Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Ibrutinib (New Therapeutic Indication: Chronic Lymphocytic Leukaemia, First-line, Combination with Venetoclax)

of 20 July 2023

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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient ibrutinib (Imbruvica) was listed for the first time on 1 November 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 23 March 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for ibrutinib in the therapeutic indication in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia according to Section 35a paragraph 5b SGB V. At its session on 5 May 2022, the G-BA approved the application to postpone the relevant date in accordance with Section 35a paragraph 5b SGB V.

On 2 August 2022, ibrutinib received an extension of the marketing authorisation for the therapeutic indication in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. The extension of the marketing authorisation for the therapeutic indication in combination with venetoclax for the treatment

of adult patients with previously untreated chronic lymphocytic leukaemia is classified as a major type 2 variation as defined according to Annex 2 number 2 letter a 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, of 12.12.2008, sentence 7).

The bundling procedure was terminated upon notification by the pharmaceutical company on 16 December 2022 that the planned additional new therapeutic indication had been withdrawn from the EMA. By letter dated 21 December 2022, the pharmaceutical company was requested, pursuant to Chapter 5 Section 11, paragraph 3 of the Rules of Procedure (VerfO) of the G-BA, to submit a complete dossier to the G-BA in due time, i.e. within 4 weeks of receipt of the letter.

The benefit assessment of ibrutinib in the therapeutic indication in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia will therefore start on 1 February 2023.

The pharmaceutical company submitted a dossier for the active ingredient ibrutinib with the new therapeutic indication in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia in due time on 18 January 2023 pursuant to Section 4, paragraph 3, number 3 of the German Regulation on the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA in conjunction with No. 3 of the resolution of 5 May 2023 on the application pursuant to Section 35a paragraph 5b SGB V (ibrutinib), according to which, if no further marketing authorisation is granted for a therapeutic indication within the six-month period and the benefit assessments commences within four weeks of the request by the G-BA.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 May 2023 on the G-BA website (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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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:

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Therapeutic indication of the resolution (resolution of 20.07.2023):

Imbruvica in combination with venetoclax 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:

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

Appropriate comparator therapy for ibrutinib in combination with venetoclax:

- Ibrutinib

or

- Ibrutinib in combination with rituximab or obinutuzumab

or

- Fludarabine in combination with cyclophosphamide and rituximab [FCR] (only for patients without genetic risk factors and < 65 years of age who are eligible for therapy with FCR on the basis of their general condition and comorbidities)

or

- Bendamustine in combination with rituximab (only for patients without genetic risk factors and who are ineligible for therapy with FCR according to the above criteria)

or

- Chlorambucil in combination with rituximab or obinutuzumab (only for patients without genetic risk factors and who are ineligible for therapy with FCR according to the above criteria)

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In addition to ibrutinib, the cytostatic agents bendamustine, chlorambucil and fludarabine; the B-cell receptor inhibitors zanubrutinib, acalabrutinib and idelalisib; the BCL-2 inhibitor venetoclax; the anti-CD-20 antibodies obinutuzumab and rituximab; and the glucocorticoids prednisolone and prednisone are available for the treatment of previously untreated CLL according to the marketing authorisation. The chronic lymphocytic leukaemia is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients cyclophosphamide, dexamethasone, doxorubicin, etoposide, mitoxantrone, vinblastine and vincristine also have a marketing authorisation for the present therapeutic indication. Some of the marketing authorisations are tied to specific concomitant active ingredients.

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

on 3. For the present therapeutic indication, the resolutions of the G-BA on the benefit assessment of medicinal products with the following new active ingredients according to Section 35a SGB V are available:
- Acalabrutinib (resolutions of 3 June 2021)
- Ibrutinib (resolutions of 1 April 2021, 20 February 2020, 15 December 2016 and 21 July 2016)
- Idelalisib (resolutions of 16 March 2017)
- Obinutuzumab (resolution of 4 November 2021)
- Venetoclax (resolutions of 15 October 2020 and 16 May 2019)
- Zanubrutinib (resolution of 15 June 2023)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

Chronic lymphocytic leukaemia (CLL) and small-cell lymphocytic lymphoma (SLL) are considered as one entity according to the WHO classification.

For the present therapeutic indication, it is presumed that the patients are in need of treatment (for example, stage C Binet). Furthermore, for the present therapeutic indication, it is assumed that an allogeneic stem cell transplantation is not indicated at the time of therapy.

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

According to both the guidelines and the written statement of DGHO e.V. (German Society for Haematology and Medical Oncology), a therapy based on a Bruton Tyrosine Kinase (BTK) inhibitor can be considered for patients with previously untreated CLL. This recommendation applies regardless of the presence of genetic risk factors. In addition to ibrutinib in combination with venetoclax, a marketing authorisation exists for ibrutinib as monotherapy or in combination with rituximab or obinutuzumab, for the BTK inhibitor acalabrutinib as monotherapy or in combination with obinutuzumab, and for the BTK inhibitor zanubrutinib as monotherapy.

In the benefit assessment of ibrutinib as monotherapy in the patient population which is unsuitable for chemoimmunotherapy and in which a 17p deletion or TP53 mutation is present, the G-BA identified a hint for a non-quantifiable additional benefit compared with best supportive care in its resolution of 21 July 2016. The benefit assessment of the combination ibrutinib + rituximab resulted in a hint for a considerable additional benefit for the sub-population of patients who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR) compared to FCR (resolution of 1 April 2021). The combination of ibrutinib + obinutuzumab was assessed by the G-BA as having a hint for a minor additional benefit compared to chlorambucil + obinutuzumab for patients who are ineligible for therapy with FCR (resolution of 1 April 2021).

For both acalabrutinib as monotherapy and in combination with obinutuzumab, the G-BA identified a hint for a minor additional benefit compared to chlorambucil in combination with obinutuzumab for patients who do not have a 17p deletion or TP53 mutation and for whom therapy with FCR is not an option (resolutions of 3 June 2021). There are no consistent recommendations for acalabrutinib as monotherapy or acalabrutinib in combination with obinutuzumab in the available guidelines. The clinical significance of acalabrutinib cannot be conclusively assessed according to the generally recognised state of medical knowledge. Acalabrutinib both as monotherapy and in combination with obinutuzumab is not determined to be an appropriate comparator therapy for the present resolution.

For zanubrutinib, the G-BA identified a hint for a minor additional benefit over bendamustine in combination with rituximab for patients without genetic risk factors who are unsuitable for therapy with FCR on the basis of their general condition and comorbidities (resolution of 15 June 2023).

No uniform recommendations for zanubrutinib emerge from the available guidelines. The clinical significance of zanubrutinib cannot be conclusively assessed according to the generally recognised state of medical knowledge. Zanubrutinib is not determined to be an appropriate comparator therapy for the present resolution.

According to the available evidence, in addition to BTK inhibitors, a therapy with the combination of venetoclax + obinutuzumab is also an option for patients, regardless of the presence of risk factors. In the resolutions of 15 October 2020, no additional benefit was identified for venetoclax in combination with obinutuzumab compared with the corresponding comparator therapies for the sub-populations investigated in each case. Since therapy alternatives with a proven additional benefit are available in a comparable treatment setting, the G-BA does not consider venetoclax in combination with obinutuzumab to be an appropriate comparator therapy.

For patients who do not have any genetic risk factors, chemoimmunotherapy can also be considered according to guidelines and the clinical experts in the written statement procedure. For patients under 65 years of age who have an appropriate general condition and who do not have any relevant comorbidities, a therapy with FCR is recommended as a priority among the chemoimmunotherapies. Chemoimmunotherapies consisting of a chemotherapeutic agent and a CD20 antibody can be considered for patients who are ineligible for therapy with FCR according to the criteria of age, general condition and comorbidities. In this respect, the focus is on the approved treatment options bendamustine in combination with rituximab (BR) as well as chlorambucil in combination with rituximab (ClbR) and chlorambucil in combination with obinutuzumab (ClbO). By resolution of 4 November 2021, the G-BA did not identify any additional benefit for obinutuzumab in combination with chlorambucil compared with the appropriate comparator therapy.

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

According to the recommendations from guidelines and taking into account the respective authorisation status, the therapy options ibrutinib as monotherapy or in combination with rituximab or obinutuzumab, fludarabine in combination with cyclophosphamide and rituximab (FCR), bendamustine in combination with rituximab [BR], chlorambucil in combination with rituximab (ClbR) or chlorambucil in combination with obinutuzumab (ClbO) are determined as appropriate comparator therapies.

The appropriate comparator therapy determined here includes several therapeutic alternatives. In this context, individual therapeutic alternatives only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

The pharmaceutical company only submits data on a sub-population in the therapeutic indication, which is why two patient populations are formed for the present resolution:

a) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without the presence of genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

b) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukaemia (CLL) with genetic risk factors

In summary, the additional benefit of ibrutinib in combination with venetoclax is assessed as follows:

a) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without the presence of genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

An additional benefit is not proven.

Justification:

For the proof of additional benefit of ibrutinib in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia, the pharmaceutical company presented the results of the GLOW study.

The GLOW study is an open-label, multicentre, randomised, controlled phase III study that has been ongoing since April 2018 and compared ibrutinib + venetoclax with chlorambucil + obinutuzumab.

The study is being conducted in 67 study sites across Europe, Asia and North America.

The study enrolled adult patients with previously untreated CLL / small cell lymphocytic lymphoma (SLL) without the presence of a deletion in the short arm of chromosome 17 (17p deletion) or a mutation of the tumour protein p53 (TP53 mutation). Patients had to be in need of treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria (as of 2008). In addition, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 2 and also had to be ≥ 65 years old or - if younger - fulfil at least 1 of the following criteria: Presence of comorbidities (Cumulative Illness Rating Scale [CIRS] > 6) and/or presence of renal impairment (creatinine clearance < 70 ml/min, estimated using Cockcroft-Gault formula).

A total of 106 patients were randomised to the intervention arm ibrutinib + venetoclax and 105 patients to the comparator arm chlorambucil + obinutuzumab. Randomisation was stratified by mutational status of the immunoglobulin heavy chain variable region (IGHV) (mutated vs unmutated vs not evaluable) as well as by the presence of a deletion on chromosome 11 (11q deletion) (yes vs no).

The administration of ibrutinib + venetoclax in the intervention arm and chlorambucil + obinutuzumab in the comparator arm is in accordance with the indications in the product information.

After discontinuation of the study medication (for example due to disease progression), follow-up therapies could be given without restrictions. Patients in both study arms were able to switch to monotherapy with ibrutinib after disease progression.

The primary endpoint of the GLOW study is PFS. Secondary endpoints were overall survival as well as endpoints of the endpoint categories morbidity, health-related quality of life and side effects.

There are a total of two data cut-offs in the dossier:

- 1st data cut-off of 26 February 2021: pre-specified primary analysis, after achieving 89 PFS events (71 events were planned).
- 4th data cut-off of 25 August 2022: non-pre-specified data cut-off with the aim of scientific publication.

Against the background that the 4th data cut-off was neither pre-specified nor requested by a regulatory authority, outcome-driven reporting cannot be ruled out. The results of the 4th data cut-off presented by the pharmaceutical company are therefore not used for the present assessment.

With its written statement, the pharmaceutical company submitted evaluations of the 3rd data cut-off of 17 January 2022 (non-pre-specified, but data cut-off requested by the European Medicines Agency (EMA)).

For the present assessment, the pre-specified data cut-off of 26 February 2021 is used for the endpoint categories of morbidity (except progression-free survival) and health-related quality of life and the 3rd data cut-off of 17 January 2022 requested by the EMA are used for the other endpoints of the categories of mortality and adverse events (AEs).

Relevant sub-population

Patients were enrolled in the GLOW study regardless of whether they were eligible for FCR therapy or not. However, the chemoimmunotherapy administered in the comparator arm consisting of chlorambucil and obinutuzumab is only suitable for patients without genetic risk

factors for whom FCR therapy is not an option, according to the specific appropriate comparator therapy. Therefore, in the dossier as well as in its written statement, the pharmaceutical company presents evaluations of a sub-population which, in its opinion, meets the criteria for treatment with chlorambucil and obinutuzumab.

In order to form the relevant sub-population from the total population of the GLOW study, the pharmaceutical company uses various criteria (age, renal function, thrombocytopenia, anaemia, autoimmune cytopenia, general condition, comorbidities, 17p, TP53, and IGHV mutational status) that may cause unsuitability for FCR therapy.

The criteria applied by the pharmaceutical company are considered by the G-BA to sufficiently reflect the sub-population relevant for the present assessment.

Taking the above criteria into account, the pharmaceutical company thus considered a total of only 47 (22.3%) of the 211 patients in the GLOW study (ibrutinib + venetoclax arm N = 23; chlorambucil + obinutuzumab arm N = 24).

Total population - application of the elevation rule

For the benefit assessment of ibrutinib in combination with ventoclax, the pharmaceutical company applies the elevation rule. The pharmaceutical company describes that there is a reduction in power due to the formation of the sub-population and that a test for an effect at the increased significance level of 15% instead of the usual 5% could be carried out for the applicability of the elevation rule, under certain conditions, in the relevant sub-population of a study, and used to assess the additional benefit.

In the present situation, the pharmaceutical company argues that the relevant sub-population and the entire study population are medically comparable patient collectives, and thus a necessary condition for the application of the elevation rule is fulfilled. However, the non-target population of the GLOW study received a therapy in the comparator arm with chlorambucil in combination with obinutuzumab that does not correspond to the appropriate comparator therapy determined by the G-BA for this population. According to the appropriate comparator therapy, chlorambucil in combination with obinutuzumab is only suitable for patients without genetic risk factors for whom therapy with FCR is not an option. The AkdÄ also states in its written statement that a comparability of the relevant sub-population and the total population is not given due to the poorer prognosis and the poorer response with an unmutated IGHV gene.

Against this background, the approach of the pharmaceutical company to apply the elevation rule is considered inappropriate by the G-BA.

Extent and probability of the additional benefit

Mortality

In the GLOW study, overall survival is defined as time from randomisation to death from any cause.

For the endpoint of overall survival, there is no statistically significant difference between ibrutinib in combination with venetoclax compared to chlorambucil in combination with obinutuzumab.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the GLOW study. It is defined as the time from randomisation to disease progression or death from any cause. Disease progression was assessed using the IWCLL 2008 criteria. The criteria were modified in the GLOW study so that the occurrence of isolated treatment-dependent lymphocytosis alone was not considered as disease progression.

PFS is statistically significantly prolonged with ibrutinib in combination with venetoclax compared to chlorambucil in combination with obinutuzumab.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "Disease progression" is not assessed according to symptoms but predominantly by means of laboratory parametric, imaging and haematological procedures. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The available data on symptomatology, health status and quality of life are used to interpret the PFS result. These data are potentially relevant for interpretation, especially if, as in the present case, disease progression as defined in the study is associated with effects on morbidity and/or quality of life.

The available data from the GLOW study do not show that the prolonged PFS with ibrutinib in combination with venetoclax is associated with an improvement in morbidity (symptomatology, health status) or quality of life. The results on the PFS endpoint are therefore not used in the present assessment.

Symptomatology

Symptomatology was assessed in the GLOW study using the symptom scales of the EORTC QLQ-C30 and the FACIT-Fatigue.

For the endpoint of diarrhoea, assessed using the EORTC QLQ-C30, there is a disadvantage of ibrutinib in combination with venetoclax.

For each of the other endpoints, there is no statistically significant difference between the treatment groups.

Overall, neither positive nor negative effects are derived for ibrutinib in combination with venetoclax with regard to symptomatology.

Health status

The health status is assessed in the GLOW study using the EQ-5D visual analogue scale (VAS).

For the endpoint of health status, there is no statistically significant difference between the treatment arms.

In the overall analysis of the results on symptomatology as well as the health status, no relevant difference for the benefit assessment between the treatment groups was found.

Quality of life

The quality of life of the GLOW study patients is assessed using the functional scales of the EORTC QLQ-C30 questionnaire.

There was no statistically significant difference between the treatment groups for any of the scales of the health-related quality of life.

The overall results show neither positive nor negative effects for ibrutinib in combination with venetoclax with regard to health-related quality of life.

Side effects

Adverse events in total

Almost all participants in the GLOW study experienced adverse events. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Specific AEs

For each of the endpoints of bleeding (AE), bleeding (severe AE), cardiac disorders (severe AE) as well as infections and infestations (severe AE), there is no statistically significant difference between the treatment groups.

For the endpoint of infusion-related reaction, the evaluation submitted by the pharmaceutical company is unsuitable for the assessment of additional benefit, but serious and severe infusion reactions are considered in the overall rates of SAEs and severe AEs.

In the overall analysis of the results on side effects, there is neither an advantage nor a disadvantage of ibrutinib in combination with venetoclax.

Overall assessment

For the assessment of the additional benefit of ibrutinib in combination with venetoclax, results are available from the GLOW study in comparison with chlorambucil in combination with obinutuzumab for the endpoint categories of mortality, morbidity, quality of life and side effects.

For the benefit assessment, the pharmaceutical company uses a sub-population of the GLOW study. These are patients without genetic risk factors who are ineligible for therapy with FCR.

For the endpoint of overall survival, there is no statistically significant difference between ibrutinib in combination with venetoclax compared to chlorambucil in combination with obinutuzumab.

With regard to symptomatology (assessed using the EORTC QLQ-C30 and FACIT-Fatigue) and health status (assessed using the EQ5D-VAS), no relevant difference for the benefit assessment was found between the treatment groups.

With regard to the endpoint category of health-related quality of life (assessed using EORTC QLQ-C30), there were neither positive nor negative effects of ibrutinib in combination with venetoclax.

For the endpoint category of side effects, there is neither an advantage nor a disadvantage of ibrutinib in combination with venetoclax.

Against the background of the small number of patients in the relevant sub-population, there is low precision of the results on the endpoints overall.

In the overall assessment, no additional benefit of ibrutinib in combination with venetoclax over chlorambucil in combination with obinutuzumab is identified for adult patients with previously untreated chronic lymphocytic leukaemia (CLL) without the presence of genetic risk factors, who are unsuitable for therapy with FCR on the basis of their general condition and comorbidities.

b) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukaemia (CLL) with genetic risk factors

An additional benefit is not proven.

Justification:

For adults with previously untreated chronic lymphocytic leukaemia (CLL) without the presence of genetic risk factors who are suitable for therapy with FCR on the basis of their general condition and comorbidities and for adults with genetic risk factors, the pharmaceutical company does not submit any data for the assessment of the additional benefit. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product "IMBRUVICA" with the active ingredient ibrutinib. The therapeutic indication assessed here is as follows: "IMBRUVICA in combination with venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)."

In the therapeutic indication under consideration, the appropriate comparator therapy was determined as follows:

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

The appropriate comparator therapy includes monotherapy with ibrutinib and combination therapy of ibrutinib in combination with rituximab or obinutuzumab, as well as chemoimmunotherapy with FCR, BR, ClbR or ClbO, with limitations for certain patients.

The pharmaceutical company only submits data on one sub-population in the therapeutic indication, which is why two sub-populations are formed for the present resolution:

a) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without the presence of genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

b) Adults with previously untreated chronic lymphocytic leukaemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukaemia (CLL) with genetic risk factors

About patient group a)

The pharmaceutical company submits data from a sub-population of the GLOW study comparing ibrutinib + venetoclax with chlorambucil + obinutuzumab.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

With regard to symptomatology (assessed using the EORTC QLQ-C30 and FACIT-Fatigue) and health status (assessed using the EQ5D-VAS), no relevant difference for the benefit assessment was found between the treatment groups.

With regard to the endpoint category of health-related quality of life (assessed using EORTC QLQ-C30), there were neither positive nor negative effects of ibrutinib in combination with venetoclax.

For the endpoint category of side effects, there is neither an advantage nor a disadvantage of ibrutinib in combination with venetoclax.

Against the background of the small number of patients in the relevant sub-population, there is low precision of the results on the endpoints overall.

In the overall assessment, no additional benefit of ibrutinib + venetoclax over chlorambucil + obinutuzumab is identified.

About patient group b)

No data are available to allow an assessment of the additional benefit. An additional benefit compared to the appropriate comparator therapy is therefore not proven.

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

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

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

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of zanubrutinib (resolution of 15 June 2023).

As already stated in the resolution on zanubrutinib, the number of patients specified in relation to the total population of all adults with newly diagnosed CLL is plausible in the order of magnitude, with minor uncertainties.

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: 6 July 2023):

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

Treatment with ibrutinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology 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 July 2023).

For the cost representation of ibrutinib in combination with venetoclax, the CLL3011 study cited in section 5.1 of the product information is used.

The publications by Fischer K. et al.[2], Eichhorst, B., et al.[3], and Goede, V., et al.[4] were used for the cost representation of fludarabine in combination with cyclophosphamide and rituximab, bendamustine in combination with rituximab as well as chlorambucil in combination with rituximab against the background of the lack of information on dosage in the respective product information. The information on the duration of treatment (6 cycles) is based on the information in the rituximab product information. According to the rituximab product information, it is administered in combination with chemotherapy for a total of 6 cycles.

Treatment period:

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 varies from patient to patient 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 the maximum treatment duration, if specified in the product information.

[2] Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicentre phase II trial of the German Chronic Lymphocytic Leukaemia Study Group. J Clin Oncol. 2012 Sep 10;30(26):3209-16 https://ascopubs.org/doi/10.1200/JCO.2011.39.2688

[3] Eichhorst, B., et al., First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): Lancet Oncol. 2016 Jul;17(7):928-942

[4] 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)	Treatment days/ patient/ year
Medicinal product to be assessed				
1st year (cycle 1-13)[5]				
Ibrutinib	Continuously, 1 x daily	365	1	365
Venetoclax	Cycle 4: 1 x daily for every 7 days in 4 dosage steps	28	1	28
	Cycle 5–13 Continuously 1 x daily	253	1	253
2nd year (cycle 14-15)				
Ibrutinib	Continuously 1 x daily	55	1	55
Venetoclax	Continuously 1 x daily	55	1	55
Appropriate comparator therapy				
Ibrutinib monotherapy				
Ibrutinib	Continuously, 1 x daily	365	1	365
Ibrutinib in combination with rituximab				
Ibrutinib	Continuously, 1 x daily	365	1	365
Rituximab[6]	Cycle 1:[5] Day 1 and 2 Cycle 2 - 6: Day 1	6	Cycle 1: 2 Cycle 2 - 6: 1	7
Ibrutinib in combination with obinutuzumab				
Ibrutinib	Continuously, 1 x daily	365	1	365
Obinutuzumab	Every 28 days on day 1, 2, 8 and 15 of cycle 1 and on day 1	6	Cycle 1: 4 Cycle 2 - 6: 1	9

[5] A cycle comprises 28 days.
[6] In cycle 1, the rituximab dose is administered on 2 days (50 mg/m² on day 1, 325 mg/m² on day 2)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	of cycle 2 - 6[7]			
Fludarabine in combination with cyclophosphamide and rituximab [FCR][8]				
Fludarabine	Day 1, 2 and 3 of a 28-day cycle	6	3	18
Cyclophosphamide	Day 1, 2 and 3 of a 28-day cycle	6	3	18
Rituximab	Day 1 of a 28-day cycle	6	1	6
Bendamustine in combination with rituximab[9]				
Bendamustine	Day 1 and 2 of a 28-day cycle	6	2	12
Rituximab	Day 1 of a 28-day cycle	6	1	6
Chlorambucil in combination with rituximab[10]				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6	2	12
Rituximab	Day 1 of a 28-day cycle	6	1	6
Chlorambucil in combination with obinutuzumab				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6	2	12
Obinutuzumab	Cycle 1: Day 1 + 2, 8 and 15 Cycle 2 - 6: Day 1 of 28-days cycle each	6	Cycle 1: 4 Cycle 2 - 6: 1	9

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

[8] Eichhorst, B., et al., First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): Lancet Oncol. 2016 Jul;17(7):928-942

[9] Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicentre phase II trial of the German Chronic Lymphocytic Leukaemia Study Group. J Clin Oncol. 2012 Sep 10;30(26):3209-16 https://ascopubs.org/doi/10.1200/JCO.2011.39.2688

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

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[11]

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
1st year (cycle 1-13)					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Venetoclax	Cycle 4:				
	20 mg	20 mg	2 x 10 mg	7.0	14 x 10 mg
	50 mg	50 mg	1 x 50 mg	7.0	7 x 50 mg
	100 mg	100 mg	100 mg	7.0	7 x 100 mg
	200 mg	200 mg	2 x 100 mg	7.0	14 x 100 mg
	Cycle 5–13				
	400 mg	400 mg	4 x 100 mg	253.0	1012 x 400 mg
2nd year (cycle 14-15)					
Ibrutinib	420 mg	420 mg	1 x 420 mg	55.0	55 x 420 mg
Venetoclax	400 mg	400 mg	4 x 100 mg	55.0	220 x 100 mg
Appropriate comparator therapy					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Ibrutinib in combination with rituximab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Rituximab	Cycle 1: Day 1: 50 mg/m² Day 2:	Cycle 1: Day 1: 95 mg Day 2:	Cycle 1: Day 1: 1 x 100 mg Day 2:	7.0	3 x 100 mg + 11 x 500 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	325 mg/m² Cycle 2 - 6: 500 mg/m²	617.5 mg cycle 2 - 6: 950 mg	2 x 100 mg + 1 x 500 mg Cycle 2 - 6: 2 x 500 mg		
Ibrutinib in combination with obinutuzumab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Obinutuzumab	Cycle 1: Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg Cycle 2 - 6 Day 1: 1000 mg	Cycle 1: Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg Cycle 2 - 6 Day 1: 1000 mg	1 x 1,000 mg	9.0	8 x 1,000 mg
Fludarabine in combination with cyclophosphamide and rituximab [FCR]					
Fludarabine	25 mg/m²	47.5 mg	1 x 50 mg	18.0	18 x 50 mg
Cyclophosphamide	250 mg/m²	475 mg	1 x 500 mg	18.0	18 x 500 mg
Rituximab	Cycle 1: 375 mg/m² Cycle 2 - 6 Day 1: 500 mg/m²	Cycle 1: 712.5 mg Cycle 2 - 6 Day 1: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6 Day 1: 2 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
Bendamustine in combination with rituximab [BR]					
Bendamustine	90 mg/m²	171 mg	1 x 100 mg + 3 x 25 mg	12.0	12 x 100 mg + 36 x 25 mg
Rituximab	Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m²	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
Chlorambucil in combination with rituximab					
Chlorambucil	0.5 mg/kg	38.5 mg	19 x 2 mg	12.0	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m²	Cycle 1: 712.5 mg	Cycle 1: 3 x 100 mg	6.0	3 x 100 mg +

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Cycle 2 - 6: 500 mg/m²	Cycle 2 - 6: 950 mg	1 x 500 mg Cycle 2 - 6: 2 x 500 mg		11 x 500 mg
Chlorambucil in combination with obinutuzumab					
Chlorambucil	0.5 mg/kg	38.5 mg	19 x 2 mg	12.0	228 x 2 mg
Obinutuzumab	Cycle 1: Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg Cycle 2 - 6 Day 1: 1000 mg	Cycle 1: Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg Cycle 2 - 6 Day 1: 1000 mg	1 x 1,000 mg	9.0	8 x 1,000 mg

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ibrutinib 420 mg	28 FCT	€ 5,852.87	€ 2.00	€ 236.41	€ 5,614.46
Venetoclax 10 mg	14 FCT	€ 86.95	€ 2.00	€ 2.99	€ 81.96
Venetoclax 50 mg	7 FCT	€ 200.46	€ 2.00	€ 7.48	€ 190.98
Venetoclax 100 mg	7 FCT	€ 389.63	€ 2.00	€ 14.96	€ 372.67
Venetoclax 100 mg	14 FCT	€ 767.97	€ 2.00	€ 29.93	€ 736.04
Venetoclax 100 mg	112 FCT	€ 5,926.27	€ 2.00	€ 239.40	€ 5,684.87
Appropriate comparator therapy					
Ibrutinib 420 mg	28 FCT	€ 5,852.87	€ 2.00	€ 236.41	€ 5,614.46
Rituximab 100 mg	2 CIS	€ 748.07	€ 2.00	€ 69.93	€ 676.14
Rituximab 500 mg	2 CIS	€ 3,639.48	€ 2.00	€ 350.68	€ 3,286.80

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
Rituximab 500 mg	1 CIS	€ 1,819.89	€ 2.00	€ 172.53	€ 1,645.36
Obinutuzumab 1000 mg	1 CIS	€ 2,649.21	€ 2.00	€ 253.73	€ 2,393.48
Cyclophosphamide 500 mg	6 PSI	€ 84.41	€ 2.00	€ 9.25	€ 73.16
Fludarabine 50 mg	1 CIS	€ 118.50	€ 2.00	€ 5.09	€ 111.41
Fludarabine 50 mg	5 DSS	€ 546.82	€ 2.00	€ 25.41	€ 519.41
Bendamustine 100 mg	1 PIC	€ 331.00	€ 2.00	€ 40.46	€ 288.54
Bendamustine 100 mg	5 PIC	€ 1,620.92	€ 2.00	€ 204.07	€ 1,414.85
Bendamustine 25 mg	1 PIC	€ 99.35	€ 2.00	€ 11.15	€ 86.20
Bendamustine 25 mg	5 PIC	€ 414.39	€ 2.00	€ 51.01	€ 361.38
Chlorambucil 2 mg	50 FCT	€ 37.73	€ 2.00	€ 2.51	€ 33.22
Abbreviations: HC = hard capsules, FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution, PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate, DSS = dry substance without solvent					

LAUER-TAXE® last revised: 01 July 2023

Costs for additionally required SHI services:

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Premedication:

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

In the context of premedication, additionally required SHI services are incurred that usually differ between the medicinal product to be assessed and rituximab as well as obinutuzumab (in the combination therapy) as an appropriate comparator therapy and are consequently taken into account as additionally required SHI services in the resolution.

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	Treatment days/ year	Costs/ patient/ year
Appropriate comparator therapy:							
Ibrutinib in combination with rituximab							
Dimetindene (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	7.0	€ 48.42
Paracetamol[12] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	7.0	€ 3.01
Ibrutinib in combination with obinutuzumab							
Dimetindene (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	9.0	€ 64.56
Paracetamol[12] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	9.0	€ 3.01
Dexamethasone [12] (5 x 4 mg IV)	10 SFI each 4 mg	€ 16.89	€ 2.00	€ 0.44	€ 14.45	9.0	€ 72.25
Fludarabine in combination with cyclophosphamide and rituximab [FCR]							
Dimetindene (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	6.0	€ 48.42
Paracetamol[12] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Bendamustine in combination with rituximab [BR]							
Dimetindene (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	6.0	€ 48.42
Paracetamol[12] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Chlorambucil in combination with rituximab							
Dimetindene (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	6.0	€ 48.42
Paracetamol[12] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Chlorambucil in combination with obinutuzumab							
Dimetindene (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	9.0	€ 64.56
Paracetamol[12] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	9.0	€ 3.01

[12] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Dexamethasone [12] (5 x 4 mg IV)	10 SFI each 4 mg	€ 16.89	€ 2.00	€ 0.44	€ 14.45	9.0	€ 72.25

Diagnosis of hepatitis B infection

Patients should be tested for HBV infection before starting treatment with ibrutinib. These examinations are also required when using rituximab, bendamustine and obinutuzumab as an appropriate comparator therapy. Since there is no regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, the costs for additionally required SHI services for tests for hepatitis B are not presented in the resolution.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation 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).

[12] Fixed reimbursement rate

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Ibrutinib

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 24 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 18 January 2023, 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 2 in conjunction with No. 3 of the resolution of 5 May 2023 on the application in accordance with Section 35a, paragraph 5b SGB V (ibrutinib).

By letter dated 26 January 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 24 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2023. The deadline for submitting statements was 23 May 2023.

The oral hearing was held on 5 June 2023.

By letter dated 6 June 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 30 June 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 11 July 2023, and the proposed resolution was approved.

At its session on 20 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 August 2021	Determination of the appropriate comparator therapy
Working group Section 35a	30 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 June 2023 6 June 2023	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 June 2023 5 July 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 July 2023	Concluding discussion of the draft resolution
Plenum	20 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 July 2023

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

Prof. Hecken