# Justification

Gemeinsamer Bundesausschuss

## to 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 Ibrutinib (New Therapeutic Indication: Chronic Lymphatic Leukaemia, First-Line, in Combination with Obinutuzumab)

of 20 February 2020

**Contents**

## 1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for 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 ibrutinib (IMBRUVICA®) was first placed on the German market on 1 November 2014.

Ibrutinib is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In its previously approved therapeutic indications, ibrutinib's sales within the German statutory health insurance system at pharmacy sales prices including VAT exceeded 50 million euros, necessitating the submission of evidence for ibrutinib in accordance with Section 5 paragraphs 1 to 6 of the Rules of Procedure (VerfO) of the G-BA to demonstrate its additional benefit compared to the appropriate comparator therapy.

On 2 August 2019, ibrutinib received marketing authorisation for a new therapeutic indication:

“IMBRUVICA in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)."

On 30 August 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ibrutinib with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 2 December 2019, 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 ibrutinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the 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 ibrutinib.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 ibrutinib (Imbruvica®) in accordance with the product information

IMBRUVICA as a single agent or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

   Fludarabine in combination with cyclophosphamide and rituximab (FCR)

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

   Bendamustine in combination with rituximab

   *or*

   Chlorambucil in combination with rituximab or obinutuzumab

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Ibrutinib

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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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. With regard to authorisation status, the active ingredients bendamustine, chlorambucil, cyclophosphamide, fludarabine, ibrutinib, idelalisib, venetoclax, obinutuzumab, rituximab, prednisolone and prednisone are available for first-line treatment of patients with CLL. CLL belongs to the group of non-Hodgkin's lymphomas, and, hence, the active ingredients cytarabine, doxorubicin, trofosfamide, vinblastine, and vincristine are also approved in principle.

On 2. Allogeneic stem cell transplantation represents a non-medicinal treatment option in the present therapeutic indication. For the therapeutic situation under consideration, however, the G-BA assumes that allogeneic stem cell transplantation is not indicated at the time of therapy, or is only feasible for a small number of individual patients and is therefore not regarded as a standard therapy in the therapeutic indication.

On 3. For the therapeutic indication under consideration, the G-BA has passed resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a of the German Social Code Book V (SGB V) for the active ingredients ibrutinib, idelalisib, obinutuzumab and venetoclax.

On 4. For the therapeutic indication under consideration, the G-BA assumes that the patients in question are those requiring treatment (e.g. stage C according to Binet).

The available evidence clearly supports the use of a combination of fludarabine, cyclophosphamide and the anti-CD20 antibody rituximab (FCR) in patients with previously untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation.

In patients ineligible for therapy with FCR, for instance due to a reduced general condition, a combination therapy of a chemotherapeutic agent and an anti-CD-20 antibody is recommended. However, on the basis of the available evidence there is no

clear therapeutic standard treatment for this patient group. In accordance with available guidelines and taking into account the respective authorisation status, the combinations bendamustine in combination with rituximab, chlorambucil in combination with rituximab or chlorambucil in combination with obinutuzumab represent equally appropriate treatment options. The available evidence also includes some recommendations for monotherapy with ibrutinib. However, the benefit assessment procedure did not identify any additional benefit for ibrutinib in the sub-population under consideration. Monotherapy with chemotherapeutic agents such as chlorambucil or bendamustine is also not recommended for previously untreated patients.

Patients with a 17p deletion and/or a TP53 mutation generally respond poorly to chemo-immunotherapy, have a comparatively rapid recurrence rate and a comparatively low life expectancy. Three active ingredients, ibrutinib, idelalisib and venetoclax, are approved for this patient group. Taking into available guidelines and the benefit assessments according to Section 35a, as well as the approved therapeutic indications of the active ingredients and combinations of active ingredients, only ibrutinib is determined as an appropriate comparator therapy for this patient population. Patients with no 17p deletion or TP53 mutation for whom chemo-immunotherapy is not indicated for other reasons, for instance due to their poor general condition or contraindications, have limited treatment options. On the basis of the available evidence, the G-BA considers it appropriate to also determine ibrutinib as an appropriate comparator therapy for this patient group.

