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: Chronic lymphocytic leukaemia, combination with chlorambucil, 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 patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy 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 February 2015, the G-BA decided on the benefit assessment of obinutuzumab in the indication "with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy" 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 chlorambucil is indicated for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

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:

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

Adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy

- Ibrutinib

or

- Ibrutinib in combination with rituximab or obinutuzumab

or

- Bendamustine in combination with rituximab (only for patients without genetic risk factors)

or

- Chlorambucil in combination with rituximab (only for patients without genetic risk factors)

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 cytostatic agents bendamustine and chlorambucil; the BTK inhibitors acalabrutinib and ibrutinib; the PI3K inhibitor idelalisib; the BCL-2 inhibitor venetoclax; the anti-CD20 antibody rituximab; and the glucocorticoids prednisolone and prednisone have a marketing authorisation for the present therapeutic indication. Chronic lymphocytic leukaemia is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients cyclophosphamide, doxorubicin, etoposide, mitoxantrone, vinblastine, vincristine and dexamethasone are also

authorised. Some of the marketing authorisations are tied to specific combination preparations.

on 2. In the present therapeutic indication, allogeneic stem cell transplantation represents a non-medicinal treatment option. However, the G-BA expects for the present therapy situation that allogeneic stem cell transplantation is not indicated at the time of therapy or eligible only in individual cases for a few patients and is therefore not included among the standard therapies in the therapeutic indication.

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

- Acalabrutinib (resolutions of 3 June 2021)
- Ibrutinib (resolutions of 1 April 2021, 20 February 2020, 15 December 2016 and 21 July 2016)
- Idelalisib (resolutions of 16 March 2017)
- Obinutuzumab (resolution of 5 February 2015)
- Venetoclax (resolutions of 15 October 2020 and 16 May 2019)

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. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

For the present therapeutic indication, it is presumed that the patients are in need of treatment (for example, stage C Binet).

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.

According to the statements of the scientific-medical societies, patients in the present therapeutic indication should be treated with a bruton tyrosine kinase (BTK) inhibitor, irrespective of the presence of genetic risk factors. According to the marketing authorisation, both the BTK inhibitor ibrutinib as monotherapy and in combination with rituximab or obinutuzumab and the BTK inhibitor acalabrutinib as monotherapy and in combination with obinutuzumab can be considered.

For ibrutinib as monotherapy, in the patient population that is unsuitable for chemo-immunotherapy and in which a 17p deletion or TP53 mutation is present, the G-BA identified a hint of a non-quantifiable additional benefit compared with best supportive care (resolution of 21 July 2016). A hint for a considerable additional benefit was identified for the combination ibrutinib + rituximab compared with FCR for the sub-population of patients eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR) (resolution of 1 April 2021). A hint for a minor additional benefit was identified for the combination ibrutinib + obinutuzumab for patients who are not eligible for therapy with FCR (resolution of 1 April 2021).

For the BTK inhibitor acalabrutinib, both in monotherapy and in combination with obinutuzumab, a hint for a minor additional benefit was identified in the benefit assessment for patients who do not have a 17p deletion or TP53 mutation and for whom therapy with FCR is not an option, compared with chlorambucil in combination with obinutuzumab (resolutions of 3 June 2021). This is still a relatively new treatment option, the therapeutic value of which cannot yet be conclusively assessed, so that acalabrutinib, both in monotherapy and in combination with obinutuzumab, is not considered an appropriate comparator therapy at the present time.

In addition to BTK inhibitors, the statements of scientific-medical societies also discuss therapy with the combination venetoclax + obinutuzumab as an alternative for patients regardless of the presence of risk factors. In the resolutions of 15 October 2020, no additional benefit was identified for venetoclax in combination with obinutuzumab compared with the corresponding comparator therapies for the sub-populations investigated in each case. Since therapy alternatives with a proven additional benefit are available in a comparable assessment situation, the G-BA also does not currently consider venetoclax in combination with obinutuzumab to be an appropriate comparator therapy.

