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 Duvelisib (chronic lymphocytic leukaemia, after ≥ 2 prior therapies)

of 21 July 2022

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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 relevant date for the first placing on the (German) market of the active ingredient duvelisib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 1 February 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 2022 on the website of the G-BA (http://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 duvelisib compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, 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 duvelisib.

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 duvelisib (Copiktra) in accordance with the product information

Copiktra monotherapy is indicated for the treatment of adult patients with:
- relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies.
- follicular lymphoma (FL) that is refractory to at least two prior systemic therapies.

Therapeutic indication of the resolution (resolution of 21.07.2022):

Copiktra monotherapy is indicated for the treatment of adult patients with:
- relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) <u>Adult patients with pretreated CLL who have not yet received a BTK inhibitor and/or BCL2 inhibitor</u>

Appropriate comparator therapy:

- Ibrutinib

or

- Venetoclax + rituximab

or

- Chemoimmunotherapy with fludarabine in combination with cyclophosphamide and rituximab (FCR) or bendamustine in combination with rituximab (BR) or chlorambucil

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

in combination with rituximab (CIbR) (only in the case of a long recurrence-free interval and the absence of genetic risk factors)

b) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor

Appropriate comparator therapy:

- Venetoclax + rituximab

c) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BCL2 inhibitor

Appropriate comparator therapy:

- Ibrutinib

d) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor and one BCL2 inhibitor

Appropriate comparator therapy:

- Patient-individual therapy with selection of:
  - idelalisib in combination with rituximab,
  - bendamustine in combination with rituximab,
  - chlorambucil in combination with rituximab and
  - best supportive care;

taking into account comorbidities, general condition, genetic risk factors as well as success and tolerability of prior therapy

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the 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 Duvelisib[2], the cytostatic agents chlorambucil, cyclophosphamide and fludarabine are available for the treatment of relapsed/refractory chronic lymphocytic leukaemia according to the authorisation status, as well as the Bruton's tyrosine kinase inhibitors acalabrutinib and ibrutinib; the BCL2 inhibitor venetoclax; the PI3K inhibitor idelalisib; the anti-CD-20 antibody rituximab and the glucocorticoids prednisolone and prednisone. The chronic lymphocytic leukaemia is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients bendamustine, cytarabine, doxorubicin, etoposide, mitoxantrone, trofosfamide, 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 part of the appropriate comparator therapy.

on 3. The following resolutions and guidelines of the G-BA exist regarding medicinal treatments in the present therapeutic indication:
Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Acalabrutinib (resolution of 5 August 2021)
- Ibrutinib (resolutions of 16 March 2017 and 21 July 2016)
- Idelalisib (resolutions of 16 March 2017 and 15 September 2016)
- Venetoclax (resolution of 16 May 2019)

on 4. The generally state of medical knowledge was illustrated by a systematic search for guidelines as well as 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.

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.

[2]The active ingredient duvelisib is not sold.

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

On the basis of the available evidence, the G-BA considers it appropriate to divide the patients into different patient populations for the appropriate comparator therapy according to the therapeutic indication, which are differentiated depending on the prior therapies - specifically with a BTK inhibitor and/or BCL2 inhibitor:

a) Adult patients with pretreated CLL who have not yet received a BTK inhibitor and/or BCL2 inhibitor

If subjects have not previously received either a BTK or a BCL2 inhibitor, the available evidence suggests that there are several treatment options. The combination therapy venetoclax + rituximab and a therapy with a BTK inhibitor are named as particularly effective treatment options by guidelines and in the written statement of the scientific-medical society.

By resolution of 16 May 2019, the G-BA identified an indication of a minor additional benefit of venetoclax + rituximab compared to BR for patients without a 17p deletion and/or TP53 mutation who have received at least one prior therapy and for whom bendamustine in combination with rituximab (BR) is the appropriate patient-individual therapy.

By resolution of 21 July 2016, the G-BA identified a hint of a non-quantifiable additional benefit of ibrutinib in the benefit assessment over ofatumumab for the patient population for whom chemotherapy is not indicated.

In both the benefit assessment for venetoclax + rituximab and for ibrutinib monotherapy, no data were available for other patient groups that relate to the present patient population. Based on the clear recommendation in guidelines as well as the written statement of the scientific-medical society, both ibrutinib and venetoclax + rituximab are determined as appropriate comparator therapies for the entire patient population a) for patients who have not yet received a BTK inhibitor and/or BCL2 inhibitor. No preference can be derived for one of the two treatment options, so that they are considered to be equally appropriate treatment options.

Acalabrutinib is another approved BTK inhibitor. By resolution of 5 August 2021, the G-BA identified a hint for a considerable additional benefit over idelalisib + rituximab for the patient population following prior therapy who have a 17p deletion or TP53 mutation or for whom chemoimmunotherapy is not indicated for other reasons. No data were available for other patient populations after prior therapy. As acalabrutinib is still a relatively new treatment option whose clinical significance cannot be conclusively assessed at present, acalabrutinib is not currently designated as an appropriate comparator therapy by the G-BA.

In addition, according to guideline recommendations and the written statement of the scientific-medical society, a repetition of the primary therapy (fludarabine + cyclophosphamide + rituximab (FCR), bendamustine + rituximab (BR), chlorambucil + rituximab (ClbR)) can also be considered for subjects who show a late relapse after

chemoimmunotherapy. It must be taken into account that chemoimmunotherapy is only indicated if the patients do not have any genetic risk factors. According to the current state of medical knowledge, the presence of a 17p deletion/ TP53 mutation and an unmutated IGHV status are considered genetic risk factors. For subjects who have a long relapse-free interval and no genetic risk factors, chemoimmunotherapy with FCR, BCR or ClbR, as well as ibrutinib and venetoclax + rituximab are considered equally appropriate treatment options.

b) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor

The present guidelines do not explicitly recommend the use of venetoclax + rituximab after the use of a BTK inhibitor. However, as stated in patient population a), there is a clear recommendation for the use of venetoclax + rituximab in patients with relapsed or refractory CLL. According to the written statement of the German Society for Haematology and Medical Oncology (DGHO), the combination venetoclax + rituximab is the standard therapy for patients with relapsed or refractory CLL. According to the written statement of the DGHO, a repetition of therapy with a BTK inhibitor does not appear to make much sense against the background of the occurrence of specific resistance mutations.

As stated for patient population a), by resolution of 16 May 2019, the G-BA identified a minor additional benefit of venetoclax + rituximab compared with BR for subjects without a 17p deletion and/or TP53 mutation who have received at least one prior therapy and for whom bendamustine in combination with rituximab (BR) is the appropriate patient-individual therapy. No data were available for the other patient populations.

It is assumed that for subjects who have already been treated with a BTK inhibitor but have not yet received therapy with venetoclax + rituximab, repeating chemoimmunotherapy is not a primary consideration.

Overall, venetoclax + rituximab is therefore determined to be the sole appropriate comparator therapy for the present patient group.

c) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BCL2 inhibitor

The guidelines do not explicitly recommend the use of ibrutinib after the use of a BCL2 inhibitor. However, as stated in patient population a), BTK inhibitors are considered a particularly effective treatment option for relapsed or refractory CLL. The critical comments of the DGHO on a possible re-treatment due to specific resistance mechanisms, as explained under patient population b), apply vice versa to a prior therapy with a BCL2 inhibitor.

As stated for patient population a), by resolution of 21 July 2016, the G-BA identified an hint of a non-quantifiable additional benefit of ibrutinib in the benefit assessment compared to ofatumumab + BSC for the patient population for whom chemotherapy is not indicated. No data were available for other patient populations.

It is assumed that for patients who have already been treated with a BCL2 inhibitor but have not yet received therapy with a BTK inhibitor, repeating chemoimmunotherapy is not a primary consideration.
Acalabrutinib is another approved BTK inhibitor for which the G-BA, in its resolution of 5 August 2021, identified a hint for a considerable additional benefit over idelalisib + rituximab for the patient population after prior therapy who have a 17p deletion, TP53 mutation or for whom chemoimmunotherapy is not indicated for other reasons. No data were available for other patient populations after prior therapy. As this is a very novel treatment option whose clinical significance cannot be conclusively assessed at present, acalabrutinib is not currently designated as an appropriate comparator therapy by the G-BA.

Overall, ibrutinib is therefore determined as the sole appropriate comparator therapy for the present patient population.

d) <u>Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor and one BCL2 inhibitor</u>

The therapy of these patients is characterised by patient-individual treatment decisions. The treatment strategy depends in particular on the genetic risk factors on the one hand and on comorbidities, general condition, success and tolerability of the prior therapy on the other.

Taking into account what has been said about the development of resistance mechanisms, patients with relapsed or refractory CLL who have already received both a BTK inhibitor and a BCL2 inhibitor should not primarily be considered for re-treatment with these substance classes.

According to the available guidelines and the written statement of the DGHO, the approved treatment option for this patient population is idelalisib in combination with rituximab. In the benefit assessment of idelalisib in combination with rituximab, an additional benefit was not proven due to lack of data in all patient groups (resolutions of 21 July 2016 and 15 September 2016). In the context of patient-individual therapy, the G-BA nevertheless considers idelalisib + rituximab to be a suitable comparator due to the limited treatment options and the recommendations of the guidelines.

Furthermore, according to the guidelines, the chemoimmunotherapies bendamustine + rituximab and chlorambucil + rituximab can be considered as approved treatment options. Patients with genetic risk factors show a poor response to chemoimmunotherapies, which is why chemoimmunotherapy is not a regular treatment option for these subjects. According to the current state of medical knowledge, the presence of a 17p deletion/ TP53 mutation and an unmutated IGHV status are considered genetic risk factors.

Due to the advanced treatment setting, the G-BA assumes a shift from CLL-specific therapy to best supportive care for a relevant percentage of patients, especially those with a poor general condition. Best Supportive Care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to

alleviate symptoms and improve quality of life. Best supportive care is only considered for patients with low life expectancy and very poor general condition.

Overall, the G-BA thus determines a patient-individual therapy for patients with prior therapy with at least one BTK inhibitor and one BCL2 inhibitor, selecting idelalisib + rituximab, bendamustine + rituximab, chlorambucil + rituximab and best supportive care, taking into account comorbidities, general condition, genetic risk factors as well as success and tolerability of the prior therapy.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of duvelisib is assessed as follows:

a) Adult patients with pretreated CLL who have not yet received a BTK inhibitor and/or BCL2 inhibitor

An additional benefit is not proven.

b) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor

An additional benefit is not proven.

c) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BCL2 inhibitor

An additional benefit is not proven.

d) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor and one BCL2 inhibitor

An additional benefit is not proven.

Justification:

The pharmaceutical company submitted the randomised, open-label, active-controlled phase III DUO study comparing duvelisib with ofatumumab in patients with CLL and small cell lymphocytic lymphoma (SLL) whose disease is refractory after at least one prior therapy for the benefit assessment.

The multicentre DUO study was conducted in Europe, the USA, Australia and New Zealand from 2014 to 2021. A total of 319 subjects were enrolled in the study, 312 of whom had CLL and 7 of whom had SLL. 196 subjects received at least 2 prior therapies, of which 95 subjects

were randomised to the duvelisib arm and 101 subjects to the ofatumumab arm. Patients who had previously received a PI3K or BTK inhibitor were excluded from the study. None of the subjects included in the study had previously received therapy with the BCL2 inhibitor venetoclax. Consequently, the pharmaceutical company also did not submit a separate evaluation for the patient groups defined via the prior therapy with BCL2 or BTK inhibitors.

In the comparator arm of the DUO study, all subjects received the anti-CD-20 antibody ofatumuab, regardless of prior therapy. This has no longer been approved for the treatment of CLL in the EU since 2019 and does not correspond to the appropriate comparator therapy defined by the G-BA for any of the patient groups. The pivotal DUO study submitted by the pharmaceutical company is therefore not suitable for proving the additional benefit of duvelisib compared to the appropriate comparator therapy.
An additional benefit of duvelisib compared to the appropriate comparator therapy is therefore not proven for patient groups a) to d).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Copiktra" with the active ingredient duvelisib. The therapeutic indication assessed here is the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia after at least two prior therapies. In the therapeutic indication to be considered, four patient groups were distinguished:

a) Adult patients with pretreated CLL who have not yet received a BTK inhibitor and/or BCL2 inhibitor

and

b) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor

and

c) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BCL2 inhibitor

and

d) Adult patients with relapsed or refractory CLL after a prior therapy with at least one BTK inhibitor and one BCL2 inhibitor.

For patient groups a) to d)

For the benefit assessment, the pharmaceutical company submits the randomised phase III DUO study comparing duvelisib with ofatumumab in patients with CLL and SLL after at least one prior therapy. All patients in the comparator arm of the study were treated with ofatumumab. Ofatumumab is currently no longer approved for the treatment of CLL. The active ingredient does not correspond to the appropriate comparator therapy for any of the

patient groups mentioned. Therefore, no data suitable for the benefit assessment of duvelisib versus the appropriate comparator therapy are available.

An additional benefit is therefore not proven for patient groups a) to d).

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

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

In the dossier on duvelisib, the pharmaceutical company determines the number of adult patients with relapsed or refractory CLL after at least two prior therapies, without providing information on the individual patient groups, which result from the appropriate comparator therapy determined by the G-BA. As the calculation of patient numbers is subject to considerable uncertainty due to methodological weaknesses, the G-BA bases the resolution on the patient numbers from the resolution on acalabrutinib (resolution of 5 August 2021). This is justified as follows:

In calculating the baseline patient numbers, the pharmaceutical company makes the assumption that the distribution of leukaemia forms in the 5-year prevalence does not differ from the distribution in new cases. This leads to uncertainty.

Furthermore, the percentage values used are only suitable to a very limited extent for determining patients with relapsed or refractory disease after at least 2 prior therapies. These were derived from follow-up observations and a transferability of these percentage values to the prevalent population is not guaranteed. In addition, the upper percentage value was collected from an extremely small patient population, and the transferability of the lower percentage value to the obtained percentage value of the 5-year prevalence is not guaranteed due to the use of a population with prior therapy.

The patient numbers presented in the benefit assessment procedure for acalabrutinib are also subject to uncertainties. The baseline of patients who have received at least one pretreatment used by the pharmaceutical company was originally based on data available in the benefit assessment of idelalisib (resolution of 19 March 2015). The uncertainties were pointed out in the corresponding evaluation. However, the calculated patient numbers for acalabrutinib were in line with the resolution on venetoclax in combination with rituximab (resolution of 16 May 2019).

Despite the uncertainties described in the procedure for acalabrutinib, the patient numbers calculated there appear more plausible. The calculation of patient numbers presented here is therefore not a clearly better estimate than the patient numbers determined in the procedure for acalabrutinib.

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 Copiktra (active ingredient: duvelisib) at the following publicly accessible link (last access: 7 June 2022):
https://www.ema.europa.eu/en/documents/product-information/copiktra-epar-product-information_en.pdf

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

No data on the safety and efficacy of duvelisib are available for patients who have received a BCL2, phosphoinositide 3-kinase or Bruton tyrosine kinase inhibitor prior to therapy with duvelisib.

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 2022; for duvelisib 15 April 2022, duvelisib is currently not sold in Germany).

The annual treatment costs shown refer to the first year of treatment.

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 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 for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Duvelisib	2 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
a) Adult patients with pretreated chronic lymphocytic leukaemia who have not yet received a BTK inhibitor and/or BCL2 inhibitor				
Ibrutinib monotherapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Ibrutinib	1 x daily	365	1	365
Venetoclax + rituximab				
Venetoclax	1 x daily	365	1	365
Rituximab	Day 1 of a 28-day cycle	6	1	6
Chemoimmunotherapy with FCR or BR or ClbR (only in the case of a long recurrence-free interval and the absence of genetic risk factors)				
Fludarabine +cyclophosphamide + rituximab (FCR)[3]				
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 + rituximab (BR)				
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 + rituximab (ClbR)[4]				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6	2	12
Rituximab	Day 1 of a 28-day cycle	6	1	6
b) Adult patients with relapsed or refractory chronic lymphocytic leukaemia after a prior therapy with at least one BTK inhibitor				
Venetoclax + rituximab				
Venetoclax	1 x daily	365	1	365
Rituximab	Day 1 of a 28-day cycle	6	1	6
c) Adult patients with relapsed or refractory chronic lymphocytic leukaemia after a prior therapy with at least one BCL2 inhibitor				
Ibrutinib monotherapy				

[3] The basis for the calculation is the total consumption for a complete treatment over 6 cycles.
[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
Ibrutinib	1 x daily	365	1	365
d) Adult patients with relapsed or refractory chronic lymphocytic leukaemia after a prior therapy with at least one BTK inhibitor and one BCL2 inhibitor				
Idelalisib in combination with rituximab				
Idelalisib	2 x daily	365	1	365
Rituximab	once on week 1, 2, 4, 6, 8, 12, 16 and 20	8	1	8
Bendamustine in combination with rituximab (BR)				
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[4]				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6	2	12
Rituximab	Day 1 of a 28-day cycle	6	1	6
Best supportive care				
Best supportive care	Different from patient to patient			

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

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					
Duvelisib	25 mg	50 mg	2 x 25 mg	365	730 x 25 mg
Best supportive care	Different from patient to patient				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
a) Adult patients with pretreated chronic lymphocytic leukaemia who have not yet received a BTK inhibitor and/or BCL2 inhibitor					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
Venetoclax + rituximab					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5ff: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5ff: 400 mg	Week 1: 2 x 10 mg Week 2: 1 x 50 mg Week 3: 1 x 100 mg Week 4: 2 x100 mg Week 5ff: 4 x100 mg	365	14 x 10 mg + 7 x 50 mg + 1,369 x 100 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	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
Chemoimmunotherapy with FCR or BR or ClbR (only in the case of a long recurrence-free interval and the absence of genetic risk factors)					
Fludarabine + cyclophosphamide + rituximab (FCR)					
Fludarabine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	18	18 x 50 mg
Cyclophosphamide	250 mg/m² = 475 mg	475 mg	1 x 500 mg	18	18 x 500 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Bendamustine + rituximab (BR)					
Bendamustine	90 mg/m² = 171 mg	171 mg	7 x 25 mg	12	84 x 25 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	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	38.5 mg	19 x 2 mg	12	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	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 relapsed or refractory chronic lymphocytic leukaemia after a prior therapy with at least one BTK inhibitor					
Venetoclax + rituximab					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5ff: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5ff: 400 mg	Week 1: 2 x 10 mg Week 2: 1 x 50 mg Week 3: 1 x 100 mg Week 4: 2 x100 mg Week 5ff: 4 x100 mg	365	14 x 10 mg + 7 x 50 mg + 1,369 x 100 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg; cycle 2 - 6: 500 mg/m² = 950 mg	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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
c) Adult patients with relapsed or refractory chronic lymphocytic leukaemia after a prior therapy with at least one BCL2 inhibitor					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
d) Adult patients with relapsed or refractory chronic lymphocytic leukaemia after a prior therapy with at least one BTK inhibitor and one BCL2 inhibitor					
idelalisib in combination with rituximab					
Idelalisib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2–8: 500 mg/m² = 950 mg	Cycle 1: 712.5 mg Cycle 2 - 8: 950 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 - 8: 2 x 500 mg	8	3 x 100 mg + 15 x 500 mg
Bendamustine in combination with rituximab					
Bendamustine	90 mg/m² = 171 mg	171 mg	7 x 25 mg	12	84 x 25 mg
Rituximab	Cycle 1: 375 mg/m² 712.5 mg; Cycle 2 - 6: 500 mg/m² = 950 mg	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 in combination with rituximab					
Chlorambucil	0.5 mg/kg = 38.5 mg	38.5 mg	19 x 2 mg	12	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg; cycle 2 - 6: 500 mg/m² 950 mg	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
Best supportive care					
Best supportive care	Different from patient to patient				

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					
Duvelisib 25 mg	56 HC	€ 5,567.52	€ 1.77	€ 314.67	€ 5,251.08
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Bendamustine 25 mg	5 PIC	€ 415.18	€ 1.77	€ 51.12	€ 362.29
Bendamustine 25 mg	1 PIC	€ 99.53	€ 1.77	€ 11.17	€ 86.59
Best supportive care	Different from patient to patient				
Chlorambucil 2 mg	50 FCT	€ 36.54	€ 1.77	€ 1.40	€ 33.37
Cyclophosphamide 500 mg	6 PSI	€ 84.55	€ 1.77	€ 9.28	€ 73.50
Fludarabine 50 mg	5 DSS	€ 546.82	€ 1.77	€ 25.41	€ 519.64
Fludarabine 50 mg	1 CIS	€ 118.50	€ 1.77	€ 5.09	€ 111.64
Ibrutinib 420 mg	28 FCT	€ 5,852.87	€ 1.77	€ 0.00	€ 5,851.10
Idelalisib 150 mg	60 FCT	€ 4,535.04	€ 1.77	€ 255.71	€ 4,277.56
Rituximab 100 mg	2 CIS	€ 717.18	€ 1.77	€ 33.50	€ 681.91
Rituximab 500 mg	1 CIS	€ 1,777.30	€ 1.77	€ 84.18	€ 1,691.35
Venetoclax 10 mg	14 FCT	€ 86.95	€ 1.77	€ 0.00	€ 85.18
Venetoclax 50 mg	7 FCT	€ 200.46	€ 1.77	€ 0.00	€ 198.69
Venetoclax 100 mg	112 FCT	€ 5,926.27	€ 1.77	€ 0.00	€ 5,924.50
Abbreviations: FCT = film-coated tablets; HC = Hard capsules; CIS = concentrate for the preparation of an infusion solution; PIE = powder 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 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.

Diagnosis of hepatitis B infection

Patients should be tested for HBV infection before starting treatment with rituximab and ibrutinib. These examinations are not required when using duvelisib as the medicinal product to be assessed. Since there is a regular difference b 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 presented in the resolution.

Premedication for prevention

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to 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 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.

In the context of premedication, additionally required SHI services are incurred that usually differ between the medicinal product to be assessed and rituximab (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	Type of service	Costs/ pack or service	Treatment days/ year	Annual treatment costs/ patient
Medicinal product to be assessed: Duvelisib				
In view of the occurrence of *Pneumocystis jirovecii* pneumonia in patients taking duvelisib, measures for prevention against *Pneumocystis jirovecii* pneumonia should be taken in all patients. This different from patient to patient and its costs cannot be quantified.				
Appropriate comparator therapy				
Ibrutinib	*HBV test*	€ 5.50	1	€ 5.50

	Hepatitis B surface antigen status (GOP number 32781)			
	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. dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[5] € 0.97[6]	6 6	€ 36.46 € 0.97
	Premedication in combination with idelalisib Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1000 mg	€ 15.19[5] € 0.97[6]	8 8	€ 48.61 € 0.97

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71

[5] After deduction of the statutory rebates according to Sections 130 and 130a SGB V.
[6] Calculated from the fixed reimbursement rate of € 1.06 minus € 0.05 (deduction according to Section 130 SGB V) and € 0.04 (deduction according to Section 130 a SB V).

per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy 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 Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 7 September 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 February 2022, the pharmaceutical company submitted a dossier for the benefit assessment of duvelisib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 2 February 2022 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 duvelisib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 2 May 2022. The deadline for submitting written statements was 23 May 2022.

The oral hearing was held on 7 June 2022.

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 12 July 2022, and the proposed resolution was approved.

At its session on 21 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 September 2021	Determination of the appropriate comparator therapy
Working group Section 35a	1 June 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2022	Conduct of the oral hearing
Working group Section 35a	15 June 2022 22 June 2022 5 July 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	12 July 2022	Concluding discussion of the draft resolution
Plenum	21 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 July 2022

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

Prof. Hecken