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

Change of the appropriate comparator therapy:

The appropriate comparator therapy was originally determined as follows:

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Fludarabine in combination with cyclophosphamide and rituximab (FCR)

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Bendamustine in combination with rituximab *or* ofatumumab

*or*

Chlorambucil in combination with rituximab *or* obinutuzumab *or* ofatumumab

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Ibrutinib

As marketing authorisation for ofatumumab was withdrawn in February 2019, the combination therapies bendamustine and chlorambucil in combination with ofatumumab are no longer considered appropriate comparator therapies.

This change in the appropriate comparator therapy neither effects the present assessment of additional benefit nor does it require a re-assessment of the benefit assessment.

### 2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ibrutinib is assessed as follows.

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

An additional benefit has not been proven for ibrutinib in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR).

Justification:

The pharmaceutical company did not present any data that would have been suitable for the assessment of additional benefit compared with the appropriate comparator therapy.

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

A hint for a minor additional benefit has been established for ibrutinib in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR).

Justification:

The benefit assessment is based on the findings of the ongoing open, randomised study iLLUMINATE, in which the combination therapy ibrutinib + obinutuzumab is compared with the combination therapy chlorambucil + obinutuzumab.

The study included adult patients with untreated CLL / small cell lymphocytic lymphoma requiring treatment according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL). To be included, patients were required to have a lymph node enlargement measurable by CT. Furthermore, the patients either had to be ≥ 65 years old or meet at least one of the following criteria: existing comorbidities (Cumulative Illness Rating Scale [CIRS] > 6, existing renal impairment (creatinine clearance < 70 ml/min, estimated by Cockroft-Gault formula), existing deletion on chromosome 17 (del17p) or a mutation of tumour protein p53 (TP53). In the test arm 113 patients and in the control arm 116 patients were stratified based on ECOG-PS (0–1 vs 2) and randomised based on cytogenetic characteristics (del17p vs deletion on chromosome 11 [del11q] without del17p vs others [neither del17p nor del11q]).

Since patients were included in the study regardless of their eligibility for FCR therapy, the pharmaceutical company established a sub-population (as well as another sub-population for sensitivity analyses) for patients who, in the company's view, were not eligible for FCR therapy. In doing so, the pharmaceutical company took into account various criteria taken from guidelines and previous benefit assessment procedures. These criteria included age, renal function, thrombocytopoenia, anaemia, autoimmune cytopoenia, general condition, comorbidities, and 17p and TP53 mutation status. These criteria were deemed sufficient to adequately represent the population under consideration.

The establishment of the sub-population resulted in slight imbalances in the two study arms in regards to disease duration, lymph node diameter and 11q-deletion patient characteristics.

In the test arm, patients, as per the product information, received ibrutinib until disease progression or until the onset of unacceptable toxicities. Treatment with obinutuzumab in the test arm and treatment with obinutuzumab + chlorambucil in the comparator arm was performed over six cycles. Each treatment was performed according to or without significant deviation from the product information.

After administration of the trial medication was discontinued, patients were offered follow-up therapy. In the comparator arm, patients had the possibility of receiving follow-up ibrutinib monotherapy.

In the test arm the median treatment duration was eight times that of the comparator arm. As side effects were recorded up to 30 days after the last dosage, the median observation period of side effects in the ibrutinib arm was significantly longer (40.5 vs 6.1 months). The morbidity observation period (EQ-5D VAS) was also longer at 40.1 vs 21.0 months.

Two data cut-offs were conducted for the iLLUMINATE study. The benefit assessment is based on the results of the second data cut-off due to its more extensive data content. This is a data cut-off that was not initially pre-specified, which was submitted to the EMA on request.

Extent and probability of the additional benefit

Mortality

The overall survival endpoint is defined in the iLLUMINATE study as time from randomisation to death from any cause.

For this endpoint, no statistically significant difference was found between the two treatment arms (hazard ratio (HR): 1.21; [95 % confidence interval (CI): 0.55; 2.68]; p value 0.638). At the time of the second data cut-off, few events had been reported in both the ibrutinib arm (n = 15 (20.5 %)) and the comparator arm (n = 12 (16.7 %)). It should be noted that the results on the overall survival endpoint are still not particularly informative, especially due to the low event rates in the study arms and the relatively short observation period.

