Justification

Gemeinsamer Bundesausschuss

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

of 15 October 2020

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the proof and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient venetoclax (Venclyxto) was listed for the first time on 1 January 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 9 March 2020, venetoclax received the marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 3 April 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient venetoclax with the new therapeutic indication (chronic lymphocytic leukaemia, first-line, in combination with obinutuzumab) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 July 2020, 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 venetoclax 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed 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 venetoclax.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of venetoclax (Venclyxto) in accordance with the product information

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for venetoclax in combination with obinutuzumab:

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)

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

Appropriate comparator therapy for venetoclax in combination with obinutuzumab:

- Bendamustine in combination with rituximab

or

- Chlorambucil in combination with rituximab or obinutuzumab

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

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

Appropriate comparator therapy for venetoclax in combination with obinutuzumab:

- Ibrutinib

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

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

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

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

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

On 1. With regard to authorisation status, the active ingredients bendamustine, chlorambucil, cyclophosphamide, fludarabine, ibrutinib, idelalisib, venetoclax, obinutuzumab, rituximab, prednisolone and prednisone are available for first-line treatment of patients with CLL. CLL belongs to the group of non-Hodgkin's lymphomas, and, hence, the active ingredients cytarabine, doxorubicin, trofosfamide, vinblastine, and vincristine are also approved in principle.

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

On 3. For the present therapeutic indication, there are no resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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

- Ibrutinib (in combination with obinutuzumab): Resolution of 20 February 2020
- Venetoclax (reassessment after expiry of orphan drug status) Resolution of 16 May 2019

- Idelalisib (in combination with rituximab) Resolution of 16 March 2017
- Idelalisib (in combination with ofatumumab): Resolution of 16 March 2017
- Ibrutinib (monotherapy): Resolution of 15 December 2016
- Ibrutinib (monotherapy; patients with 17p deletion or a TP53 mutation): Resolution of 21 July 2016
- Obinutuzumab (in combination with chlorambucil): Resolution of 5 February 2015

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

Based on the evidence available, the combination of fludarabine, cyclophosphamide and the anti-CD20 antibody rituximab (FCR) represents the recommended first-line treatment for fit patients with CLL without 17p deletion or TP53 mutation.

In patients ineligible for therapy with FCR, for instance because of a reduced general condition, a combination therapy of a chemotherapeutic agent and an anti-CD-20 antibody is recommended. However, based on the evidence, there is no clear therapeutic standard treatment for this patient group. In accordance with available guidelines and taking into account the respective authorisation status, the combinations bendamustine in combination with rituximab, chlorambucil in combination with rituximab or chlorambucil in combination with obinutuzumab represent equally appropriate treatment options. The evidence also includes some recommendations for monotherapy with ibrutinib. In the benefit assessment of 15 December 2016, no additional benefit was found for ibrutinib compared with the appropriate comparator therapy (chemo-immunotherapy according to the doctor's instructions, taking into account authorisation status). The benefit assessment was based on a non-adjusted indirect comparison with the bridge comparator chlorambucil. The studies used differed in terms of relevant criteria. The proof submitted could therefore not be used to determine the additional benefit of ibrutinib compared with the appropriate comparator therapy. In the case of ibrutinib in combination with obinutuzumab, the resolution of 20 February 2020 found a minor additional benefit compared with chlorambucil in combination with obinutuzumab. This is based exclusively on advantages in the side effects category, although here only a hint for an additional benefit was derived because of strongly diverging observation periods in the treatment arms. For the reasons mentioned above, neither monotherapy with ibrutinib nor combination therapy of ibrutinib with obinutuzumab are determined to be appropriate comparator therapies. Monotherapy with chemotherapeutic agents such as chlorambucil or bendamustine is also not recommended for previously untreated patients.

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

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

2.1.3 Extent and probability of the additional benefit

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

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

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

Justification:

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

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

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

Justification:

The benefit assessment is based on the findings of the ongoing open-label, randomised CLL14 study in which the combination therapy venetoclax + obinutuzumab is compared with the combination therapy chlorambucil + obinutuzumab.

