Section 35a	4 January 2024 17 January 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 February 2024

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

Prof. Hecken