With regard to the overall survival endpoint, no additional benefit for ibrutinib in combination with obinutuzumab has been proven.

Morbidity

*Progression-free survival (PFS IRC)*

The primary endpoint of the iLLUMINATE study is progression-free survival, assessed by an independent review committee (IRC). It is operationalised as the time from randomisation to the onset of disease progression (as per the criteria of the IWCL (International Workshop on Chronic Lymphocytic Leukemia)) or death. The IRC assessed the data only up to the first data cut-off. A significantly longer progression-free survival was demonstrated in patients treated with ibrutinib in combination with obinutuzumab vs chlorambucil in combination with obinutuzumab (HR: 0.25; [95% CI: 0.14; 0.46]; p value < 0.0001).

The PFS endpoint is a combined endpoint composed of endpoints of the "mortality" and "morbidity" categories. The endpoint component mortality is already surveyed via the endpoint overall survival as an independent endpoint. The morbidity component "disease progression" is assessed according to IWCL criteria and thus predominantly by means of laboratory parametric, imaging and haematological procedures. Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on additional benefit remains unaffected.

*Health status*

In the iLLUMINATE study, health status is assessed using EQ-5D VAS. The pharmaceutical company has presented analyses of mean change in health status from start of study to each respective time of measurement. This revealed a statistically significant difference to the

detriment of ibrutinib + obinutuzumab. However, the 95% confidence interval is not completely outside the irrelevance range of −0.2 to 0.2. Consequently, it cannot be concluded with sufficient certainty that the effects are clinically relevant in each case.

Quality of life

No quality of life data was collected in the iLLUMINATE study.

Side effects

*Adverse events (AEs) in total*

The results for the “combined adverse events” endpoint are presented only on a supplementary basis.

98.6 % of the patients treated with ibrutinib + obinutuzumab and 97.2 % with chlorambucil + obinutuzumab suffered an adverse event.

*Serious adverse events (SAEs)*

The event time analyses reveal a statistically significant difference in favour of ibrutinib + obinutuzumab (HR: 0.52; [95% CI: 0.28; 0.97]; p = 0.040). In the ibrutinib arm, 42 patients (57.5%) experienced a SAE compared to 27 patients (38.0%) in the comparator arm. The sex of patients was an effect modifier.

*Severe adverse events (CTCAE grade ≥ 3)*

A statistically significant benefit in favour of ibrutinib + obinutuzumab was found in the event time analyses (HR: 0.48; [95% CI: 0.31; 0.73]; p < 0.001). 58 patients (79.5 %) in the test arm and 55 patients (77.5 %) in the comparator arm experienced an event. Both sex and age of patients were effect modifiers.

*Discontinuation due to AEs (≥ 1 active ingredient)*

With regard to the "termination due to AEs" endpoint, no significantly difference between the two study arms was identified (HR: 0.51; [95% CI: 0.17; 1.50]; p = 0.220).

*Specific AEs*

Specific AEs were selected by the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.

In detail, for the specific AEs "reactions associated with infusion (PT, AEs)", "severe neutropoenia (PT, CTCAE grade ≥ 3)" and "nausea (PT, AEs)", a statistically significant difference in favour of ibrutinib + obinutuzumab was observed. The "neutropoenia" endpoint is subject to the sex and CIRS (Cumulative Illness Rating Scale) effect modifiers. For the specific AEs "cardiac disorders" and “skin and subcutaneous tissue disorders" (SOC, AEs)", a statistically significant difference was observed to the detriment of ibrutinib + obinutuzumab. No statistically significant difference between the two treatment arms was observed for the endpoint "Infections and infestations (SOC, AEs)".

Effect modifications were identified for SAEs and severe (CTCAE grade ≥ 3) AEs and severe neutropoenia (CTCAE grade ≥ 3). For women, a statistically significant benefit was found both in relation to serious AEs (HR: 0.24; [95% CI: 0.07; 0.87]; p = 0.029, severe AEs (CTCAE grade ≥ 3; HR: 0.18; [95% CI: 0.07; 0.44]; p < 0.001) and severe neutopoenias (CTCAE grade ≥ 3; HR: 0.09; [95% CI: 0.02; 0,42]; p = 0.002), whereas there was no statistically significant difference for men.

