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 (Chronic Lymphoblastic Leukaemia, First-line, in Combination with Rituximab)

From 1 April 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 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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient Ibrutinib (Imbruvica) was listed for the first time on 01 November 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 28 August 2020, Imbruvica received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

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

Within the previously approved therapeutic indications, the sales volume of Ibrutinib with the statutory health insurance at pharmacy retail prices, including value-added tax exceeded € 50 million. Proof must therefore be provided for Ibrutinib in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 25 September 2020, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company

has 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 (combined with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL)). The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 4 January 2021 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA 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 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 ibrutinib (Imbruvica) in accordance with the product information

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

Therapeutic indication of the resolution (resolution from 01.04.2021):

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with previously untreated chronic lymphocytic leukaemia, 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, not eligible for therapy with FCR

– Bendamustine in combination with rituximab

or

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

– Chlorambucil in combination with rituximab or obinutuzumab

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to 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 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 a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. Approved for this therapeutic indication are acalabrutinib, ibrutinib, idelalisib and venetoclax ; the anti-CD-20 antibodies obinutuzumab and rituximab; the cytostatics bendamustine, chlorambucil, cyclophosphamide and fludarabine; as well as the glucocorticoids prednisone and prednisolone. Chronic lymphocytic leukaemia is assigned to non-Hodgkin lymphoma. Accordingly, the drugs cytarabine, doxorubicin, trofosfamide, vinblastine and vincristine are also approved. The approvals are partly tied to certain combination partners.

on 2. Allogeneic stem cell transplantation is, in the present therapeutic indication, 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 therapy situation.

on 3. For the present therapeutic indication, the G-BA has passed resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredients ibrutinib, idelalisib, obinutuzumab and venetoclax.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines and reviews of clinical studies in the present indication.

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

According to the available evidence, patients with previously untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation who are physically fit are

primarily treated with intensive chemoimmunotherapy consisting of fludarabine, cyclophosphamide and rituximab (FCR). To assess whether a patient can be treated with FCR, the general condition, co-morbidities, organ functions and age are all taken into account.

If patients cannot be treated with FCR chemoimmunotherapy (sub-population b), guidelines recommend a combination therapy consisting of a chemotherapeutic agent and a CD20 antibody. According to the marketing authorisation, bendamustine in combination with rituximab and chlorambucil in combination with either rituximab or obinutuzumab are considered appropriate.

Due to the clear inferiority to chemoimmunotherapy, the guidelines do not recommend mono-chemotherapy as first-line therapy for either fit or unfit patients.

According to the statements of the AkdÄ, monotherapy with ibrutinib or combination therapy consisting of ibrutinib or venetoclax and a monoclonal antibody (MoAb) directed against CD20 is also possible for patients in good general condition. Regarding the use of ibrutinib, however, the AkdÄ points out that the guidelines on which it is based have not yet taken into account more recent results on sometimes severe cardiovascular side effects.

For ibrutinib monotherapy, no additional benefit could be determined in the benefit assessment published in the decision of 15 December 2016 in the respective subpopulations. In the resolution of 20 February 2020, a hint of a minor additional benefit was determined for ibrutinib in combination with the anti-CD20 moAK obinutuzumab in the sub-population of patients who are not eligible for therapy with FCR. This additional benefit was based on an advantage in the side effects category, although conclusions could only be made for the first 6 months of therapy based on the time-to-event analysis presented. The current clinical value of this combination is still unclear based on the AkdÄ's statements. The combination of venetoclax and the anti-CD20-MoAb obinutuzumab is a relatively new therapeutic option. In the resolution of 15 October 2020, no additional benefit was determined for the respective sub-populations either. Also, acalabrutinib has recently been approved as monotherapy or in combination with obinutuzumab to treat patients with previously untreated CLL. A benefit assessment procedure is currently being carried out for this combination. The status of this new therapy is also unclear at present. Overall, both in the subpopulation of patients for whom therapy with FCR is an option and for those for whom therapy with FCR is not an option, the G-BA considers ibrutinib as monotherapy or in combination with obinutuzumab and venetoclax in combination with obinutuzumab as well as acalabrutinib as monotherapy or in combination with obinutuzumab currently not an appropriate comparator therapy. Following the recommendations from guidelines and considering the respective authorisation status, the combinations bendamustine in combination with rituximab, chlorambucil combined with rituximab or chlorambucil in combination with obinutuzumab is equally appropriate treatment options for patients who are not eligible for therapy with FCR.