The study included adult patients with previously untreated CLL requiring treatment in accordance with the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria[2]. The patients also had to have comorbidities, defined by a Cumulative Illness Rating Scale (CIRS) of > 6 or impaired renal function (creatinine clearance of < 70 ml/min). A total of 432 patients were included in the CLL14 study; 216 patients were randomised to the test arm and 216 to the control arm. The patients were stratified by Binet stage (A vs B vs C) and geographical region (United States / Canada / Central America vs Australia / New Zealand vs Western Europe vs Central and Eastern Europe vs Latin America)

For the evaluation, the pharmaceutical company formed two sub-populations, which were assigned the patient populations b) and c). 148 patients were assigned to patient population b) and 258 patients were assigned to patient population c).

[2] Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H *et al.* Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008; 111(12): 5446–5456.

The primary endpoint of the study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, symptomatology, health-related quality of life, and adverse events (AEs).

Three data cut-offs were conducted for the CLL14 study. For the benefit assessment, the 3rd data cut-off of 23 August 2019 was used. This was requested by the European Medicines Agency (EMA) and submitted in the dossier by the pharmaceutical company.

Implementation of the appropriate comparator therapy:

Treatment with venetoclax and obinutuzumab was carried out for 12 (venetoclax) and 6 cycles (obinutuzumab) according to the product information. Chlorambucil was administered for 12 cycles.

The determination of the appropriate comparator therapy (bendamustine in combination with rituximab or chlorambucil in combination with either rituximab or obinutuzumab) indicates that the marketing authorisation of the medicinal products must be taken into account. The product information on chlorambucil does not explicitly state the duration of therapy in combination with obinutuzumab. The product information of obinutuzumab specifies a treatment duration of 6 cycles for the combination with chlorambucil. Section 5.1 of the product information also indicates a treatment duration of 6 cycles for chlorambucil in the context of combination therapy. The German S3 guideline of 2018 recommends a treatment duration of 6 cycles for chlorambucil.

In order to prove that an administration of 12 cycles of chlorambucil within the scope of a combination therapy with obinutuzumab is sufficiently comparable to an administration of 6 cycles of chlorambucil in combination with obinutuzumab with regard to relevant side effects, the pharmaceutical company submitted time-to-event analysis on the relevant side effects of the CLL14 study during the written statement procedure. According to the pharmaceutical company, the low number of patients with therapy discontinuation also speaks for the good tolerability of chlorambucil treatment beyond cycle 6. The pharmaceutical company also presented a descriptive compilation of different studies in the therapeutic indication of venetoclax, from which a similar safety profile for the treatment of chlorambucil over 12 cycles compared with 6 cycles was derived. This descriptive compilation compares data for the most common adverse events and basic tolerability endpoints of CLL14 with data from the CLL11 and iLLUMINATE studies (both 6 cycles of chlorambucil in combination with obinutuzumab).

The assessment of the G-BA is made with regard to the question of whether the CLL14 study with an administration of 12 cycles of chlorambucil as part of a combination therapy with obinutuzumab is suitable as a comparator for assessing the additional benefit of venetoclax + obinutuzumab. In this respect, the statistical significance of the data presented is limited. The G-BA evaluates the low rate of therapy discontinuation as a hint for the good tolerability of chlorambucil beyond 6 cycles. This was also confirmed by the clinical experts during the written statement procedure. According to the experts, a relevant additional toxicity compared with a shorter treatment duration of 6 cycles would not be expected. According to the respondents, a treatment duration of chlorambucil over 12 cycles in the context of combination therapy with obinutuzumab is well tolerated (depending on therapy response and side effects) and at least partly reflects the German health care context. According to this, a treatment duration of 6-12 cycles of chlorambucil would represent a standard in the current health care situation. The German S3 guideline of 2018 would not reflect the current status in this respect.

The G-BA concluded that the CLL14 study with a treatment duration of 12 cycles of chlorambucil as a comparator in the context of a combination therapy with obinutuzumab is suitable for assessing the additional benefit of venetoclax + obinutuzumab despite remaining uncertainties.

Relevant patient populations

When assigning patients to patient populations, the pharmaceutical company uses the IGHV mutation status as a decision criterion for identifying patients for whom chemo-immunotherapy is not suitable and assigns patients with an unmutated IGHV status to patient population c).