When interpreting this result, relevant uncertainties resulting from the small number of patients in the respective sub-groups should be taken into account.

The sex effect modification is a relevant result in the context of the benefit assessment. However, the available data is not sufficient to derive separate statements with the necessary certainty on additional benefit.

In summary, with regards to the side effects endpoints, a benefit was demonstrated for occurrence of serious adverse events and severe (CTCAE grade ≥ 3) adverse events for ibrutinib + obinutuzumab. In detail, the benefits are particularly evident with regard to acutely occurring side effects. The benefit with regard to severe neutropoenia (CTCAE grade ≥ 3) is not associated with a benefit with regard to the occurrence of infections. Due to the short period of observation in the comparator arm, on the basis of the event time analyses it is only possible to arrive at comparative statements for the period of the first six months of therapy. Comparative conclusions regarding longer-term side effects cannot be made on the basis of the data.

Overall, therefore, with regards to the side effects category, a minor benefit for the combination ibrutinib + obinutuzumab was established.

Overall assessment/conclusion

The benefit assessment of ibrutinib in combination with obinutuzumab to treat adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR) draws on data from the iLLUMINATE study on mortality, morbidity and side effects compared with chlorambucil in combination with obinutuzumab.

With regards to overall survival, no statistically significant difference was established between the two treatment arms. An additional benefit for this endpoint is therefore not proven. In this context, it should be noted that the results on the overall survival endpoint are still not particularly informative, especially due to the low event rates in the study arms and the relatively short observation period.

With regards to the morbidity category, no clinically relevant difference in health status between ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab could be established with sufficient certainty using EQ-5D VAS.

Data on quality of life were not collected in the iLLUMINATE study.

In the side effects category, ibrutinib + obinutuzumab was shown to be beneficial with regard to serious adverse events and severe (CTCAE grade ≥ 3) adverse events. The benefits are evident in detail especially in the case of acutely occurring side effects. Due to the short period of observation in the comparator arm, on the basis of the event time analyses it is, nevertheless, only possible to arrive at comparative statements for the period of the first six months of therapy.

Overall, a minor additional benefit has been established for ibrutinib in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR).

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of an open, randomised controlled trial. The risk of bias across endpoints is classified as low.

However, in the side-effects category, the primary basis for identification of an additional benefit, a high risk of bias must be assumed. This is particularly attributable to the significantly diverging observational periods of 40.5 months in the test arm vs 6.1 months in the control arm, making a comparison on the basis of event time analyses only possible for the 6.1 months.

As a result, in the overall view, the reliability of data for the additional benefit determined is considered as a hint.

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

An additional benefit has not been proven for therapy with ibrutinib in combination with obinutuzumab to treat adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons.

Justification:

The pharmaceutical company presented a descriptive comparison of individual study arms. To this end, to investigate the combination ibrutinib + obinutuzumab, the company drew on the iLLUMINATE study. To establish the appropriate comparator therapy of ibrutinib monotherapy, the company incorporated studies by Burger (2019), Woyach (2018) and Ahn (2018).

As described by the pharmaceutical company, a dramatic effect is missing which would allow to establish an additional benefit given the heterogeneous design of the studies at hand.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient ibrutinib.

The therapeutic indication assessed here is as follows: Ibrutinib in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Ibrutinib has received marketing authorisation as an orphan drug.

In the therapeutic indication to be considered, three patient groups were distinguished:

a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Patient group a):

The appropriate comparator therapy was determined by the G-BA as follows:

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)

The pharmaceutical company has not submitted data to prove an additional benefit. Thus, an additional benefit is not proven.

Patient group b):

The appropriate comparator therapy was determined by the G-BA as follows:

- Bendamustine in combination with rituximab

*or*

- Chlorambucil in combination with rituximab or obinutuzumab

To prove an additional benefit, the pharmaceutical company submitted findings from a sub-population of the iLLUMINATE study, which compared ibrutinib + obinutuzumab with chlorambucil + obinutuzumab.