According to the available evidence, chemo-immunotherapy can also be considered for the treatment of non-pretreated CLL in patients without genetic risk factors. In case of unsuitability for treatment with a full dose of fludarabine, as addressed in the present therapeutic indication, a combination therapy consisting of a chemotherapeutic agent and a CD20 antibody may therefore be considered. According to the marketing authorisation, these can be bendamustine in combination with rituximab as well as chlorambucil in combination with rituximab.

Regarding the genetic risk factors, the statement of the scientific-medical societies states, in addition to the already considered factors 17p deletion and TP53 mutation, an unmutated immunoglobulin heavy chain variable (IGHV) region and a complex karyotype. Compared to the other risk factors, the complex karyotype is not given the same importance in the evidence. Accordingly, the G-BA considers genetic risk factors: Presence of a 17p deletion / TP53 mutation or an unmutated immunoglobulin heavy chain variable region (IGHV).

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

<u>Change of the appropriate comparator therapy</u>

Originally, the appropriate comparator therapy was determined as follows:

- bendamustine in combination with rituximab

or

- chlorambucil in combination with rituximab

The change in the appropriate comparator therapy takes into account, in particular, the statements of scientific-medical societies and experts. Accordingly, ibrutinib in monotherapy as well as in combination with obinutzumab or rituximab is also considered appropriate comparator therapies in the therapeutic indication to be evaluated. In addition to the previously considered factors 17p deletion and TP53 mutation, an unmutated immunoglobulin heavy chain variable (IGHV) region is now also considered a genetic risk

factor, which leads to the fact that bendamustine and chlorambucil each in combination with rituximab are not considered an appropriate comparator therapy for these patients.

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:

An additional benefit is not proven.

Adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy

Justification:

For the proof of additional benefit, the pharmaceutical company presented the results of the randomised, 3-arm, open-label, multicentre phase III CLL11 study in the dossier. Only the study arms obinutuzumab + chlorambucil and rituximab + chlorambucil are relevant for the present assessment.

The study included patients with non-pretreated cluster-of-differentiation (CD)20+ CLL requiring treatment according to the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria. 333 patients were randomised to the obinutuzumab + chlorambucil study arm and 330 patients to the rituximab + chlorambucil study arm.

In both study arms, therapy was largely carried out in accordance with the product information, with the exception of premedication for obinutuzumab administration, which is only in accordance with the requirements of the product information in version G of the study protocol.

Since the study did not only include patients who were not eligible for a full dose of fludarabine, the pharmaceutical company submitted evaluations for a relevant sub-population. Only data for the endpoint categories mortality, morbidity and health-related quality of life were provided for the sub-population, but not for the category side effects.

Progression-free survival (PFS) is the primary endpoint of the CLL11 study. Secondary patient-relevant endpoints included overall survival, endpoints regarding symptomatology, health-related quality of life, and side effects.

The CLL11 study was terminated in August 2017. There are three data cut-offs, two of which were planned a priori (09.05.2013 and 10.10.2017). Another data cut-off (11.05.2015) was not prespecified, which is why it is not relevant for the benefit assessment.

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

The IQWiG stated in the dossier assessment that the results of the CLL11 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 on all endpoints for any of the submitted data cut-offs, especially not for the final data cut-off. For the final data cut-off 10.10.2017, the pharmaceutical company only presented evaluations on mortality and adverse events in Module 4. The evaluations presented for patient-reported endpoints in the categories morbidity and quality of life are based on the interim data cut-off from 09.05.2013. No adequate justification is provided by the pharmaceutical company regarding this. It can be assumed that data on patient-reported endpoints were added to the final data cut-off to a relevant extent.

Furthermore, the evaluations of the EORTC QLQ-C30 are not adequate. Although a longer-term follow-up was conducted, data at follow-up were only provided at month 3, which was not prespecified for any evaluation. Due to the lack of information on endpoint-specific observation durations, it is also not possible to assess whether the evaluations of the responder analyses on the relative risk are adequate. The evaluation of continuous data on the EORTC QLQ-C30 is also associated with uncertainties.

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 the 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.

Furthermore, data on the sub-population of patients not eligible for a full dose of fludarabine are missing in the side effects category. Only data on the total population are available, of which only 75% represent the relevant sub-population. The pharmaceutical company did not provide a plausible explanation of the extent to which the results of the overall population can be transferred to the sub-population. Also, for adverse events, only evaluations using relative risk were presented for the estimation of which the endpoint-specific observation durations are required. However, these are missing.

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. The finding that an appropriate assessment of the additional benefit is not possible due to the inadequate and incomplete data preparation applies independently of the change in the appropriate comparator therapy implemented in the present procedure.

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, paragraph 1, sentence 4, of the Rules of Procedure of the G-BA that an additional benefit is not 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 chlorambucil is indicated for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

Obinutuzumab has received marketing authorisation as an orphan drug.

The appropriate comparator therapy was determined to be:

- Ibrutinib

or

- Ibrutinib in combination with rituximab or obinutuzumab

or

- Bendamustine in combination with rituximab (only for patients without genetic risk factors)

or

- Chlorambucil in combination with rituximab (only for patients without genetic risk factors)

For the proof of additional benefit, results from the CLL11 study comparing obinutuzumab + chlorambucil to rituximab + chlorambucil were presented.

Irrespective of the change in the appropriate comparator therapy in the present study, 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, analyses of all endpoints collected were not available for any of the data cut-offs, especially not for the final one. Furthermore, the evaluations on patient-reported endpoints were not adequate. In addition, the results presented on common adverse events were incomplete. It should also be taken into account that only evaluations of the overall population were presented for the side effects but not for the relevant sub-population.

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 February 2015. The derivation of the figures was generally considered to be comprehensible. Uncertainties existed, among other things, with regard to the transferability of the data on the percentage of patients requiring treatment to the German health care context and the percentage of patients who are not suitable for therapy with a full dose of fludarabine. 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: 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 chronic lymphocytic leukaemia.

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).

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

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	Cycle 1: Day 1+ 2, 8 and 15, cycle 2 – 6: Day 1 of 28-days cycle each	6 cycles	4 (cycle 1) 1 (cycle 2– 6)	9
Chlorambucil[2]	Day 1 and 15 of 28-days cycle	6 cycles	2	12
Appropriate comparator therapy				
Ibrutinib				
Ibrutinib	Continuously, 1 x daily	365	1	365
Ibrutinib + rituximab				
Ibrutinib	Continuously, 1 x daily	365	1	365
Rituximab	Day 1[3] of a 28-days cycle	6 cycles	1	7

[2] Goede, V., et al., Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med, 2014. 370(12): p. 1101-10

[3] In cycle 1, the rituximab dose is applied on 2 days (50 mg / m² on day 1, 325 mg / m² on day 2.

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient /year	Treatment duration/ treatment (days)	Days of treatment/ patient /year
Ibrutinib + obinutuzumab				
Ibrutinib	Continuously, 1 x daily	365	1	365
Obinutuzumab	every 28 days on day 1 + 2, 8 and 15 of cycle 1 and on day 1 of cycle 2 – 6[4]	6 cycles	1	9
Bendamustine + rituximab (BR) [5]				
Bendamustine	Day 1 and 2 of 28-days cycle	6 cycles	2	12
Rituximab	Day 1 of 28-days cycle	6 cycles	1	6
Chlorambucil + rituximab (ClbR)**Fehler! Textmarke nicht definiert.**				
Chlorambucil	Day 1 and 15 of 28-days cycle	6 cycles	2	12
Rituximab	Day 1 of 28-days cycle	6 cycles	1	6

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916. [6]

[4] The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg).