This comprises a total of 258 patients of which 12% have a 17p deletion, 16% have a TP53 mutation, and 95% have an unmutated IGHV status. However, the significance of the IGHV mutation status as a therapy-relevant decision criterion cannot yet be conclusively assessed. According to the statements of the clinical experts during the written statement procedure, patients with non-mutated IGHV status have an overall worse prognosis and a shorter response to chemo-immunotherapy than patients with mutated IGHV status. The experts also pointed out that in the German health care context, the IGHV mutation status is increasingly determined before the start of therapy and is also increasingly used as a therapy-relevant decision criterion with ibrutinib ± anti-CD20 antibodies being primarily recommended for patients with an unmutated IGHV status. However, FCR or other chemo-immunotherapies are also still mentioned as possible therapy options. The pharmaceutical company does not provide sufficient justification in the dossier as to why patients with an unmutated IGHV gene should regularly not receive chemo-immunotherapy. Most of the patients from the CLL14 study were assigned to patient population c) by the pharmaceutical company solely because of an unmutated IGHV gene. It therefore remains unclear how many of these patients could also be assigned to patient population b). The patient population for whom FCR therapy is not suitable but who could be treated with chemo-immunotherapy may not be fully covered by this approach. In the CLL14 study, these patients were also treated with chemo-immunotherapy (chlorambucil + obinutuzumab) in the control group. An evaluation of a sub-population of the CLL14 study independent of the IGHV mutation status for patient population b) was not submitted by the pharmaceutical company despite corresponding criticism in the benefit assessment of the IQWiG.

Because of the regular exclusion of patients with non-mutated IGHV status from patient population b) in the CLL14 study by the pharmaceutical company, the G-BA believes that there are great uncertainties, particularly with regard to a possible bias.

For these reasons, the evaluations of the CLL14 study for patient population b) presented by the pharmaceutical company are not suitable, from the perspective of the G-BA, to be able to assess the additional benefit of venetoclax + obinutuzumab.

The results of the CLL14 study are presented below:

CLL14 study: Venetoclax + obinutuzumab vs chlorambucil + obinutuzumab[3]

Relevant sub-population: Population 2 (148 patients, not suitable for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR), IGHV status exclusively mutated)

Mortality

Endpoint	**Venetoclax + obinutuzumab**		**Chlorambucil + obinutuzumab**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD) [a]
Overall survival/mortality					
	71	n.a. 7 (9.9)	77	n.a. 4 (5.2)	2.20 [0.63; 7.67] 0.207

Morbidity

Endpoint	**Venetoclax + obinutuzumab**		**Chlorambucil + obinutuzumab**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute Difference (AD) [a]
Progression-free survival (PFS) (presented additionally [b])					
	71	n.a. [n.c., n.c.] 9 (12.7)	77	42.9 [40.7; n.c.] 25 (32.5)	0.40 [0.18; 0.87] 0.017 n.a.
EORTC QLQ-C30 symptom scales [c]					
Fatigue	67	7.4 [3.8; 20.4] 41 (61.2)	73	7.5 [3.0; 26.3] 44 (60.3)	0.90 [0.57; 1.43] 0.655

(Continuation)

[3] Data from the dossier assessment of the IQWiG (A20-39) and the addendum (A20-76) unless otherwise indicated.

Endpoint	Venetoclax + obinutuzumab			Chlorambucil + obinutuzumab			Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*		N	Median time to event in months [95% CI] *Patients with event n (%)*		Hazard Ratio [95% CI] p value Absolute Difference (AD) [a]
Nausea and vomiting	67	n.a. [9.0; n.c.] 30 (44.8)		73	n.a. [34.9; n.c.] 27 (37.0)		1.16 [0.67; 2.00] 0.599
Pain	67	10.3 [4.8; 17.2] 43 (64.2)		73	9.3 [4.7; 23.2] 46 (63.0)		1.09 [0.69; 1.71] 0.717
Dyspnoea	67	n.a. [25.6; n.c.] 28 (41.8)		73	25.2 [13.1; n.c.] 36 (49.3)		0.71 [0.42; 1.20] 0.190
Insomnia	67	12.6 [4.7; n.c.] 37 (55.2)		73	n.a. [9.5; n.c.] 34 (46.6)		1.38 [0.84; 2.26] 0.203
Loss of appetite	67	24.3 [10.6; n.c.] 32 (47.8)		73	n.a. [40.5; n.c.] 25 (34.2)		1.53 [0.86; 2.70] 0.145
Constipation	67	22.6 [5.7; n.c.] 36 (53.7)		73	n.a. [19.8; n.c.] 30 (41.1)		1.21 [0.73; 2.02] 0.453
Health status [d] (EQ-5D VAS)							
7 points	66	18.2 [5.4; n.c.] 33 (50.0)		73	34.6 [4.9; n.c.] 34 (46.6)		1.01 [0.61; 1.67] 0.960
10 points	66	22.9 [5.6; n.c.] 32 (48.5)		73	n.a. [5.2; n.c.] 33 (45.2)		1.00 [0.60; 1.66] > 0.999
	N	Values at the start of study MV (SD)	Change MV (SE)	N	Values at the start of study MV (SD)	Change MV (SE)	Mean difference [95% CI] p value
Severity of symptoms							
MDASI Total Symptom Severity [e]	68	1.92 (1.79)	−0.51 (0.14)	72	1.31 (1.16)	−0.59 (0.13)	0.08 [−0.24; 0.40] 0.622
Impairment of everyday life through symptoms							
MDASI Symptom Interference [e]	67	2.28 (2.39)	−0.71 (0.21)	72	1.84 (2.44)	−1.08 (0.19)	0.37 [−0.11; 0.86] 0.133

Health-related quality of life

Endpoint	**Venetoclax + obinutuzumab**		**Chlorambucil + Obinutuzumab**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value
EORTC QLQ-C30 functional scales[f]					
Global health status	67	7.1 [4.9; 35.0] 42 (62.7)	73	7.8 [4.4; n.c.] 42 (57.5)	0.99 [0.63; 1.57] 0.987
Physical functioning	67	18.2 [5.6; n.c.] 36 (53.7)	73	n.a. [23.0; n.c.] 32 (43.8)	1.24 [0.74; 2.05] 0.410
Role functioning	67	11.6 [3.6; 35.2] 40 (59.7)	73	18.5 [7.5; n.c.] 41 (56.2)	1.08 [0.68; 1.71] 0.742
Cognitive functioning	67	9.7 [5.7; 29.2] 40 (59.7)	73	12.2 [3.9; n.c.] 41 (56.2)	1.07 [0.66; 1.72] 0.786
Emotional functioning	67	n.a. [9.0; n.c.] 31 (46.3)	73	n.a. [23.8; n.c.] 27 (37.0)	1.47 [0.84; 2.58] 0.174
Social functioning	67	4.9 [3.7; 26.0] 41 (61.2)	73	9.4 [4.8; 36.4] 42 (57.5)	1.09 [0.69; 1.73] 0.698

Side effects

Endpoint	Venetoclax + obinutuzumab		Chlorambucil + Obinutuzumab		Intervention vs control
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	Hazard Ratio [95% CI] p value
Adverse events (AE) (presented additionally)					
	70	0.0 [n.c.; n.c.] 68 (97.1)	77	0.0 [n.c.; n.c.] 77 (100)	–
Serious adverse events (SAE)					
	70	15.9 [13.4; 19.3] 34 (48.6)	77	23.4 [14.8; 32.1] 31 (40.3)	1.10 [0.67; 1.83] 0.673
Severe adverse events (CTCAE grade 3 or 4)					
	70	1.0 [0.3; 2.6] 57 (81.4)	77	1.3 [0.2; 5.6] 59 (76.6)	1.15 [0.79; 1.66] 0.428
Discontinuation because of AEs [g]					
	70	n.a. [n.c.; n.c.] 10 (14.3)	77	n.a. [n.c.; n.c.] 12 (15.6)	0.943 [0.41; 2.18] 0.891
Specific adverse events					
Respiratory, thoracic, and mediastinal disorders (SOC, SAE)		17.9 [17.9; 19.3] 7 (10.0)		37.7 [n.c.; n.c.] 1 (1.3)	– [h] 0.008

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Data from: Dossier on venetoclax Module 4 of 3 April 2020
[c] Defined as an increase of the score by ≥ 10 points
[d] Time to deterioration (decrease) of the score by at least 7 or 10 points compared with baseline
[e] Higher values on the scale correspond to a higher symptom severity or impairment; a negative group difference means an advantage for venetoclax + obinutuzumab
[f] Defined as a decrease of the score by ≥ 10 points
[g] Discontinuation of at least one active ingredient component
[h] No representation of effect estimation and CI because not informative

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR = hazard ratio; CI = confidence interval; MDASI = MD Anderson Symptom Inventory; MV

= mean value; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; SD = standard deviation; SE = standard error; SOC = system organ class; vs = versus

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

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

Justification:

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

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient venetoclax. The therapeutic indication assessed here is as follows: Venetoclax in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). In the therapeutic indication to be considered, three patient groups were distinguished:

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

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

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

Patient group a):

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

− Fludarabine in combination with cyclophosphamide and rituximab (FCR)

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

Patient group b):

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

– Bendamustine in combination with rituximab

or

− Chlorambucil in combination with rituximab or obinutuzumab

The pharmaceutical company has not submitted suitable data to prove an additional benefit. A sub-population formed by the pharmaceutical company may not fully cover the population of patients for whom FCR therapy is not suitable but who could be treated with chemo-immunotherapy. Thus, an additional benefit is not proven.

Patient group c):

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

− Ibrutinib

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

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

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

Patient numbers are based on the resolutions on ibrutinib of 20 January 2020 and were already used in the resolutions on ibrutinib of 15 December 2016 (patient populations 1, 2, and 3) and 21 July 2016 (patient population 3). As already stated in the resolution of 15 December 2016, their derivation is subject to uncertainties. For patient group 1, an overestimation should be assumed. This results in a tendency to underestimate patient groups 2 and 3.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Venclyxto (active ingredient: venetoclax) at the following publicly accessible link (last access: 7 May 2020):

https://www.ema.europa.eu/documents/product-information/venclyxto-epar-product-information_de.pdf

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2020).

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

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

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 different for each

individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Venetoclax	every 28 days, on 22–28 of Cycle 1, on Day 1–28 of Cycles 2–12	12 cycles	7–28	315
Obinutuzumab	every 28 days on day 1 + 2, 8 and 15 of cycle 1 and on day 1 of cycles 2–-6	6 cycles	1	9
Appropriate comparator therapy				
a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)				
Fludarabine + cyclophosphamide + rituximab (FCR)				
Fludarabine	every 28 days on day 1, 2, and 3	6 cycles	3	18
Cyclophosphamide	every 28 days on day 1, 2, and 3	6 cycles	3	18
Rituximab	every 28 days on day 1	6 cycles	1	6

(Continuation)

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)				
Bendamustine + rituximab (BR)[4]				
Bendamustine	every 28 days on day 1 and 2	6 cycles	2	12
Rituximab	every 28 days on day 1, (cycle 1 day 0)	6 cycles	1	6
Chlorambucil + rituximab (ClbR)[5]				
Chlorambucil	every 28 days on day 1 and 15	6 cycles	2	12
Rituximab	every 28 days on day 1	6 cycles	1	6
Chlorambucil + obinutuzumab				
Chlorambucil	every 28 days on day 1 and 15	6 cycles	2	12
Obinutuzumab	every 28 days on day 1 + 2, 8 and 15 of cycle 1 and on day 1 of cycles 2–6	6 cycles	1	9
c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons				
Ibrutinib				
Ibrutinib	continuously, 1 × daily	365	1	365

[4] Fischer K *et al.* Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukaemia: a multi-centre phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011 Sep 10; 29 (26): 3559–66.

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

Usage and consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916). [6]

Designation of the therapy	Dosage/ application	Dose/patient/ treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 onwards: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 onwards: 400 mg	Week 1: 2 × 10 mg Week 2: 1 × 50 mg Week 3: 1 × 100 mg Week 4: 2 × 100 mg Week 5 onwards: 4 × 100 mg	315	14 × 10 mg 7 × 50 mg 1 169 × 100 mg
Obinutuzumab	Cycle 1 Day 1: 100 mg Day 2: 900 mg Day 8: 1,000 mg day 15: 1,000 mg Cycle 2–6 Day 1: 1,000 mg	1,000 mg	1 × 1,000 mg	9	8 × 1,000 mg
Appropriate comparator therapy					
a) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)					
Fludarabine + cyclophosphamide + rituximab (FCR)[7]					
Fludarabine	25 mg/m²	47.5 mg	1 × 50 mg	18	18 × 50 mg
Cyclophosphamide	250 mg/m²	475 mg	1 × 500 mg	18	18 × 500 mg
Rituximab	Cycle 1:	Cycle 1:	Cycle 1:	6	3 × 100 mg

[6] Federal health reporting. Average body measurements of the population (2017, both sexes), www.gbe-bund.de
[7] The basis for the calculation is the total consumption for a complete treatment over 6 cycles.