In the mortality category, no statistically significant difference was found between the treatment arms.

Similarly, for the morbidity category no differences that could be interpreted with sufficient certainty as clinically relevant could be identified.

No quality of life data was collected.

In the side effects category a statistically significant benefit was shown for SAEs and severe (CTCAE grade ≥ 3) AEs. These are particularly evident with regard to acutely occurring side effects. On the basis of the event-time analyses, however, comparative statements can only be derived for the first six months of treatment.

Overall, the G-BA has identified a minor additional benefit on account of the benefits in the side effects category.

In particular due to the significantly diverging observational periods for side effects, the reliability of the finding of an additional benefit is considered as a hint.

Patient group c):

The appropriate comparator therapy was determined by the G-BA as follows:

- Ibrutinib

The pharmaceutical company presented a descriptive comparison of individual arms of the iLLUMINATE study and the studies by Burger (2019), Woyach (2018) and Ahn (2018).

The additional benefit cannot be assessed based on the evidence provided. Thus, 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).

Patient numbers are based on the data from the pharmaceutical company's dossier. These figures were already the basis for the resolutions on ibrutinib of 15 December 2016 (patient populations 1, 2 and 3) and of 21 July 2016 (patient population 3). As already stated in the resolution of 15 December 2016, their derivation is subject to uncertainties. For patient group 1, an overestimate should be assumed. This results in a tendency to underestimate patient groups 2 and 3.

## 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 Imbruvica® (active ingredient: ibrutinib) at the following publicly accessible link (last access: 2 January 2020):

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

Treatment with ibrutinib in combination with obinutuzumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with chronic lymphocytic leukaemia.

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2020).

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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 employed in calculating the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment duration:

| Designation of the therapy | Treatment mode | Number of treatments/patient/year | Treatment duration/treatment (days) | Treatment days/patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Ibrutinib | continuously, 1 × daily | 365 | 1 | 365 |
| Obinutuzumab | every 28 days on day 1 + 2, 8 and 15 of cycle 1 and on day 1 of cycles 2–6 | 6 cycles | 1 | 9 |
| Appropriate comparator therapy | | | | |
| a) For patients for whom treatment with fludarabine in combination with cyclophosphamide and rituximab is feasible | | | | |
| Fludarabine + cyclophosphamide + rituximab (FCR) | | | | |
| Fludarabine | every 28 days on day 1, 2, and 3 | 6 cycles | 3 | 18 |
| Cyclophosphamide | every 28 days on day 1, 2, and 3 | 6 cycles | 3 | 18 |
| Rituximab | every 28 days on day 1 | 6 cycles | 1 | 6 |
| b) For patients for whom treatment with FCR is not feasible: | | | | |
| Bendamustine + rituximab (BR)[2] | | | | |
| Bendamustine | every 28 days on day 1 and 2 | 6 cycles | 2 | 12 |
| Rituximab | every 28 days on day 1, (cycle 1 day 0) | 6 cycles | 1 | 6 |
| Chlorambucil + rituximab (ClbR)[3] | | | | |

[2] 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.
[3] Goede V *et al.* Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20; 370(12):1101–10.

| Designation of the therapy | Treatment mode | Number of treatments/patient/year | Treatment duration/treatment (days) | Treatment days/patient/ year |
|---|---|---|---|---|
| Chlorambucil | every 28 days on day 1 and 15 | 6 cycles | 2 | 12 |
| Rituximab | every 28 days on day 1 | 6 cycles | 1 | 6 |
| Chlorambucil + obinutuzumab | | | | |
| Chlorambucil | every 28 days on day 1 and 15 | 6 cycles | 2 | 12 |
| Obinutuzumab | every 28 days on day 1 + 2, 8 and 15 of cycle 1 and on day 1 of cycles 2–6 | 6 cycles | 1 | 9 |
| c) For patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons | | | | |
| Ibrutinib | | | | |
| Ibrutinib | continuously, 1 × daily | 365 | 1 | 365 |

Usage and consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[4].

| Designation of the therapy | Dosage/ application | Dosage/patient/treatment days | Consumption by potency/treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Ibrutinib | 420 mg | 420 mg | 1 × 420 mg | 365 | 365 × 420 |