On the other hand, for patients with a 17p deletion and/or a TP53 mutation, these guidelines provide a clear recommendation for therapy with ibrutinib following the statements of the AkdÄ. The reason is that these patients under treatment with chemoimmunotherapy generally have a poor response rate, a comparatively rapid occurrence of relapses and a comparatively low life expectancy. In addition to ibrutinib, two other active ingredients, idelalisib and venetoclax, have been approved for this group of patients. However, the guideline recommendations and the statements of the AkdÄ primarily focus on ibrutinib. Considering these recommendations and the benefit assessments carried out, as well as taking into account the approved therapeutic indication of the active ingredients and combinations of active ingredients, only ibrutinib is determined as the appropriate comparator therapy for this patient population. Therapy options are limited for patients without a 17p deletion or TP53 mutation for whom chemoimmunotherapy is unsuitable, e.g. because of their poor general condition or

contraindications. Based on the existing evidence, the G-BA considers it appropriate to designate ibrutinib as an appropriate comparator therapy for this patient group.

The findings made in Annex XII do not limit the scope for treatment required to fulfil the medical treatment order.

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, eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

There is a hint for a considerable additional benefit for ibrutinib in combination with rituximab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia eligible for therapy with FCR.

Justification:

To prove the additional benefit, the pharmaceutical company presented results from a relevant sub-population of the E1912/PCYC-1126e-CA study (hereinafter ECOG-E1912).

The ECOG-E1912 study is an open, randomised controlled trial in which ibrutinib in combination with rituximab is compared to immunochemotherapy of fludarabine + cyclophosphamide + rituximab. The study is being carried out at 201 centres located exclusively in the USA and is still ongoing.

The study included adult patients with untreated CLL requiring treatment according iwCLL (International Workshop on Chronic Lymphocytic Leukaemia) criteria or small-cell lymphocytic lymphoma (SLL) according to WHO criteria. The presence of a 17p deletion was an exclusion criterion for the study.

The randomisation in the intervention or control arm was carried out in a ratio of 2:1 and stratified according to the characteristics age (<60 years vs ≥ 60 years), ECOG-PS (0 or 1 vs 2), Rai stage (I- II vs III-IV) and cytogenetic status at the time of enrolment (11q deletion vs other).

To form the relevant subpopulation of patients suitable for FCR therapy, the pharmaceutical company defined the criteria TP53 mutation (unmutated), creatinine clearance (≥ 70 ml/min), age (≤ 65 years), ECOG-PS (< 2), Cumulative Illness Rating Scale (CIRS) (≤ 6), number of platelets (≥ 100,000/µl) and haemoglobin (≥ 10 g/dl). Thus, the pharmaceutical company followed the procedure in previous benefit assessments.

The formation of the relevant sub-population, from the original 529 patients included in study 141 remained in the intervention arm and 65 in the control arm. The average age of the sub-population was 55. 85% of the patients presented Rai stage 0, I or II and thus a mild illness. 82% of patients in the ibrutinib arm and 91% of patients in the FCR arm had CLL. After the sub-populations were formed, there were noticeable differences between the treatment arms about the feature duration of illness at the time of enrolment (intervention arm: 9.7 months; control arm: 17.0 months). Furthermore, there are clear imbalances regarding the feature Immunoglobulin Heavy Chain Variable Region (IGHV) mutation status: 70% of the patients had non-mutated IGHV in the test arm and 49% in the control arm, while 20% presented a mutated IGHV in the test arm and 31% in the control arm. The IGHV status was unknown for 11% of the patients in the trial arm and 20% of the patients in the control arm.

The rituximab dose in cycle 1 was divided into 2 partial doses in the control arm in deviation from the product information. Apart from that, the applications in the intervention and control arms were compliant with marketing authorisation: In the intervention arm, ibrutinib was

administered until disease progression or until unacceptable intolerance, and rituximab was administered in cycles 2 to 7. In the control arm, FCR therapy was carried out in 6 cycles.

No data on subsequent therapies are available in the ECOG-E1912 study.

The pharmaceutical company submitted results for 2 data cut-offs. Concerning overall survival, the results of the 2nd data cut-off requested by the EMA from 2 August 2019. This only includes evaluations on overall survival and the primary endpoint PFS (progression-free survival). Accordingly, for the other endpoints, the results of the 1st data cut-off from 17 July 2018 are considered.

