Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): 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 chemotherapy, first-line)

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 5 April 2018, the G-BA decided on the benefit assessment of obinutuzumab in the therapeutic indication "previously untreated 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 chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced FL.

Therapeutic indication of the resolution (resolution of 04.11.2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients with previously untreated follicular lymphoma (FL)

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

- Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)

  or
- Rituximab in combination with cyclophosphamide, vincristine and prednisolone (CVP)

  or
- Rituximab in combination with bendamustine

followed by rituximab maintenance treatment for patients who have responded to induction therapy.

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. In addition to obinutuzumab, the active ingredients ibritumomab tiuxetan, interferon alfa-2b and rituximab have a marketing authorisation for the present therapeutic indication. Follicular lymphomas are a type of non-Hodgkin lymphoma. Accordingly, bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, mitoxantrone, vinblastine, vincristine, dexamethasone, prednisone and prednisolone are also approved.

on 2. In the indication of previously untreated follicular lymphoma, radiotherapy can be considered a non-medicinal treatment. However, for the present therapeutic situation, it is assumed that radiotherapy is not indicated.

on 3. There are no resolutions of the G-BA for the present therapeutic indication.

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based 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.

First of all, it is assumed in the determination of the appropriate comparator therapies that no follicular lymphomas grade 3b are subsumed under the present therapeutic indication since this subentity is usually assigned to the aggressive non-Hodgkin lymphomas.

Furthermore, it is assumed that the patients in the present therapy situation 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 or radiotherapy is not considered.

The available evidence clearly recommends a therapy consisting of an anti-CD20 antibody plus chemotherapy for patients in advanced stages. In addition to the obinutuzumab to be evaluated here, the anti-CD20-antibody rituximab is mentioned.

According to guidelines, different chemotherapy regimens can be considered, which are combined with the anti-CD20 antibody rituximab. Based on the available evidence, bendamustine and CHOP are mentioned as preferred chemotherapy components for primary therapy. Furthermore, CVP is also mentioned. Overall, it cannot be deduced that of these rituximab-chemotherapy combinations, a particular one is clearly superior to the others or would be regularly preferred. Thus, rituximab in combination with bendamustine or CHOP or CVP is determined to be equally appropriate options in the context of the appropriate comparator therapy.

According to the available evidence, patients who show a response to chemoimmunotherapy should receive maintenance treatment with an anti-CD20 antibody. Accordingly, maintenance treatment with rituximab is also determined as a component of the appropriate comparator therapy.

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:

- Rituximab in combination with chemotherapy (preferably in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincristine and prednisolone (CVP) or bendamustine)

Based on current guideline recommendations and taking into account the statements of scientific-medical societies in the present procedure, the immunochemotherapies to be used preferably beforehand are determined as the sole options to be used within the scope of the appropriate comparator therapy in the present therapeutic indication.

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:

Patients with previously untreated follicular lymphoma (FL)

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 GALLIUM study in the dossier.

The study included previously untreated patients with CD20-positive indolent non-Hodgkin lymphoma. In addition to patients with advanced follicular lymphoma requiring therapy (stages II with bulky disease, III and IV according to Ann Arbor classification), patients with marginal zone lymphoma were also included. Patients with follicular lymphoma grade 3b were excluded from the study. A total of 702 patients were randomised to the intervention arm (obinutuzumab + chemotherapy) and 699 patients to the control arm (rituximab + chemotherapy). Of these, 601 patients each in both arms represent the relevant sub-population with follicular lymphoma. Randomisation was stratified by chemotherapy, geographic region, and disease severity according to Follicular Lymphoma International Prognostic Index (FLIPI).

In the test arm, obinutuzumab was used as induction therapy in combination with the chemotherapy regimens CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), CVP (cyclophosphamide, vincristine, prednisolone) or bendamustine. These chemotherapy regimens were also used in combination with rituximab in the control arm as induction therapy. The study centres made the selection for the respective chemotherapy regimen. Patients who had shown a response to induction received maintenance treatment with obinutuzumab in the test arm or with rituximab in the control arm until disease progression or up to 2 years. The applied dosages and number of cycles followed the product information or the guidelines and consensus recommendations.

Progression-free survival (PFS) is the primary endpoint of the GALLIUM study. Secondary endpoints were overall survival and endpoints in the categories morbidity, health-related quality of life and side effects.

The GALLIUM study is still ongoing. To date, five data cut-offs are available, three of which were planned a priori (24.10.2012, 20.02.2014 and 31.01.2016) and two of which were requested by the Food and Drug Administration (FDA) 10.09.2016 and 03.03.2017).