[4] Federal health reporting. Average body measurements of the population (2017, both sexes), www.gbe-bund.de

| Designation of the therapy | Dosage/ application | Dosage/patient/treatment days | Consumption by potency/treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | | | | | mg |
| Obinutuzumab | Cycle 1<br>Day 1: 100 mg day 2: 900 mg day 8: 1,000 mg day 15: 1,000 mg<br>Cycle 2–6:<br>Day 1: 1,000 mg | 1,000 mg | 1 × 1,000 mg | 9 | 8 × 1,000 mg |
| Appropriate comparator therapy | | | | | |
| a) For patients for whom treatment with fludarabine in combination with cyclophosphamide and rituximab is feasible | | | | | |
| Fludarabine + cyclophosphamide + rituximab (FCR)[5] | | | | | |
| Fludarabine | 25 mg/m$^2$ | 47.5 mg | 1 × 50 mg | 18 | 18 × 50 mg |
| Cyclophosphamide | 250 mg/m$^2$ | 475 mg | 1 × 500 mg | 18 | 18 × 500 mg |
| Rituximab | Cycle 1:<br>375 mg/m$^2$<br>Cycle 2–6:<br>500 mg/m$^2$ | Cycle 1:<br>712.5 mg<br>Cycle 2–6:<br>950 mg | Cycle 1:<br>3 × 100 mg<br>1 × 500 mg<br>Cycle 2–6:<br>2 × 500 mg | 6 | 3 × 100 mg<br>11 × 500 mg |
| b) For patients for whom treatment with FCR is not feasible: | | | | | |
| Bendamustine + rituximab (BR) | | | | | |
| Bendamustine | 70 mg/m$^2$ | 133 mg | 6 × 25 mg | 12 | 72 × 25mg |
| Rituximab | Cycle 1:<br>375 mg/m$^2$<br>Cycle 2–6:<br>500 mg/m$^2$ | Cycle 1:<br>712.5 mg<br>Cycle 2–6:<br>950 mg | Cycle 1:<br>3 × 100 mg<br>1 × 500 mg<br>Cycle 2–6:<br>2 × 500 mg | 6 | 3 × 100 mg<br>11 × 500 mg |
| Chlorambucil + rituximab (ClbR) | | | | | |
| Chlorambucil | 0.5 mg/kg | 38.5 mg | 19 × 2 mg | 12 | 228 × 2 mg |
| Rituximab | Cycle 1:<br>375 mg/m$^2$<br>Cycle 2–6:<br>500 mg/m$^2$ | Cycle 1:<br>712.5 mg<br>Cycle 2–6:<br>~ 950 mg | Cycle 1:<br>3 × 100 mg<br>1 × 500 mg<br>Cycle 2–6:<br>2 × 500 mg | 6 | 3 × 100 mg<br>11 × 500 mg |
| Chlorambucil + obinutuzumab | | | | | |

[5] The basis for the calculation is the total consumption for a complete treatment over 6 cycles.

| Designation of the therapy | Dosage/ application | Dosage/patient/treatment days | Consumption by potency/treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Chlorambucil | 0.5 mg/kg | 38.5 mg | 19 × 2 mg | 12 | 228 × 2 mg |
| Obinutuzumab | Cycle 1<br>Day 1: 100 mg day 2: 900 mg day 8: 1,000 mg day 15: 1,000 mg<br>Cycle 2–6:<br>Day 1: 1,000 mg | 1,000 mg | 1 × 1,000 mg | 9 | 8 × 1,000 mg |
| c) For patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons | | | | | |
| Ibrutinib | | | | | |
| Ibrutinib | 420 mg | 420 mg | 1 × 420 mg | 365 | 365 × 420 mg |

Costs:

**Costs of the medicinal product:**

| Designation of the therapy | Package 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 | | | | | |
| Ibrutinib 420 mg | 28 FCT | € 5,978.75 | € 1.77 | € 0.00 | € 5,976.98 |
| Obinutuzumab 1,000 mg | 1 CIS | € 3,489.34 | € 1.77 | € 0.00 | € 3,487.57 |
| Appropriate comparator therapy | | | | | |
| Bendamustine 25 mg | 5 DSS | € 374.54 | € 1.77 | € 17.25 | € 355.52 |
| Chlorambucil 2 mg | 50 FCT | € 137.48 | € 1.77 | € 67.76 | € 67.95 |
| Cyclophosphamide 500 mg | 6 DSS | € 81.98 | € 1.77 | € 8.98 | € 71.23 |
| Fluadarabine 50 mg | 5 DSS | € 546.58 | € 1.77 | € 25.41 | € 519.40 |
| Fluadarabine 50 mg | 1 vial | € 118.26 | € 1.77 | € 5.09 | € 111.40 |
| Ibrutinib 420 mg | 28 FCT | € 5,978.75 | € 1.77 | € 0.00 | € 5,976.98 |
| Rituximab 100 mg | 2 CIS | € 716.94 | € 1.77 | € 39.08 | € 676.09 |
| Rituximab 500 mg | 1 CIS | € 1,777.06 | € 1.77 | € 98.21 | € 1,677.08 |

| Designation of the therapy | Package size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Acronyms: FCT = film-coated tablets; CIS = concentrate for infusion solution; DSS = dry substance without solvent | | | | | |

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2020

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 standard expenditure in the course of the treatment are not shown.

| Designation of the therapy | Type of service | Cost per package or service | Treatment days per year | Annual costs per patient |
|---|---|---|---|---|
| Ibrutinib | HBV test<br>Hepatitis B surface antigen status (fee schedule number 32781) | € 5.50 | 1 | € 5.50 |
| | Hepatitis B antibody status (fee schedule number 32614) | € 5.90 | 1 | € 5.90 |
| Rituximab | HBV test<br>Hepatitis B surface antigen status (fee schedule number 32781) | € 5.50 | 1 | € 5.50 |
| | Hepatitis B antibody status (fee schedule number 32614) | € 5.90 | 1 | € 5.90 |
| | Pre-medication<br>Antihistamines<br>e.g. dimetindene i.v. 4 mg<br>Antipyretics<br>e.g. Paracetamol 2 x 500 mg | <br><br>€ 14.88<br><br>€ 1.36[6] | <br><br>6<br><br>6 | <br><br>€ 44.64<br><br>€ 1.36 |

[6] Non-prescription medicinal products that are reimbursable at the expense of the SHI in accordance with Section 12, paragraph 7 AM-RL (information as accompanying medication in the product information of the prescription medicinal product) are not subject to the current medicinal product price regulation. Instead, for these, in accordance with Section 129, paragraph 5a SGB V when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

| | | | | |
|---|---|---|---|---|
| Obinutuzumab | HBV test<br>Hepatitis B surface antigen status (fee schedule number 32781) | € 5.50 | 1 | € 5.50 |
| | Hepatitis B antibody status (fee schedule number 32614) | € 5.90 | 1 | € 5.90 |
| | Pre-medication<br>Corticosteroid<br>e.g. dexamethasone i.v. 5 × 4 mg<br>Antihistamines<br>e.g. dimetindene i.v. 4 mg<br>Antipyretics<br>e.g. Paracetamol 2 x 500 mg | <br>€ 14.44[7]<br><br>€ 14.88<br><br>€ 1.36[6] | <br>9<br><br>9<br><br>9 | <br>€ 72.20<br><br>€ 59.52<br><br>€ 1.36 |

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

## 3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 November 2018.

On 30 August 2019, the pharmaceutical company submitted a dossier for the benefit assessment of ibrutinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

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Based on a fixed reimbursement rate.

By letter dated 2 September 2019 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 ibrutinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 6 January 2020.

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 were discussed at the session of the subcommittee on 11 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal Products | 27 November 2018 | Determination of the appropriate comparator therapy |
| Subcommittee Medicinal Products | 6 January 2020 | Conduct of the oral hearing |
| Working group Section 35a | 15 January 2020<br>22 January 2020<br>5 February 2020 | Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure |
| Subcommittee Medicinal Products | 11 February 2020 | Concluding discussion of the draft resolution |
| Plenum | 20 February 2020 | Adoption of the resolution on the amendment of Annex XII of the AM-RL |

Berlin, 20 February 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken