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 (follicular lymphoma, 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 follicular lymphoma (FL) that is refractory to at least two prior systemic therapies.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with follicular lymphoma that is refractory to at least two prior systemic therapies

Appropriate comparator therapy for duvelisib:

- Patient-individual therapy taking into account prior therapy, course of the disease and general condition

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

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. For the present therapeutic indication, in addition to duvelisib,[2] the active ingredients idelalisib, interferon alfa-2a[2], interferon alfa-2b, lenalidomide, obinutuzumab, rituximab, yttrium-90 radiolabelled ibritumomab tiuxetan, mosunetuzumab and tisagenlecleucel are approved. Follicular lymphomas are a type of non-Hodgkin lymphoma. Accordingly, bendamustine, bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, mitoxantrone, trofosfamide, vinblastine, vincristine, dexamethasone, methylprednisolone, prednisone and prednisolone are also approved.

on 2. In the present therapeutic indication, radiotherapy as well as allogeneic or autologous stem cell transplant can be considered as non-medicinal treatments. However, it is assumed that neither radiotherapy nor autologous or allogeneic stem cell transplant is indicated at the time of therapy with duvelisib for the present treatment setting.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- obinutuzumab (resolutions of 4 November 2021 and 15 December 2016)
- idelalisib (resolution of 19 March 2015)

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use):

- Use of fludarabine in low or intermediate malignant B-non-Hodgkin lymphoma (B-NHL) other than chronic lymphocytic leukaemia (CLL) as specified in the marketing authorisation

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into

[2] The active ingredients duvelisib and interferon alfa-2a are not sold.

account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

In the present case, the determination of the appropriate comparator therapy is based on the assumption that duvelisib is not primarily considered for the treatment of diagnostically identified follicular lymphoma grade 3b. This sub-entity is usually assigned to the aggressive non-Hodgkin lymphomas.

In addition, it is assumed that the patients in the present treatment setting have an indication for systemic antineoplastic therapy due to a correspondingly extensive-stage of the disease, in particular with regard to a symptomatic course (e.g. according to the GELF criteria), and therefore, among other things, a watch-and-wait strategy or a radiotherapy is not considered.

For patients with a relapse or progression of the disease requiring treatment, systemic therapy is recommended in guidelines. The available evidence[3,4,5] mentions various treatment options:

- Bendamustine + rituximab / obinutuzumab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab/ obinutuzumab
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab/ obinutuzumab
- FCM (fludarabine, cyclophosphamide, mitoxantrone) + rituximab/ obinutuzumab
- Chlorambucil + rituximab
- Cyclophosphamide + rituximab
- FM (fludarabine + mitoxantrone) + rituximab/ obinutuzumab
- ICE (ifosfamide, carboplatin, etoposide) + rituximab/ obinutuzumab
- MCP (mitoxantrone, chlorambucil, prednisone) + rituximab/ obinutuzumab
- DHAP (dexamethasone, ara-C/cytarabine, cisplatin) + rituximab/ obinutuzumab
- Lenalidomide + rituximab
- Rituximab monotherapy
- Yttrium-90 radiolabelled ibritumomab tiuxetan
- Idelalisib

In the case of a relapse, the choice of therapy depends on the prior therapy, the course of the disease and the patient's general condition.

According to the S3 guideline, patients with relapse or progression of the disease longer than 2 years after chemoimmunotherapy should be given chemoimmunotherapy again. If the first-line therapy was rituximab in combination with bendamustine, R-CVP or R-MCP, this can also be repeated.

According to the S3 guideline, patients who relapse less than two years after chemoimmunotherapy should be given at least an alternative chemotherapy regimen (e.g. CVP/CHOP instead of bendamustine) in case of renewed chemoimmunotherapy -

[3] Guideline programme in oncology (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies), 2020 Therapy and after-care for patients with follicular lymphoma; long version 1.0.
[4] National Institute for Health and Care Excellence (NICE), 2016. Non-Hodgekin lymphoma: diagnosis and management.
[5] National Comprehensive Cancer Network (NCCN), 2021. B-cell lymphomas. NCCN evidence blocks. Version 3.

secondary to transplantation strategies. In case of relapse during or within 6 months after rituximab therapy, obinutuzumab should be considered as an antibody if chemoimmunotherapy is indicated again. For elderly or comorbid patients for whom chemotherapy is not feasible, monotherapy with rituximab may also be a treatment option.

In addition, the active ingredient idelalisib can represent a treatment option for patients who have responded insufficiently to the last chemotherapy and/or immunotherapy (with disease progression within 6 months).

If therapy with idelalisib or intensive salvage therapy is not possible and no experimental approach is available in studies, treatment with lenalidomide in combination with rituximab can be given.

Radioimmunotherapy (yttrium-90 radiolabelled ibritumomab tiuxetan) may be used in relapsed patients with bone marrow infiltration < 20% if the patient is not eligible for immunochemotherapy or chemotherapy.

However, individual components of the combination therapies recommended in guidelines are not approved in the present indication of follicular lymphoma: Carboplatin, cisplatin, fludarabine, ifosfamide. Obinutuzumab is only approved in the present therapeutic indication in combination with bendamustine. There is a discrepancy between medicinal products approved in the indication of follicular lymphoma and those used in health care/recommended by the guidelines. Fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab (R-FCM) can be prescribed off-label according to the Pharmaceuticals Directive (Annex VI; Off-Label Use) in eligible patients with low or intermediate malignant non-Hodgkin lymphomas of the B-cell series and resistance to CHOP (with or without rituximab).

With mosunetuzumab and tisagenlecleucel, two further treatment options are available that have been approved in the present therapeutic indication and are still quite new in terms of treatment, the therapeutic significance of which cannot yet be conclusively assessed. Both active ingredients are currently in the benefit assessment procedure. Both active ingredients are therefore currently not components of the appropriate comparator therapy.

In the context of a clinical study, the treatment options listed above in the guidelines are considered suitable comparators for patient-individual therapy.

If there is a response to a combination therapy of chemotherapy with rituximab or chemotherapy with obinutuzumab, maintenance treatment should be offered with rituximab or obinutuzumab accordingly.

However, the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

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:

Adult patients with follicular lymphoma that is refractory to at least two prior systemic therapies

An additional benefit is not proven.

Justification:

For the proof of additional benefit, the pharmaceutical company submitted in the dossier the results of the multicentre, open-label, single-arm DYNAMO (IPI-145-06) study for the treatment of adults with follicular lymphoma refractory to at least two prior systemic therapies.

The single-arm DYNAMO study enrolled patients with indolent non-Hodgkin lymphoma (N=129), including patients with follicular lymphoma (FL; N=83), small cell lymphocytic lymphoma (SLL) and marginal zone lymphoma (MZL), who were treated with duvelisib in the study. In the dossier, the pharmaceutical company presented evaluations of the population of patients with follicular lymphoma refractory to at least two prior systemic therapies (N=73). Patients with follicular lymphoma grade 3b and/or clinical evidence of transformation to a more aggressive subtype or pre-treatment with a phosphoinositide 3-kinase (PI3K) or Bruton's tyrosine kinase (BTK) inhibitor were excluded from the study.

The completed study was conducted at 56 study sites in 12 countries in Europe and North America. The primary endpoint of the study was objective response rate (ORR). Other endpoints were overall survival, progression-free survival as well as other endpoints in the categories of morbidity, health-related quality of life and side effects.

The pharmaceutical company submitted data on the 1st data cut-off from 07.04.2016 and on the 2nd data cut-off from 18.05.2018. The pharmaceutical company did not submit any evaluations for the final data cut-off from 18.11.2020 in the dossier. The evaluations of the final data cut-off were submitted subsequently within the framework of the written statement procedure. The pharmaceutical company did not present any data on the appropriate comparator therapy and did not make a comparison with the appropriate comparator therapy.

Conclusion

Overall, the results presented from the DYNAMO study are not suitable for proving an additional benefit compared to the appropriate comparator therapy, as they do not allow a comparison with the appropriate comparator therapy. Therefore, an additional benefit of duvelisib as monotherapy in adult patients with follicular lymphoma refractory to at least two prior systemic therapies is not proven.

2.1.4 Summary of the assessment

Therefore, the present assessment concerns the benefit assessment of the medicinal product Copiktra with the active ingredient duvelisib. The therapeutic indication assessed here is as follows:

"A Copiktra monotherapy is used to treat adult patients with: follicular lymphoma (FL) that is refractory to at least two prior systemic therapies."

The G-BA determined a patient-individual therapy as the appropriate comparator therapy, taking into account the prior therapy, the course of the disease and the general condition.

For the benefit assessment, the pharmaceutical company submits the results of the multicentre, open-label, single-arm DYNAMO (IPI-145-06) study for the treatment of adults with follicular lymphoma refractory to at least two prior systemic therapies. No data were presented that would allow a comparison with the appropriate comparator therapy.

The data presented are not suitable to prove an additional benefit compared to the appropriate comparator therapy, which is why an additional benefit of duvelisib as monotherapy in adult patients with follicular lymphoma that is refractory to at least two previous systemic therapies is not proven.

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

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

The procedure of the pharmaceutical company is mathematically comprehensible in principle. However, the number of patients in the target population determined by the pharmaceutical company is subject to considerable uncertainty due to methodological weaknesses. With regard to the upper limit, an overestimation can be assumed, as the upper percentage value of patients with ≥ 2 prior therapies who require further therapy was collected from an inappropriate patient population. The number of patients is therefore rather to be expected in the lower area of the range.

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 April 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 adults with follicular lymphoma.

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).

For the presentation of the costs, one year is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued prematurely due to non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

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.

In the present therapeutic indication, the product information for obinutuzumab specifies an induction regimen in combination with bendamustine over 6 cycles. Section 5.1 of the product information for obinutuzumab specifies the single dose for bendamustine in combination with obinutuzumab as 90 mg/m^{2}. The induction phase is followed by the administration of obinutuzumab as a single agent in the form of maintenance treatment once every 2 months for a period of 2 years or until disease progression.

The FCM regime (fludarabine, cyclophosphamide and mitoxantrone) involves the prescription of approved medicinal products in unapproved therapeutic indications (so-called off-label use). Information on the mode of treatment and consumption was taken from Annex VI to Section K of the Pharmaceuticals Directive.[6] Accordingly, the treatment duration is given with a range of 4 - 8 cycles.

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
Appropriate comparator therapy				
Patient-individual therapy[a]				

[6] https://www.g-ba.de/downloads/83-691-720/AM-RL-VI-Off-label-2022-03-03.pdf (last access: 30 May 2022).

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bendamustine + rituximab[7]				
Bendamustine	*Induction therapy* on day 1 and 2 of a 28-day cycle	6	2	12
Rituximab	*Induction therapy:* Day 1 of a 28-day cycle	6	1	6
	Maintenance treatment: every 56 days	3	1	3
Bendamustine + obinutuzumab				
Bendamustine	*Induction therapy:* Day 1 and 2 of a 28-day cycle	6	2	12
Obinutuzumab	*Induction therapy:* 28-days cycles; Cycle 1: Day 1, 8 and 15 Cycles 2 to 6: Day 1	6	Cycle 1: 3 Cycle 2 to 6: 1	8
	Maintenance treatment: every 56 days	3	1	3
CHOP[7] *(cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab*				
Cyclophosphamide	Day 1 of a 21-day cycle	6	1	6
Doxorubicin	Day 1 of a 21-day cycle	6	1	6
Vincristine	Day 1 of a 21-day cycle	6	1	6
Prednisolone[8]	Day 1 – 5 of a 21-day cycle	6	5	30
Rituximab	Induction therapy	6	1	6

[7] Flinn IW etal. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014 May 8;123(19):2944-52.
[8] Instead of prednisone, the comparable and less expensive prednisolone was presented due to the principle of economic efficiency.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Day 1 of a 21-day cycle			
	Maintenance treatment every 56 days	4	1	4
CVP[9] (cyclophosphamide, vincristine, prednisolone) + rituximab				
Cyclophosphamide	Day 1 of a 21-day cycle	8	1	8
Vincristine	Day 1 of a 21-day cycle	8	1	8
Prednisolone	Day 1 – 5 of a 21-day cycle	8	5	40
Rituximab	*Induction therapy:* Day 1 of a 21-day cycle	6	1	6
	Maintenance treatment: every 56 days	4	1	4
FCM (fludarabine, cyclophosphamide, mitoxantrone) + rituximab[6]				
Fludarabine	Day 1 – 3 of a 28-day cycle	4 - 8	3	12 - 24
Cyclophosphamide	Day 1 – 3 of a 28-day cycle	4 - 8	3	12 - 24
Mitoxantrone	Day 1 of a 28-day cycle	4 - 8	1	4 - 8
Rituximab	Day 1[10] of a 28-day cycle	4 - 8	1	4 - 8
Chlorambucil + rituximab				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6	2	12
Rituximab	Day 1 of a 28-day cycle	6	1	6
Cyclophosphamide + rituximab				

[9] Sarkozy et al. Risk Factors and Outcomes for Patients With Follicular Lymphoma Who Had Histologic Transformation After Response to First-Line Immunochemotherapy in the PRIMA Trial. J Clin Oncol. 2016 Aug 1;34(22):2575-82.
[10] If there is a risk of tumour lysis syndrome, the first cycle of rituximab may be administered on day 0 at least 24 hours before the start of cytostatic chemotherapy.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cyclophosphamide	Day 1 of a 21-day cycle	8	1	8
Rituximab	*Induction therapy:* Day 1 of a 21-day cycle	6	1	6
	Maintenance treatment: 1 x every 56 days	4	1	4
MCP (mitoxantrone, chlorambucil, prednisone) + rituximab[11]				
Mitoxantrone	Day 1 and 2 of a 28-day cycle	6 - 8	2	12 - 16
Chlorambucil	3 x on day 1 - 5 of a 28-day cycle	6 - 8	5	30 - 40
Prednisolone[12]	Day 1 – 5 of a 28-day cycle	6 - 8	5	30 - 40
Rituximab	*Induction therapy:* Day 1 of a 28-day cycle	6 - 8[13]	1	6 - 8
Lenalidomide + rituximab				
Lenalidomide	Day 1 - 21 of a 28-day cycle	12	21	252
Rituximab	*Induction therapy:* Day 1, 8, 15 and 22 of a 28-day cycle	1	4	4
	Maintenance treatment: Day 1 of a 28-day cycle	4	1	4
Rituximab monotherapy				
Rituximab	*Induction therapy:*	1	4	4

[11] Nickenig et al. (2006): German Low-Grade Lymphoma Study Group. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower haematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomised trial of the German Low-Grade Lymphoma Study Group. Cancer. 2006 Sep 1;107(5):1014-22. doi: 10.1002/cncr.22093. PMID: 16878325.

[12] Instead of prednisone, the comparable and less expensive prednisolone was presented due to the principle of economic efficiency.

[13] The product information of rituximab states the number of cycles for induction therapy as up to 8.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Day 1, 8, 15 and 22 of a 28-day cycle			
	Maintenance treatment: Day 1 of a 28-day cycle	4	1	4
Yttrium-90 radiolabelled ibritumomab tiuxetan pretreated with rituximab				
Yttrium-90 radiolabelled ibritumomab tiuxetan	Single dose	1	1	1
Rituximab	2 x within 9 days (day 1 and day 7, 8 or 9 prior to administration of ibritumomab)	2	1	2
Idelalisib monotherapy				
Idelalisib	2 x daily	365	1	365
[a] The active ingredients or combinations of active ingredients CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab, CVP (cyclophosphamide, vincristine, prednisolone) + obinutuzumab , FM (fludarabine + mitoxantrone) + rituximab/ obinutuzumab, ICE (ifosfamide, carboplatin, etoposide) + rituximab/ obinutuzumab, FCM (fludarabine, cyclophosphamide, mitoxantrone) + obinutuzumab, MCP (mitoxantrone, chlorambucil, prednisone) + obinutuzumab and DHAP (dexamethasone, ara-C/cytarabine, cisplatin) + rituximab/ obinutuzumab are suitable comparators for the present benefit assessment in the context of patient-individual therapy. However, these active ingredients or combinations of active ingredients are not approved in the present therapeutic indication, and therefore, no costs are presented for these active ingredients or combinations of active ingredients.				

Consumption:

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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[14]

[14] 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
Medicinal product to be assessed					
Duvelisib	25 mg	50 mg	2 x 25 mg	365	730 x 25 mg
Appropriate comparator therapy					
Patient-individual therapy[a]					
Bendamustine + rituximab					
Bendamustine	90 mg/m² = 171 mg	171 mg	7 x 25 mg	12	84 x 25 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	9	27 x 100 mg + 9 x 500 mg
Bendamustine + obinutuzumab					
Bendamustine	90 mg/m² = 171 mg	171 mg	7 x 25 mg	12	84 x 25 mg
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	11	11 x 1,000 mg
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab					
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 500 mg + 1 x 1,000 mg	6	6 x 500 mg + 6 x 1,000 mg
Doxorubicin	50 mg/m² = 95 mg	95 mg	1 x 100 mg	6	6 x 100 mg
Vincristine	1.4 mg/m², maximum 2 mg	2 mg	1 x 2 mg	6	6 x 2 mg
Prednisolone[8]	100 mg	100 mg	2 x 50 mg	30	60 x 50 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	10	30 x 100 mg + 10 x 500 mg
CVP (cyclophosphamide, vincristine, prednisolone) + rituximab					
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 500 mg + 1 x 1,000 mg	8	8 x 500 mg + 8 x 1,000 mg
Vincristine	1.4 mg/m², maximum 2 mg	2 mg	1 x 2 mg	8	8 x 2 mg
Prednisolone	100 mg	100 mg	2 x 50 mg	40	80 x 50 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	10	30 x 100 mg + 10 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
FCM (fludarabine, cyclophosphamide, mitoxantrone) + rituximab					
Fludarabine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	12 – 24	12 x 50 mg – 24 x 50 mg
Cyclophosphamide	200 mg/m² = 380 mg	380 mg	1 x 500 mg	12 - 24	12 x 500 mg – 24 x 500 mg
Mitoxantrone	8 mg/ mg² = 15.2 mg	15.2 mg	1 x 20 mg	4 - 8	4 x 20 mg – 8 x 20 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	4 - 8	4 x 500 mg + 12 x 100 mg – 8 x 500 mg + 24 x 100 mg
Chlorambucil + 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	712.5 mg – 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
Cyclophosphamide + rituximab					
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 500 mg + 1 x 1,000 mg	8	8 x 500 mg + 8 x 1,000 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	10	30 x 100 mg + 10 x 500 mg
MCP (mitoxantrone, chlorambucil, prednisone) + rituximab					
Mitoxantrone	8 mg/m² = 15.2 mg	15.2 mg	1 x 20 mg	12 – 16	12 x 20 mg – 16 x 20 mg
Chlorambucil	3 mg/m² = 5.7 mg	17.1 mg	9 x 2 mg	30 - 40	270 x 2 mg – 360 x 2 mg
Prednisolone[12]	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	30 - 40	30 x 50 mg – 40 x 50 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	6 - 8	(6 x 500 mg + 18 x 100 mg) – (8 x

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					500 mg + 24 x 100 mg)
Lenalidomide + rituximab					
Lenalidomide	20 mg	20 mg	1 x 20 mg	252	252 x 20 mg
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg
Rituximab monotherapy					
Rituximab	375 mg/ m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg
Yttrium-90 radiolabelled ibritumomab tiuxetan pretreated with rituximab					
Ibritumomab tiuxetan	2.08 mg	2.08 mg	3.2 mg	1	3.2 mg
Yttrium-90 chloride	15 MBq/kg (max. 1,200 MBq) = 1,155 MBq	1,155 MBq	1,155 MBq	1	1,155 MBq
Rituximab	250 mg/m² = 475 mg	475 mg	1 x 500 mg	2	2 x 500 mg
Idelalisib monotherapy					
Idelalisib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg

[a] The active ingredients or combinations of active ingredients CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab, CVP (cyclophosphamide, vincristine, prednisolone) + obinutuzumab , FM (fludarabine + mitoxantrone) + rituximab/ obinutuzumab, ICE (ifosfamide, carboplatin, etoposide) + rituximab/ obinutuzumab, FCM (fludarabine, cyclophosphamide, mitoxantrone) + obinutuzumab, MCP (mitoxantrone, chlorambucil, prednisone) + obinutuzumab and DHAP (dexamethasone, ara-C/cytarabine, cisplatin) + rituximab/ obinutuzumab are suitable comparators for the present benefit assessment in the context of patient-individual therapy. However, these active ingredients or combinations of active ingredients are not approved in the present therapeutic indication, and therefore, no costs are presented for these active ingredients or combinations of active ingredients.

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
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
Chlorambucil 2 mg	50 FCT	€ 36.54	€ 1.77	€ 1.40	€ 33.37
Cyclophosphamide 1000 mg	6 PSI	€ 127.65	€ 1.77	€ 6.44	€ 119.44
Cyclophosphamide 1000 mg	1 PSI	€ 30.68	€ 1.77	€ 1.07	€ 27.84
Cyclophosphamide 500 mg	6 PSI	€ 84.55	€ 1.77	€ 9.28	€ 73.50
Cyclophosphamide 500 mg	1 PSI	€ 23.49	€ 1.77	€ 1,55	€ 20.17
Doxorubicin 100 mg	1 CIS	€ 285.75	€ 1.77	€ 0.00	€ 283.98
Fludarabine 50 mg [15]	5 DSS	€ 546.82	€ 1.77	€ 25.41	€ 519.64
Idelalisib 150 mg	60 FCT	€ 4,535.04	€ 1.77	€ 255.71	€ 4,277.56
Lenalidomide 20 mg	21 HC	€ 212.11	€ 1.77	€ 25.41	€ 184.93
Mitoxantrone 20 mg	1 CIS	€ 235.54	€ 1.77	€ 10.64	€ 223.13
Obinutuzumab 1,000 mg	1 CIS	€ 3,489.58	€ 1.77	€ 0.00	€ 3,487.81
Prednisolone 50 mg[16]	50 TAB	€ 31.40	€ 1.77	€ 1.59	€ 28.04
Prednisolone 50 mg[16]	10 TAB	€ 15.16	€ 1.77	€ 0.31	€ 13.08
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
Vincristine 2 mg	1 SFI	€ 37.63	€ 1.77	€ 1.25	€ 34.61
Ibritumomab tiuxetan 3.2 mg	Kit for 1 radioactive medicine (VIA)	€ 14,706.57	€ 1.77	€ 839.30	€ 13,865.50
Abbreviations: VIA = vials; FCT = film-coated tablets; HC = Hard capsules; CIS = concentrate for the preparation of an infusion solution; PiE = powder for solution for infusion, PIC =					

[15] The following pharmaceutical companies have issued an acknowledgement of intended use for their fludarabine-containing medicinal products, which means that their medicinal products can be prescribed for off-label use in follicular lymphoma: Actavis Nordic A/S and Actavis Group PTC ehf., Genzyme Europe B.V. as a subsidiary of Sanofi Aventis, HEXAL AG, Neocorp AG, TEVA GmbH.

[16] 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
powder for the preparation of an infusion solution concentrate; DSS = dry substance without solvent; TAB = tablets					

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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 obinutuzumab. These examinations are not required when using duvelisib as the medicinal product to be assessed. Since there is a 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 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 as an appropriate comparator therapy and are consequently taken into account as additionally required SHI services in the resolution.

Application of a radionuclide

Additionally required SHI services for the use of yttrium-90 radiolabelled ibritumomab tiuxetan according to the product information and package information leaflet are given by the use of a radionuclide. There is a GOP in the EBM for radionuclide therapy (GOP 17372).

Designation of the therapy	Type of service	Costs/ pack/ 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				
Obinutuzumab	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
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 (in combination with cyclophosphamide, CHOP, CVP) Antihistamines e.g. dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[17] € 0.97[18]	10 10	€ 60.76 € 0.97
	Premedication (in combination with FCM) Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg	€ 15.19[17] € 0.97[18]	4 - 8 4 - 8	€ 24.30 - € 48.61 € 0.97

[17] After deduction of the statutory rebates according to Sections 130 and 130a SGB V
[18] 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 130a SB V).

	Antipyretics e.g. paracetamol oral 1,000 mg			
	Premedication (in combination with chlorambucil) Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[17] € 0.97[18]	6 6	€ 36.46 € 0.97
	Premedication (in combination with lenalidomide or as monotherapy) Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[17] € 0.97[18]	8 8	€ 48.61 € 0.97
	Premedication in combination with bendamustine Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[17] € 0.97[18]	9 9	€ 54.68 € 0.97
	Premedication in combination with MCP Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[17] € 0.97[18]	6 – 8 6 - 8	€ 36.46 - € 48.61 € 0.97

	Premedication (in case of pretreatment for treatment with yttrium-90 radiolabelled ibritumomab tiuxetan) Antihistamines e.g. Dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	€ 15.19[17] € 0.97[18]	2 2	€ 12.15 € 0.97
Yttrium-90 radiolabelled ibritumomab tiuxetan	Additional flat rate Radionuclide therapy (GOP 17372)	€ 35.39	1	€ 35.39

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but 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 22 June 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 29 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	22 June 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