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 Obinutuzumab (exceeding € 50 million turnover limit: Follicular lymphoma, combination with bendamustine, rituximab-refractory)

of 4 November 2021

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 studies 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 benefits,
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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient obinutuzumab (Gazyvaro) was listed for the first time on 15 August 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Gazyvaro for the treatment of adults with previously untreated follicular lymphoma (FL) is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In its session on 15 December 2016, the G-BA decided on the benefit assessment of obinutuzumab in the therapeutic indication "rituximab-refractory follicular lymphoma" 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 €50 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being

requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 3 February 2021, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 15 May 2021 due to exceeding the €50 million turnover limit. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 10 May 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 16 August 2021, 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 obinutuzumab compared to 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 addenda 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 obinutuzumab.

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 obinutuzumab (Gazyvaro®) in accordance with the product information

Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Therapeutic indication of the resolution (resolution of 04.11.2021):

see the approved therapeutic indication

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Appropriate comparator therapy for obinutuzumab in combination with bendamustine:

- Patient-individual therapy with a selection of bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and CVP (cyclophosphamide, vincristine and prednisolone); taking into account prior therapy and type and duration of response

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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 Federal Joint Committee has already determined the patient-relevant benefit 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Approved for this therapeutic indication are, in addition to obinutuzumab in combination with bendamustine, the active ingredients yttrium-90 radiolabelled ibritumomab tiuxetan, idelalisib, interferon alfa-2a, interferon alfa-2b, lenalidomide and rituximab. Follicular lymphoma is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients bendamustine, bleomycin, chlorambucil, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, methotrexate, mitoxantrone, prednisolone, prednisone, trofosfamide, vinblastine and vincristine are also approved.

Some of the marketing authorisations are tied to specific combination preparations. Medicinal products with explicit marketing authorisation for the treatment of highly malignant non-Hodgkin lymphoma and follicular lymphoma grade 3b were not included.

on 2. In the planned therapeutic indication, radiotherapy, as well as allogeneic and autologous stem cell transplantations, can be considered as non-medicinal treatment. However, it is assumed that allogeneic or autologous stem cell transplantations, as well as radiotherapy with curative intent, are not an option at the time of treatment.

Non-medicinal treatment options were therefore not considered in determining the appropriate comparator therapy.

on 3. For the present therapeutic indication, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Obinutuzumab: Resolution of 15.12.2016
- Idelalisib: Resolution of 16 March 2017

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (last revised: 5 May 2015):

- Off-label indication for fludarabine: In combination with cyclophosphamide, mitoxantrone, and rituximab (FCM-R) in eligible patients with low- or intermediate-grade non-Hodgkin lymphoma of the B-cell series (CD20 positive NHL, including lymphocytic, lympho-plasmocytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell, marginal zone, non-multiple myeloma, non-hair cell leukaemia) and resistance to CHOP (with or without rituximab).

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 therapeutic indication.

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

In the present therapeutic indication, it is assumed that the patients have an indication for systemic antineoplastic therapy due to a correspondingly advanced stage of the disease, in particular with regard to a symptomatic course (e.g. according to the GELF criteria), and therefore, among other things, a watch-and-wait strategy is not considered. It is also assumed that allogeneic or autologous stem cell transplantations, as well as radiotherapy with curative intent, are not an option at the time of treatment. Previous radiotherapy with curative intent is not interpreted as a line of therapy in relation to the planned therapeutic indication.

In the first-line treatment of follicular lymphoma, the combination of chemotherapy with rituximab represents the standard of care according to the generally recognised state of medical knowledge in patients for whom (medicinal) treatment is indicated and have no treatment restriction. If a relapse occurs during therapy or within six months after initial chemotherapy with rituximab, a refractory therapy situation is present.