Extent and probability of the additional benefit

Mortality

Overall survival

For overall survival, there was a statistically significant difference in favour of ibrutinib in combination with rituximab compared to immunochemotherapy FCR (hazard ratio (HR): 0.06 [95% confidence interval (CI): 0.01; 0.48]; p value < 0.001). It should be noted here that no event had occurred in the intervention arm up to the point in time of the 2nd data cut-off. To calculate the effect estimator and the confidence interval, a result had to be simulated in this arm. At this point in time, 7 events had occurred in the comparison arm.

It should be noted that the significance of the event rates is limited due to the previously low event rates. Given the size of the effect and even considering the limitations, the advantage in overall survival with ibrutinib + rituximab is classified as a clear therapeutic improvement.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint in the ECOG-E1912 study. In the present case, the endpoint is operationalised as the time from randomisation to disease progression or death from any cause. The assessment of disease progression is done by the ECOG-ACRIN Data Safety Monitoring Committee on the basis of iwCLL criteria. At the time of the 2nd data cut-off there was a statistically significant advantage in favour of ibrutinib + rituximab (HR: 0.25; [95% CI: 0.14; 0.48]; p < 0.0001).

The PFS endpoint is a combined endpoint composed of endpoints of the "mortality" and "morbidity" categories. The "mortality" endpoint component is already assessed via the "overall survival" endpoint 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 into consideration the aforementioned aspects, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

FACT-Leu TOI

In the ECOG-E12 study, only the FACT-Leu modules *Well-being* and *Functional Well-being* and the leukaemia-specific module were used in the FACT-Leu TOI assessment. The modules on social/family and emotional well-being, on the other hand, were not taken into account. Considering this, the FACT-Leu TOI is assigned to the morbidity category.

The FACT-Leu-TOI was collected up to 3 years after the time of enrolment. For the benefit assessment, the pharmaceutical company presented MMRM evaluations on the mean change in the course of the study compared to the start of the study.

There were no statistically significant differences between the two treatment arms.

Overall, there are, therefore neither advantages nor disadvantages for ibrutinib in combination with rituximab for this endpoint.

Quality of life

No data on quality of life are available. The assessment using FACT-Leu TOI was assigned to the endpoint category morbidity.

Side effects

The side effects were recorded in both study arms up to 30 days after the end of therapy or 1 day before the start of subsequent therapy. Due to the strongly differing treatment duration in the treatment arms, the median observation duration for this endpoint diverged significantly in both study arms (intervention arm: 34.1 months vs control arm 4.8 months). Therefore, based on the time-to-event analysis in the side effects category, only comparative statements can be derived for the first 9 months.

Adverse events (AE) in total

The results for the endpoint total adverse events are only presented supplementary.

In both the intervention arm and the control arm, 100% of patients suffered an adverse event.

Serious adverse events (SAE)

No evaluations are available for this endpoint.

Severe adverse events (CTCAE grade ≥ 3)

The time-to-event analyses show a statistically significant difference to the advantage of ibrutinib in combination with rituximab.

Discontinuation because of AE (≥ 1 component)

Concerning the endpoint discontinuation due to AEs, there was a statistically significant difference in favour of ibrutinib + rituximab.

Specific AEs

The selection of specific AEs was made according to the methodology of the IQWiG using events based on frequency and differences between treatment arms and taking into account patient relevance.

In detail, when looking at the specific adverse events for the endpoints "Infection of the upper respiratory tract (PT, AEs)", "Nausea (PT, AEs)", "Constipation (PT, AEs)", "Vomiting (PT, AEs) ", " Decreased appetite (PT, AEs) ", " Pollakiuria (PT, AEs) ", "Lymphopenia (PT, severe AEs) ", "Leukopenia (PT, severe AEs) "," Febrile neutropenia (PT, severe AEs)", "Thrombocytopenia (PT, severe AEs)", "and "Hyperglycaemia (PT, severe AEs)" all showed statistically significant differences in favour of ibrutinib in combination with rituximab.

For the specific AEs, "Haemorrhage (SMQ haemorrhage terms [excl. laboratory terms], AEs)", "Contusion (PT, AEs)", "Leukocytosis (PT, severe AEs)" and "Lymphocytosis (PT, severe AEs)", the time-to-event analysis show a statistically significant disadvantage for ibrutinib in combination with rituximab compared to FCR.

As in the comparator arm, no event has occurred, no time-to-event analysis are performed for the endpoints "Severe haemorrhage (SMQ haemorrhage terms [excl. laboratory terms], serious AEs)" and "Cardiac disorders (SOC, serious AEs)".