[5] Fischer K et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011 Sep 10; 29(26):3559-66

[6] Federal Health Reporting. Average body measurements of the population (2017, both genders), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Obinutuzumab	Cycle 1: Day 1: 100 mg Day 2: 900 mg Day 8: 1,000 mg Day 15: 1,000 mg Cycle 2 - 6 Day 1: 1,000 mg	1,000 mg	1 x 1,000 mg	9	8 x 1,000 mg
Chlorambucil	0.5 mg/kg	38.5 mg	19 x 2 mg	12	228 x 2 mg
Appropriate comparator therapy					
Ibrutinib					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
Ibrutinib + rituximab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
Rituximab	Cycle 1: 375 mg/m^2 Cycle 2 - 6: 500 mg/m^2	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	7	3 x 100 mg + 11 x 500 mg
Ibrutinib + obinutuzumab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
Obinutuzumab	Cycle 1: Day 1: 100 Mg Day 2: 900 mg Day 8: 1,000 mg Day 15: 1.000 mg Cycle 2 - 6 Day 1: 1,000	1,000 mg	1 x 1,000 mg	9	8 x 1,000 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Mg				
Bendamustine + rituximab (BR)					
Bendamustine	70 mg/m²	133 mg	5 x 100 mg + 2 x 25 mg	12	12 x 100 mg + 24 x 25 mg
Rituximab	Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m²	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	6	3 x 100 mg 11 x 500 mg
Chlorambucil + rituximab (ClbR)					
Chlorambucil	0.5 mg/kg	38.5 mg	19 x 2 mg	12	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m²	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	6	3 x 100 mg 11 x 500 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 1,000 mg	1 CIS	€ 3,489.34	€ 1.77	€ 0.00	€ 3,487.57
Chlorambucil 2 mg	50 FCT	€ 36.31	€ 1.77	€ 1.40	€ 33.14

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
Appropriate comparator therapy					
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	1 PTK	€ 96.47	€ 1.77	€ 10.81	€ 83.89
Bendamustine 25 mg	5 PIC	€ 402.03	€ 1.77	€ 49.49	€ 350.77
Chlorambucil 2 mg	50 FCT	€ 36.31	€ 1.77	€ 1.40	€ 33.14
Ibrutinib 420 mg	28 FCT	€ 5,772.62	€ 1.77	€ 0.00	€ 5,770.85
Obinutuzumab 1000 mg	1 CIS	€ 3,489.34	€ 1.77	€ 0.00	€ 3,487.57
Rituximab 100 mg	2 CIS	€ 716.94	€ 1.77	€ 33.50	€ 681.67
Rituximab 500 mg	1 CIS	€ 1,777.06	€ 1.77	€ 84.18	€ 1,691.11
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 15 October 2021

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 or service	Treatment days per year	Annual costs per patient
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
	Premedication Antihistamines e.g. dimetindene IV 4 mg Antipyretics e.g. paracetamol 2 x 500 mg	€ 14.95 € 1,36[8]	6 -7 6 -7	€ 44.85 € 1.36
	HBV test	€ 5.50	1	€ 5.50

Obinutuzumab	Hepatitis B surface antigen status (GOP number 32781)			
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
	Premedication Corticosteroid e.g. dexamethasone 5 x 4 mg Antihistamines e.g. dimetindene IV 4 mg Antipyretics e.g. paracetamol 2 x 500 mg	 € 14.44[7] € 14.95 € 1.36[8]	 9 9 9	 € 72.20 € 59.80 € 1.36
Ibrutinib	*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.

[7] Fixed reimbursement rate

[8] Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Section 12, paragraph 7, of the AM-RL (information as concomitant medication in the product information of the prescription medicinal product) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003: FB Paracetamol tablets 20 pieces = 1.50 € (pharmacy discount according to Section 130 paragraph 1 and 2, 5% from FB; manufacturer discount = 0.06 €)

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 July 2019, 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 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	9 July 2019	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