On the usability of the study results presented in the dossier:

The IQWiG stated in the dossier assessment that the results of the GALLIUM 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 current data cut-off. For the current data

cut-off 10.10.2017, the pharmaceutical company only presented evaluations on mortality and adverse events in Module 4. The evaluations presented for the category quality of life are based on the data cut-off of 31.01.2016. No adequate justification is provided by the pharmaceutical company 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, the pharmaceutical company had already presented evaluations on the quality of life based on the more recent data cut-off of 10.09.2016 for the benefit assessment in the course of the marketing authorisation in 2017.

Furthermore, with regard to the evaluations of health-related quality of life, it must be noted that these are inadequately prepared. Quality of life was assessed in the GALLIUM 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.

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 final data cut-off study results. 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 VerfO 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 chemotherapy, followed by Gazyvaro maintenance treatment in patients achieving a response, is indicated for the treatment of patients with previously untreated follicular lymphoma (FL).

Obinutuzumab has received marketing authorisation as an orphan drug.

The appropriate comparator therapy was determined to be:

- Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)

  or
- Rituximab in combination with cyclophosphamide, vincristine and prednisolone (CVP)

  or
- Rituximab in combination with bendamustine

followed by rituximab maintenance treatment for patients who have responded to induction therapy.

The results of the GALLIUM study (obinutuzumab vs rituximab, each in combination with CHOP, CVP or bendamustine) were presented to prove the additional benefit.

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 not suitable for a proper assessment of the additional benefit due to the inadequate 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 of 5 April 2018. These figures are also subject to uncertainties, which relate in particular to the percentage of patients receiving chemoimmunotherapy, the percentage of patients with a transition from monitoring wait-and-see approach to chemoimmunotherapy, and the underlying mortality rate. Notwithstanding these uncertainties, however, these patient numbers are not called into question by the numbers calculated by the pharmaceutical company in the present proceeding.

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: 19 August 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).

According to the product information of obinutuzumab and rituximab, an induction therapy of 6-8 cycles is initially performed in the present therapeutic indication, depending on the selected combination chemotherapy. The induction phase is followed by the administration

of obinutuzumab or rituximab 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)	Treatment days/ patient/ year
Medicinal product to be assessed				
Obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)				
Obinutuzumab	*Induction therapy* Cycle 1: Day 1, 8 and 15 Cycle 2-8: Day 1 of a 21-days cycle	8 cycles	Cycle 1: 3 Cycle 2 to 8: 1	10
	Maintenance treatment once every 56 days	3 cycles	1	3
Cyclophosphamide	Day 1 of 21-days cycle	6 cycles	1	6
Doxorubicin	Day 1 of 21-days cycle	6 cycles	1	6
Vincristine	Day 1 of 21-days cycle	6 cycles	1	6
Prednisolone	Day 1 to 5 of 21-day cycle	6 cycles	5	30
Obinutuzumab in combination with cyclophosphamide, vincristine and prednisolone (CVP)				
Obinutuzumab	*Induction therapy* Cycle 1: Day 1, 8 and 15 Cycle 2-8: Day 1 of a 21-days cycle	8 cycles	Cycle 1: 3 Cycle 2 to 8: 1	10

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient//year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Maintenance treatment once every 56 days	3 cycles	1	3
Cyclophosphamide	Day 1 of 21-days cycle	8 cycles	1	8
Vincristine	Day 1 of 21-days cycle	8 cycles	1	8
Prednisolone	Day 1 of 21-days cycle	8 cycles	5	40
Obinutuzumab in combination with bendamustine				
Obinutuzumab	*Induction therapy* Cycle 1: Day 1, 8 and 15 Cycle 2-6: Day 1 of a 28-days cycle	6 cycles	Cycle 1: 3 Cycle 2 to 6: 1	8
	Maintenance treatment once every 56 days	3 cycles	1	3
Bendamustine	Day 1 and 2 of a 28-days cycle each	6 cycles	2	12
Appropriate comparator therapy				
Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP))[2]				
Rituximab	*Induction therapy* Day 1 of 21-days cycle	6 cycles	1	6
	Maintenance treatment once every 56 days	4 cycles	1	4
Cyclophosphamide	Day 1 of 21-days cycle	6 cycles	1	6

[2] Flinn IW etal. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014 May 8;123(19):2944-52.

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient//year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Doxorubicin	Day 1 of 21-days cycle	6 cycles	1	6
Vincristine	Day 1 of 21-days cycle	6 cycles	1	6
Prednisolone	Day 1 to 5 of 21-day cycle	6 cycles	5	30
Rituximab in combination with cyclophosphamide, vincristine and prednisolone (CVP)[2]				
Rituximab	*Induction therapy* Day 1 of 21-days cycle	6 cycles	1	6
	Maintenance treatment once every 56 days	4 cycles	1	4
Cyclophosphamide	Day 1 of 21-days cycle	6 cycles	1	6
Vincristine	Day 1 of 21-days cycle	6 cycles	1	6
Prednisolone	Day 1 to 5 of 21-day cycle	6 cycles	5	30
Rituximab in combination with bendamustine[2]				
Rituximab	Day 1 of 28-days cycle	6 cycles	1	6
	Maintenance treatment once every 56 days	3 cycles	1	3
Bendamustine	Day 1 and 2 of 28-days cycle	6 cycles	2	12

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"[3] 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 in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)					
Obinutuzumab	1000 mg	1000 mg	1 x 1000 mg	13	13 x 1000 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1425 mg	1 x 1000 mg 1 x 500 mg	6	6 x 1000 mg 6 x 500 mg
Doxorubicin	50 mg/m²	95 mg	1 x 100 mg	6	6 x 100 mg
Vincristine	1.4 mg/m² max. 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
Obinutuzumab in combination with cyclophosphamide, vincristine and prednisolone (CVP)					
Obinutuzumab	1000 mg	1000 mg	1 x 1000 mg	13	13 x 1000 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1425 mg	1 x 1000 mg 1 x 500 mg	8	8 x 1000 mg 8 x 500 mg
Vincristine	1.4 mg/m² max. 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
Obinutuzumab in combination with bendamustine					
Obinutuzumab	1000 mg	1000 mg	1 x 1000 mg	11	11 x 1000 mg
Bendamustine	90 mg/m² = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg 36 x 25 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)[4]					
Rituximab	375 mg/ m² = 712,5 mg	712.5 mg	1 x 500 mg 3 x 100 mg	10	30 x 100 mg 10 x 500 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1425 mg	1 x 1000 mg 1 x 500 mg	6	6 x 1000 mg 6 x 500 mg
Doxorubicin	50 mg/m²	95 mg	1 x 100 mg	6	6 x 100 mg
Vincristine	1.4 mg/m² max. 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
Rituximab in combination with cyclophosphamide, vincristine and prednisolone (CVP)[4]					
Rituximab	375 mg/ m² = 712,5 mg	712.5 mg	1 x 500 mg 3 x 100 mg	10	30 x 100 mg 10 x 500 mg
Cyclophosphamide	750 mg/m² = 1,425 mg	1425 mg	1 x 1000 mg 1 x 500 mg	6	6 x 1000 mg 6 x 500 mg
Vincristine	1.4 mg/m² max. 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
Rituximab in combination with bendamustine[4]					
Rituximab	375 mg/ m² = 712,5 mg	712.5 mg	1 x 500 mg 3 x 100 mg	9	27 x 100 mg 9 x 500 mg
Bendamustine	90 mg/m² = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg 36 x 25 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

[4] Flinn IW etal. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014 May 8;123(19):2944-52.

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	€ 3487.57
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
Cyclophosphamide 1,000 mg	6 PSI	€ 123.70	€ 1.77	€ 6.24	€ 115.69
Cyclophosphamide 1,000 mg	1 PSI	€ 29.82	€ 1.77	€ 1.04	€ 27.01
Cyclophosphamide 500 mg	6 PSI	€ 81.98	€ 1.77	€ 8.98	€ 71.23
Cyclophosphamide 500 mg	1 PSI	€ 22.86	€ 1.77	€ 1.50	€ 19.59
Doxorubicin 100 mg[5]	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[5]	50 TAB	€ 31.17	€ 1.77	€ 1.57	€ 27.83
Prednisolone 50 mg[5]	10 TAB	€ 14.92	€ 1.77	€ 0.30	€ 12.85
Appropriate comparator therapy					
Rituximab 500 mg	1 CIS	€ 1,777.06	€ 1.77	€ 84.18	€ 1,691.11
Rituximab 100 mg	2 CIS	€ 716.94	€ 1.77	€ 33.50	€ 681.67
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

[5] 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
Cyclophosphamide 1,000 mg	6 PSI	€ 123.70	€ 1.77	€ 6.24	€ 115.69
Cyclophosphamide 1,000 mg	1 PSI	€ 29.82	€ 1.77	€ 1.04	€ 27.01
Cyclophosphamide 500 mg	6 PSI	€ 81.98	€ 1.77	€ 8.98	€ 71.23
Cyclophosphamide 500 mg	1 PSI	€ 22.86	€ 1.77	€ 1.50	€ 19.59
Doxorubicin 100 mg[5]	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[5]	50 TAB	€ 31.17	€ 1.77	€ 1.57	€ 27.83
Prednisolone 50 mg[5]	10 TAB	€ 14.92	€ 1.77	€ 0.30	€ 12.85
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; ; PSI = powder for solution for injection; 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.

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
Obinutu-zumab	*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
Rituximab	*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 9 August 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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 1, sentence 6 VerfO.

By letter dated 14 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	9 August 2016	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