Overall, in the side effects category, there are predominantly advantages for ibrutinib in combination with rituximab compared to therapy with FCR. This can be seen for the overall rates of severe AEs and discontinuation due to AEs, as well as in detail for the specific AEs. No data on SAEs are available. When considering the adverse events, it has to be noticed that due to the short observation period in the control arm, comparative statements based on the time-to-event analysis can be derived only for the first 9 months after randomisation. For the longer term occurring side effects, no statements can be made based on the time-to-event analysis. While ibrutinib + rituximab therapy with ibrutinib is planned until progression, the use of FCR is limited to 6 cycles.

<u>Overall assessment / conclusion</u>

For evaluating the additional benefit of ibrutinib in combination with rituximab in adult patients with previously untreated chronic lymphocytic leukaemia eligible for treatment with FCR, there are data of a relevant sub-population of the study ECOG-E12 compared to FCR for the endpoint categories mortality, morbidity and side effects.

Concerning overall survival, there is a statistically significant advantage of ibrutinib in combination with rituximab over FCR. As a limitation, it has to be considered that only a very small number of events occurred up to the underlying 2nd data cut-off. However, regardless of this limitation, the benefit can be classified as a clear therapeutic improvement due to the size of the effect.

Based on the data collected using FACT-Leu TOI, there was no statistically significant difference between the two treatment arms in the category morbidity.

The data presented by the pharmaceutical company for the category quality of life were assigned to the category morbidity in the benefit assessment. There are, therefore, no assessable data in the category quality of life.

There were advantages about the overall rates of severe AEs and therapy discontinuation due to AEs under ibrutinib + rituximab for the endpoint category side effects. When looking at the specific AEs, there are also predominantly advantages in the intervention arm. It has to be taken into account that only comparative statements for the period of the first 9 months after randomisation can be derived on the basis of the time-to-event analysis. For the longer term occurring side effects, no statements can be made based on the time-to-event analysis. While ibrutinib + rituximab therapy with ibrutinib is planned until progression, the use of FCR is limited to 6 cycles.

Overall, there is, therefore, a clear advantage in overall survival and, at the same time, predominantly advantages in the category side effects.

Overall, based on the available data for ibrutinib in combination with rituximab for adult patients with previously untreated chronic lymphocytic leukaemia and eligible for an FCR therapy, a considerable additional benefit compared to FCR combination therapy can be derived.

Reliability of data (probability of additional benefit)

Data from the open, randomised, controlled study ECOG-E12 are available.

Due to the open study designs, all endpoints present a high risk of bias except the endpoints overall survival and the endpoints concerning severe AEs (CTCAE grade ≥ 3).

Regarding the overall endpoint survival, uncertainties remain since the assessment is based on very small numbers of events.

For the endpoints in the category side effects, uncertainties arise due to the short observation time in the control arm. As a result, only comparative statements for the first 9 months after randomisation can be derived based on the time-to-event analyses.

There are uncertainties concerning the assessments using FACT-Leu TOI due to a diverging questionnaire response in both study arms in the category morbidity.

Uncertainties also exist due to the formation of the sub-population. Among them are imbalances between the study arms concerning the duration of the disease at the time of enrolment.

Overall, the limitations mentioned above lead to the conclusion that the reliability of data drawn for the additional benefit is classified as a hint.

b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR

An additional benefit is not proven for ibrutinib in combination with rituximab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR.

Justification:

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

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons

An additional benefit is not proven for ibrutinib in combination with rituximab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons.

Justification:

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

2.1.4 Limitation of the period of validity of the resolution

The period of validity of the statements made in the resolution on the patient population a) "Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for a therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)" finds its legal basis in Section 35a (3) sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

The present benefit assessment is based on the results of the 2nd data cut-off from 2 August 2019 for the endpoint overall survival and the results of the 1st data cut-off from 17 July 2018 for further endpoints. The 2nd data cut-off was requested by the EMA. The 1st data cut-off, on the other hand, is a pre-specified interim analysis of the PFS, with which the pre-specified effectiveness criterion for the PFS was achieved. At this point in time, there was only a very small number of events in the outcome overall survival. According to the study protocol, the secondary endpoint overall survival was tested the first time when the efficacy criterion for the PFS was reached. This testing should continue annually until reaching the criteria for the premature end of the study or the occurrence of 125 deaths.

Since clinical data concerning the overall survival are expected to be relevant for the assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of ibrutinib.

For this purpose, the G-BA considers a limitation for the resolution until 01 April 2024 to be appropriate.

Conditions for the limitation:

For the renewed benefit assessment after the expiry of the deadline, the dossier should be submitted with all patient-relevant endpoints. In this case, for the endpoint overall survival, the data based on the data cut-off before the deadline of the annual data cut-offs regarding the overall survival should be considered.

A change in the time limit can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of ibrutinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of ibrutinib (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO).

The possibility that a benefit assessment for ibrutinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is 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 rituximab 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 CLL, eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

b) Adult patients with previously untreated CLL, not eligible for therapy with FCR

c) Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons

Patient group a)

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

– FCR

The pharmaceutical company presents data from a relevant subpopulation of the RCT ECOG-E1912 (ibrutinib + rituximab vs FCR).

Data on overall survival (OS), morbidity and adverse events (AEs) are available.

With regard to the OS, ibrutinib + rituximab presents a statistically significant advantage, which is evaluated as a clear therapeutic improvement in therapeutic benefit.

In terms of morbidity, there is no statistically significant difference.

There are advantages for ibrutinib + rituximab with regard to severe AEs and discontinuation due to AEs. When looking at the specific AEs, there are also predominantly advantages for ibrutinib + rituximab in detail.

Uncertainties arise specifically due to the low number of OS events and since the time-to-event analysis for the AEs only allows comparative statements for the first 9 months after randomisation.

Overall, due to the significant advantage in OS and the benefits to the AEs, it is possible to determine a hint of a considerable additional benefit for ibrutinib + rituximab.

The resolution for this group of patients is limited until 1 April 2024.

Patient group b)

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

– Bendamustine in combination with rituximab

or

– Chlorambucil in combination with rituximab or obinutuzumab

The pharmaceutical company did not submit any data to prove the additional benefit. Thus, an additional benefit is not proven.

Patient group c)

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

– Ibrutinib

The pharmaceutical company did not submit any data to prove the additional benefit. Thus, an additional benefit is not proven.

2.2 Number of patients or demarcation of patients eligible for treatment

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

The patient numbers are based on the information from the pharmaceutical company's dossier. The figures were already in line with the resolutions on ibrutinib of 15 December 2016 and 20 January 2020 (patient population 1, 2 and 3) as well as of 21 July 2016 (patient population 3) and also the resolution on venetoclax (patient population 1, 2 and 3) of 15 October 2020. As already stated concerning the resolution of 15 December 2016, the derivation is subject to uncertainties. An overestimation tends to be assumed for patient group 1. This tends to result in an underestimation for 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: 29 January 2021):
https://www.ema.europa.eu/documents/product-information/imbruvica-epar-product-information_de.pdf

Treatment with ibrutinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in treating patients with multiple myeloma.

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 March 2021):

To improve comparability, the costs of the medicinal products were approximated both based on the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. 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 used to calculate the "number of treatments/patient/year", time intervals between individual treatments, and 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)	Days of treatment/ patient/ year
Medicinal product to be assessed:				
Ibrutinib	continuously, 1 x daily	365	1	365
Rituximab	Day 1[2] of 28 day cycle	6 cycles	1	6
Appropriate comparator therapy				
a) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR				
Fludarabin + cyclophosphamide + rituximab (FCR)[3]				
Fludarabine	Day 1, 2 and 3 of 28 day cycle	6 cycles	3	18
Cyclophosphamide	Day 1, 2 and 3 of 28 day cycle	6 cycles	3	18
Rituximab	Day 1 of 28 day cycle	6 cycles	1	6
b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR				
Bendamustine + rituximab (BR)[4]				
Bendamustine	Day 1 and 2 of 28 day cycle	6 cycles	2	12
Rituximab	Day 1 of 28 day cycle	6 cycles	1	6
Chlorambucil + rituximab (ClbR)[5]				
Chlorambucil	Day 1 and 15 of 28 day cycle	6 cycles	2	12
Rituximab	Day 1 of 28 day cycle	6 cycles	1	6
Chlorambucil + obinutuzumab				
Chlorambucil	Day 1 and 15 of 28 day cycle	6 cycles	2	12

[2]In cycle 1, the rituximab dose is applied on 2 days (50 mg / m² on day 1, 325 mg / m² on day 2).
[3]The basis for the calculation is the total consumption for a complete treatment over 6 cycles.
[4] 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
[5] Goede, V., et al., Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.N Engl J Med, 2014. 370(12): p. 1101-10