According to the current S3 guideline, in case of relapse during or within 6 months after rituximab therapy, obinutuzumab should be considered as an antibody if chemoimmunotherapy is indicated again. Marketing authorisation of obinutuzumab in relapse exists only in combination with bendamustine. Also, according to statements of the scientific-medical societies in the written statement procedure, the treatment with obinutuzumab and bendamustine is preferred for rituximab-refractory patients. For patients who relapse within two years after combination therapy with rituximab and bendamustine, there is no approved alternative chemoimmunotherapy; according to the S3 guideline, therapy with obinutuzumab and another chemotherapy regimen may be appropriate.

According to the S3 guideline, patients who relapse less than two years after chemoimmunotherapy should be given at least an alternative chemotherapy regimen (e.g. CVP/CHOP instead of bendamustine) - secondary to transplantation strategies.

Radioimmunotherapy (yttrium-90 ibritumomab tiuxetan) may be used in relapsed patients with bone marrow infiltration < 20% if the patient is not eligible for immunochemotherapy or chemotherapy.

According to the S3 guideline, radioimmunotherapy is therefore not a suitable treatment option for patients eligible for treatment with obinutuzumab in combination with bendamustine, according to the present therapeutic indication.

Treatment with the primary goal of symptom relief and improvement of quality of life (best supportive care) is, according to the statement of the scientific-medical society, only a treatment option for patients for whom either no treatment is indicated or who are fundamentally untreatable. For patients eligible for the treatment with obinutuzumab in combination with bendamustine, best supportive care is therefore not a treatment option.

Special case constellation of the present assessment

The medicinal product under assessment (obinutuzumab, invented name: Gazyvaro) in combination with bendamustine has already been approved in the present therapeutic indication since 13 June 2016. This involved the marketing authorisation regarding a new therapeutic indication. Since this marketing authorisation, obinutuzumab has been available in the reality of care for the treatment of patients in this therapeutic indication for more than 5 years. According to the S3 guideline, obinutuzumab can be used in combination with bendamustine as well as in combination with chemotherapies that are not approved.

For the benefit assessment, according to Section 35a SGB V, a comparison with the active ingredient itself, specifically a comparison of identical therapies, is ruled out regarding the question of the benefit assessment. Similarly, obinutuzumab, in combination with an unapproved combination of active ingredients mentioned in guidelines, does not represent an appropriate comparator therapy specifically for the present benefit assessment.

After the initial benefit assessment for obinutuzumab in the present therapeutic indication (resolution of the G-BA of 15 December 2016) was conducted on the basis of the regulations for orphan drugs, this is the first benefit assessment of the medicinal product to be assessed in comparison with an appropriate comparator therapy.

In this particular constellation, the G-BA considers it appropriate to determine a patient-individual therapy with a selection of bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and CVP (cyclophosphamide, vincristine and prednisolone), taking into account prior therapy and type and duration of response to be taken as a basis for the present benefit assessment.

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

Change of the appropriate comparator therapy:

Originally, the appropriate comparator therapy was determined as follows:

- Patient-individual therapy with selection of chemotherapies, yttrium-90 radiolabelled ibritumomab tiuxetan, and best supportive care; taking into account prior therapy, disease course, and general condition

Taking into account the statements of scientific-medical societies in the present proceedings, yttrium-90 radiolabelled ibritumomab tiuxetan and best supportive care are no longer considered as possible treatment options within a patient-individual therapy. In addition, bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CVP (cyclophosphamide, vincristine and prednisolone) are explicitly identified as possible chemotherapy options in the context of patient-individual therapy.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

2.1.3 Extent and probability of the additional benefit

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

Adults with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

An additional benefit is not proven.

Justification:

For the proof of additional benefit, the pharmaceutical company presented the results of the randomised, controlled, open-label, multicentre phase III GADOLIN study in the dossier.

The study included adult patients with rituximab-refractory indolent non-Hodgkin lymphoma. Refractarity was defined as a lack of treatment response or progression within 6 months of receiving the last dose of rituximab therapy as monotherapy or in combination with chemotherapy.

A total of 204 patients were randomised to the intervention arm (obinutuzumab in combination with bendamustine) and 209 patients to the comparator arm (bendamustine). Randomisation was stratified by indolent non-Hodgkin lymphoma subtype (follicular vs other), type of refractarity (rituximab monotherapy vs rituximab in combination with chemotherapy), number of prior therapies (≤ 2 vs > 2), and geographic region. The sub-population of patients with follicular lymphoma comprises a total of 335 patients. Of these, 164 patients were included in the intervention arm, and 171 patients were included in the comparison arm of the study.

The treatment in the intervention arm of the GADOLIN study was carried out in accordance with the product information on obinutuzumab; the administration of bendamustine in the comparator arm deviated from the requirements in the product information. According to the product information, the treatment is not limited to a maximum of 6 cycles but should be given for at least 6 cycles. In addition, the product information specifies a shorter cycle duration (21 days each).

The primary endpoint of the study was progression-free survival (PFS). Secondary endpoints were overall survival and endpoints of the endpoint categories morbidity, health-related quality of life and side effects.

There are six data cut-offs for the GADOLIN study, four of which were planned a priori (30.11.2018, 01.09.2014, 29.07.2013 and 18.04.2011), one of which was requested by the Food and Drug Administration (FDA) (01.05.2015), and one of which was an unplanned interim analysis after an observation period of approximately 30 months (01.04.2016).

<u>On the usability of the study results presented in the dossier:</u>

The IQWiG stated in the dossier assessment that the results of the GADOLIN study presented by the pharmaceutical company in the dossier were incomplete and inadequately prepared. As a result, the IQWiG was unable to adequately assess the study data, so that the results of the study as a whole were not considered usable for the benefit assessment.

In IQWiG's dossier assessment, the overall deficiencies in the dossier are considered to be serious. The finding of incompleteness of content is based specifically on the following deficiencies, described in summary here.

The pharmaceutical company did not submit complete evaluations for any of the submitted data cut-offs on all endpoints, especially not for the final data cut-off. For the final data cut-off of 30.11.2018, the pharmaceutical company only submits evaluations for endpoints in the mortality and side effects categories in Module 4. The evaluations presented for patient-reported endpoints in the categories morbidity and health-related quality of life are based on an earlier data cut-off from 01.09.2014. The pharmaceutical company provides no adequate justification regarding this. It can be assumed that data on quality of life were added to the

current data cut-off to a relevant extent. Furthermore, for the assessment procedure of the G-BA in the course of the marketing authorisation in 2016, the pharmaceutical company already submitted evaluations for the patient-reported endpoints for a more recent data cut-off from 01.05.2015, which was carried out at the request of the Food and Drug Administration (FDA).

Furthermore, with regard to the evaluations of health-related quality of life, it must be noted that these are inadequately prepared. Health-related quality of life was assessed in the GADOLIN study using FACT-Lym, which is composed of 5 subscales. In the dossier, the company presents separate evaluations of the FACT-G and the FACT-LymS subscales, but no evaluations of the total FACT-Lym score, although these were planned according to the study design. In addition, with regard to the submitted responder analyses, it is to be noted, among other things, that the pharmaceutical company submitted them without justification only at selected evaluation dates. Data on return rates were incomplete and were only available for selected evaluation dates.

Also, the analyses presented from a mixed model for repeated measures (MMRM) for the FACT-G and the FACT-LymS subscale cannot be conclusively interpreted due to missing data. This concerns the percentage of patients per treatment arm who were still alive at the survey time point with a usable questionnaire, their inclusion in the evaluation, and information on the time point or period to which the effect estimate relates.

In addition, the data on adverse events submitted by the pharmaceutical company is incomplete. According to Annex II to Chapter 5 of the Rules of Procedure, all events that occurred in ≥ 10 patients and in ≥ 1% of patients in a study arm must be reported, regardless of the severity grade. The pharmaceutical company did not comply with this and only presented a subset of the adverse events. Only adverse events independent of severity grade that occurred in ≥ 10% of patients in a study arm were presented. For severe AEs and SAEs, the company provides evaluations of the threshold value ≥ 5 % of the patients in a study arm.

Against the background of the incompleteness of the data, there is no need to further address the question of whether or to what extent the appropriate comparator therapy can be considered to have been implemented in the GADOLIN study.

In conclusion, IQWiG states that, overall, due to the incomplete data, an adequate weighing of the benefits and harms and thus an assessment of the additional benefit of obinutuzumab compared to the appropriate comparator therapy is not possible. A presentation of the usable study results contained in the dossier was also omitted.

After detailed consideration of IQWiG's discussion of the deficiencies in the dossier, the G-BA concurs with the IQWiG's assessment and, for its part, states that according to Chapter 5, Section 18, paragraph 1 of the Rules of Procedure of the G-BA, the preparation of the documents in the dossier deviates to an extent from the requirements specified in Chapter 5, Section 9 VerfO des G-BA, which is contrary to a proper assessment of the additional benefit.

In accordance with the regulation in Chapter 5, Section 18 of the Rules of Procedure of the G-BA, the benefit assessment examines whether there is evidence of an additional benefit for the medicinal product compared to the appropriate comparator therapy. The validity and completeness of the information in the dossier are also checked. The dossier template in Annex II must be used for compiling the documents. The data according to Chapter 5, Section 9, paragraphs 1, 4 to 8 of the Rules of Procedure of the G-BA must be prepared and submitted in accordance with the requirements specified in Modules 1 to 5.

The preparation of the pharmaceutical company's data presented here does not comply with the requirements laid down in Chapter 5, Section 9 of the Rules of Procedure (VerfO) and

proves to be inadequate and incomplete so that it doesn't allow a proper assessment of the additional benefit. Subsequently, the G-BA determines in accordance with Chapter 5, Section 18, sentence 4, of the Rules of Procedure of the G-BA that an additional benefit has not been proven.

In the written statement procedure, the pharmaceutical company submitted extensive evaluations of the study results of the final data cut-off. In this regard, IQWiG discussed at the oral hearing that the subsequently submitted data are very extensive, unstructured data that have not been prepared in accordance with Annex II to Chapter 5 of the Rules of Procedure and therefore do not represent a remedy for the incompleteness of the content. The extensive amount of unstructured data also makes it difficult to check for completeness. In this respect, regardless of the fact that the pharmaceutical company has the right according to Chapter 5, Section 19, paragraphs 1 and 2 of the Rules of Procedure of the G-BA, to comment on the benefit assessment of the medicinal product both in writing and orally upon publication of the benefit assessment on the website of the Federal Joint Committee and that the written and oral comments are included in the resolution on the adoption of the benefit assessment according to Section 92, paragraph 1, sentence 2, number 6 SGB V, it is the sole responsibility of the pharmaceutical company according to Section 5 paragraph 1 sentence 1 of the AM-NutzV to prove in the dossier the additional benefit of the medicinal product with a new active ingredient. According to Section 5, paragraph 1, sentence 2 AM-NutzV, the G-BA has no official duty to investigate.

The evaluations submitted with the written statement were therefore not suitable to enable a proper assessment of the additional benefit due to the inadequate processing. As a result, it must be concluded that the additional benefit according to Chapter 5, Section 18, paragraph 1, sentence 4 of the Rules of Procedure of the G-BA is not proven.

2.1.4 Summary of the assessment

The present evaluation is a new benefit assessment of the active ingredient obinutuzumab due to the exceeding of the €50 million turnover limit.

Obinutuzumab in combination with bendamustine is indicated for patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Obinutuzumab has received marketing authorisation as an orphan drug.

The appropriate comparator therapy was determined to be:

- Patient-individual therapy with selection of bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and CVP (cyclophosphamide, vincristine and prednisolone); taking into account prior therapy and type and duration of response

For the proof of an additional benefit, results of the GADOLIN study were presented (obinutuzumab + bendamustine vs bendamustine).

The preparation of the study data in the dossier proved to be seriously inadequate and incomplete in terms of content, which is an obstacle to a proper assessment of the additional benefit.

In the dossier, evaluations of all endpoints collected were not available for any of the data cut-offs, especially not for the current one. Furthermore, the evaluations of health-related quality

of life were inadequate. In addition, the results presented on common adverse events were incomplete.

The evaluations submitted with the written statement were also inadequate for an appropriate assessment of the additional benefit due to the insufficient processing.

Therefore, the result is that an additional benefit is not proven.

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

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

The resolution is based on the patient numbers from the resolution on obinutuzumab dated 15.12.2016. Although some of the criticisms from the previous assessment were addressed in the present dossier and more recent incidence data were used for the current derivation, the patient numbers presented do not question the previous resolution's patient numbers due to the existing uncertainties and lack of conclusive evaluability.

According to IQWiG's assessment, the data on patient numbers can still be regarded as uncertain and cannot be conclusively assessed.

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 Gazyvaro (active ingredient: obinutuzumab) at the following publicly accessible link (last access: 3 September 2021):
https://www.ema.europa.eu/en/documents/product-information/gazyvaro-epar-product-information_en.pdf

Treatment with obinutuzumab should only be initiated and monitored by specialists in internal medicine, haematology and, oncology experienced in the treatment of patients with follicular lymphoma.

Obinutuzumab (Gazyvaro®) should be used under conditions where full resuscitation equipment is immediately available.

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: 15 October 2021).

In the present therapeutic indication, the product information for obinutuzumab specifies an induction regimen in combination with bendamustine over 6 cycles. Section 5.1 of the product information for obinutuzumab specifies the single dose for bendamustine in combination with obinutuzumab as 90 mg/m^{2}. The induction phase is followed by the administration of

obinutuzumab as a single agent in the form of maintenance treatment once every 2 months for a period of 2 years or until disease progression.

For the presentation of the costs, one year is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier due to non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

The maximum cumulative dosage for doxorubicin is 550 mg/m^2.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Obinutuzumab	*Induction therapy:* 28-days cycles; Cycle 1: Day 1, 8 and 15 Cycles 2 to 6: Day 1	6 cycles	Cycle 1: 3 days Cycle 2 to 6: 1 day	8
	Maintenance treatment: once every 56 days	3	1	3
Bendamustine	*Induction therapy:* 28-days cycles; Day 1 and 2	6 cycles	2	12
Appropriate comparator therapy				
Patient-individual therapy with selection of:				
Chemotherapy				
Bendamustine				
Bendamustine	21-days cycles; Day 1 and 2	17.4 cycles	2	34.8
CHOP[2]				
Cyclophosphamide	Day 1, 21-day cycle	6	1	6
Doxorubicin	Day 1, 21-day cycle	6	1	6

[2] Van Oers et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol. 2010 Jun 10;28(17):2853-8

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Vincristine	Day 1, 21-day cycle	6	1	6
Prednisolone	Day 1 -5, 21-day cycle	6	5	30
CVP[3]				
Cyclophosphamide	Day 1, 21-day cycle	8	1	8
Vincristine	Day 1, 21-day cycle	8	1	8
Prednisolone	Day 1 -5, 21-day cycle	8	5	40

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2018 – body measurements of the population"[4] were applied (average body height: 1.72 m, average body weight: 77.0 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Obinutuzumab	1000 mg	1,000 mg	1 x 1000 mg	11	11 x 1,000 mg
Bendamustine	90 mg/m² = 171 mg[5]	171 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg + 36 x 25 mg
Appropriate comparator therapy					
Patient-individual therapy with selection of:					

[3] Sarkozy et al. Risk Factors and Outcomes for Patients With Follicular Lymphoma Who Had Histologic Transformation After Response to First-Line Immunochemotherapy in the PRIMA Trial. J Clin Oncol. 2016 Aug 1;34(22):2575-82.

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

[5] Dosage according to section 5.1 of the product information of obinutuzumab

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Chemotherapy					
Bendamustine	120 mg/m^2 = 228 mg	228 mg	2 x 100 mg + 2 x 25 mg	34.8	69.6 x 100 mg + 69.6 x 25 mg
CHOP					
Cyclophosphamide	750 mg/m^2 = 1425 mg	1,425 mg	1 x 500 mg 1 x 1000 mg	6.0	6 x 500 mg 6 x 1000 mg
Doxorubicin	50 mg/m^2 = 95 mg	95 mg	1 x 100 mg	6.0	6 x 100 mg
Vincristine	1.4 mg/m^2, maximum 2 mg	2 mg	1 x 2 mg	6	6 x 2 mg
Prednisolone	100 mg	100 mg	2 x 50 mg	30	60 x 50 mg
CVP					
Cyclophosphamide	750 mg/m^2 = 1425 mg	1,425 mg	1 x 500 mg 1 x 1000 mg	8.0	8 x 500 mg 8 x 1000 mg
Vincristine	1.4 mg/m^2, maximum 2 mg	2 mg	1 x 2 mg	8	8 x 2 mg
Prednisolone	100 mg	100 mg	2 x 50 mg	40	80 x 50 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 based on the costs per pack after deduction of the statutory rebates.

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					
Obinutuzumab 1000 mg	1 CIS	€ 3,489.34	€ 1.77	€ 0.00	€ 3,487.57
Bendamustine 100 mg	5 PIC	€ 1,573.68	€ 1.77	€ 197.94	€ 1,373.97
Bendamustine 100 mg	1 PIC	€ 321.15	€ 1.77	€ 39.25	€ 280.13
Bendamustine 25 mg	5 PIC	€ 402.03	€ 1.77	€ 49.49	€ 350.77
Bendamustine 25 mg	1 PIC	€ 96.47	€ 1.77	€ 10.81	€ 83.89
Appropriate comparator therapy					
Bendamustine 100 mg	5 PIC	€ 1,573.68	€ 1.77	€ 197.94	€ 1,373.97
Bendamustine 25 mg	5 PIC	€ 402.03	€ 1.77	€ 49.49	€ 350.77
Cyclophosphamide 1,000 mg	6 PSI	€ 123.70	€ 1.77	€ 6.24	€ 115.69
Cyclophosphamide 500 mg	6 PSI	€ 81.98	€ 1.77	€ 8.98	€ 71.23
Doxorubicin 100 mg[6]	1 CIS	€ 285.52	€ 1.77	€ 0.00	€ 283.75
Vincristine 2 mg	1 SFI	€ 37.39	€ 1.77	€ 1.25	€ 34.37
Prednisolone 50 mg**Fehler! Textmarke nicht definiert.**	10 TAB	€ 14.92	€ 1.77	€ 0.30	€ 12.85
Prednisolone 50 mg[6]	50 TAB	€ 31.17	€ 1.77	€ 1.57	€ 27.83
Designation of the therapy	Cost/performance				
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIC/PSI = powder for solution for infusion; TAB = Tablets					

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Costs for additionally required SHI services:

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

[6] Fixed reimbursement rate

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.

Designation of the therapy	Type of service	Costs per pack/ service	Days of treatment/ year	Annual treatment costs/ patient
Obinutuzumab	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90

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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but instead 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 sales 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.

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 28 July 2015, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 May 2021.

On 10 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of obinutuzumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 11 May 2021, in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 obinutuzumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 16 August 2021. The deadline for submitting written statements was 6 September 2021.

The oral hearing was held on 27 September 2021.

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 26 October 2021, and the proposed resolution was approved.

At its session on 4 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	28 July 2015	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	25 May 2021	New determination of the appropriate comparator therapy
Working group Section 35a	15 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	27 September 2021	Conduct of the oral hearing
Working group Section 35a	6 October 2021 20 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	26 October 2021	Concluding discussion of the draft resolution
Plenum	4 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 November 2021

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

Prof. Hecken