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Obinutuzumab	Cycle 1: Day 1+ 2, 8 and 15, cycle 2 – 6: Day 1 of 28 day cycle each	6 cycles	4 (cycle 1) 1 (cycle 2– 6)	9
c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons.				
Ibrutinib				
Ibrutinib	continuously, 1 x daily	365	1	365

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). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916.[6]

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 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
Appropriate comparator therapy					
a) Adult patients with previously untreated chronic lymphocytic leukaemia, eligible for therapy with FCR					
Fludarabin + cyclophosphamide + rituximab (FCR)					
Fludarabine	25 mg/m²	47,5 mg	1 x 50 mg	18	18 x 50 mg
Cyclo-phosphamide	250 mg/m²	475 mg	1 x 500 mg	18	18 x 500 mg

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

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
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	6	3 x 100 mg 11 x 500 mg
b) Adult patients with previously untreated chronic lymphocytic leukaemia, not eligible for therapy with FCR					
Bendamustine + rituximab (BR)					
Bendamustine	70 mg/m^2	133 mg	6 x 25 mg	12	72 x 25mg
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	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/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	6	3 x 100 mg 11 x 500 mg
Chlorambucil + obinutuzumab					
Chlorambucil	0.5 mg/kg	38,5 mg	19 x 2 mg	12	228 x 2 mg
Obinutu-zumab	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
c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53 mutation or unsuitable for chemoimmunotherapy due to other reasons.					
Ibrutinib					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg

Costs:

Costs of the medicinal product:

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:					
Ibrutinib 420 mg	28 FTA	€ 5,772.62	€ 1.77	€ 0.00	€ 5,770.85
Rituximab 100 mg	2 IFC	€ 716.94	€ 1.77	€ 39.08	€ 676.09
Rituximab 500 mg	1 IFC	€ 1,777.06	€ 1.77	€ 98.21	€ 1,677.08
Appropriate comparator therapy					
Bendamustine 25 mg	5 PIC	€ 402.03	€ 1.77	€ 49.49	€ 350.77
Chlorambucil 2 mg	50 FTA	€ 36.31	€ 1.77	€ 1.40	€ 33.14
Cyclophosphamid 500 mg	6 PIE	€ 81.98	€ 1.77	€ 8.98	€ 71.23
Fludarabine 50 mg	5 DSS	€ 546.58	€ 1.77	€ 25.41	€ 519.40
Fludarabine 50 mg	1 CII	€ 118.26	€ 1.77	€ 5.09	€ 111.40
Ibrutinib 420 mg	28 FTA	€ 5,772.62	€ 1.77	€ 0.00	€ 5,770.85
Obinutuzumab 1000 mg	1 IFC	€ 3,489.34	€ 1.77	€ 0.00	€ 3,487.57
Rituximab 100 mg	2 IFC	€ 716.94	€ 1.77	€ 39.08	€ 676.09
Rituximab 500 mg	1 IFC	€ 1,777.06	€ 1.77	€ 98.21	€ 1,677.08
Abbreviations: FTA = film-coated tablets; IFC/CII = concentrate for the preparation of an infusion solution; PIE = powder for concentrate for solution for infusion, PIC = powder for the preparation of an infusion solution concentrate; DSS = dry substance without solvent					

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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 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	Days of treatment per year	Annual costs per patient
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
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. dimetinden 4 mg	€ 14.93	6	€ 44.79
	Antipyretics e.g. paracetamol 2 x 500 mg	€ 1.36	6	€ 1.36
Obinutuzumab	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
	Premedication Corticosteroid e.g. dexamethasone 5 x 4 mg	€ 14.44[7]	9	€ 72.20
	Antihistamines e.g. dimetinden 4 mg	€ 14.93	9	€ 59.72
	Antipyretics e.g. paracetamol 2 x 500 mg	€ 1.36[8]	9	€ 1.36

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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum of € 81 per ready-to-use preparation and for the production of parenteral

On the basis of a fixed amount

[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 accompanying 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 €)

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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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 23 June 2020.

On 25 September 2020, 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.

By letter dated 28 September 2020, 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 23 December 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 4 January 2021. The deadline for submitting written statements was 25 January 2021.

The oral hearing was held on 8 February 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 were discussed at the session of the subcommittee on 23 March 2021, and the draft resolution was approved.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 January 2016	Determination of the appropriate comparator therapy
Working group Section 35a	2 February 2021	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	8 February 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 February 2021 16 February 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 March 2021	Concluding consultation of the draft resolution
Plenum	1 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 April 2021

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

Prof. Hecken