Designation of the therapy	Dosage/ application	Dose/patient/ treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
	375 mg/m^2 Cycle 2–6: 500 mg/m^2	712.5 mg Cycle 2–6: 950 mg	3 × 100 mg 1 × 500 mg Cycle 2–6: 2 × 500 mg		11 × 500 mg

(Continuation)

Designation of the therapy	Dosage/ application	Dose/patient/ treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
b) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who are not eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)					
Bendamustine + rituximab (BR)					
Bendamustine	70 mg/m²	133 mg	6 × 25 mg	12	72 × 25mg
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 × 100 mg 1 × 500 mg Cycle 2–6: 2 × 500 mg	6	3 × 100 mg 11 × 500 mg
Chlorambucil + rituximab (ClbR)					
Chlorambucil	0.5 mg/kg	38.5 mg	19 × 2 mg	12	228 × 2 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 × 100 mg 1 × 500 mg Cycle 2–6: 2 × 500 mg	6	3 × 100 mg 11 × 500 mg
Chlorambucil + obinutuzumab					
Chlorambucil	0.5 mg/kg	38.5 mg	19 × 2 mg	12	228 × 2 mg
Obinutuzumab	Cycle 1 Day 1: 100 mg Day 2: 900 mg Day 8: 1,000 mg day 15: 1,000 mg Cycle 2–6 Day 1: 1,000 mg	1,000 mg	1 × 1,000 mg	9	8 × 1,000 mg
c) Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons					
Ibrutinib					
Ibrutinib	420 mg	420 mg	1 × 420 mg	365	365 × 420 mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Venetoclax 10 mg	14 FCT	€ 86.12	€ 86.12	€ 86.12	€ 86.12
Venetoclax 50 mg	7 FCT	€ 201.81	€ 201.81	€ 201.81	€ 201.81
Venetoclax 100 mg	112 FCT	€ 6,035.81	€ 6,035.81	€ 6,035.81	€ 6,035.81
Venetoclax 100 mg	14 FCT	€ 782.03	€ 1.77	€ 0.00	€ 780.26
Obinutuzumab 1,000 mg	1 CIS	€ 3,401.38	€ 1.77	€ 0.00	€ 3,399.61
Appropriate comparator therapy					
Bendamustine 25 mg	5 PIC	€ 365.10	€ 1.77	€ 17.25	€ 346.08
Chlorambucil 2 mg	50 FCT	€ 134.01	€ 1.77	€ 67.30	€ 64.94
Cyclophosphamide 500 mg	6 PIJ	€ 79.91	€ 1.77	€ 8.98	€ 69.16
Fludarabine 50 mg	5 TSS	€ 532.80	€ 1.77	€ 25.41	€ 505.62
Fludarabine 50 mg	1 KII	€ 115.28	€ 1.77	€ 5.09	€ 108.42
Ibrutinib 420 mg	28 FCT	€ 5,627.09	€ 1.77	€ 0.00	€ 5,625.32
Rituximab 100 mg	2 CIS	€ 698.87	€ 1.77	€ 39.08	€ 658.02
Rituximab 500 mg	1 CIS	€ 1,732.26	€ 1.77	€ 98.21	€ 1,632.28

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services:

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

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

Designation of the therapy	Type of service	Cost per package or service	Treatment days per year	Annual costs per patient
Rituximab	HBV test Hepatitis B surface antigen status (fee schedule number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (fee schedule number 32614)	€ 5.90	1	€ 5.90
	Pre-medication Antihistamines e.g. dimetindene i.v. 4 mg Antipyretics e.g. Paracetamol 2 x 500 mg	€ 14.46 € 1.33[8]	6 6	€ 28.92 € 1.33
Obinutuzumab	HBV test Hepatitis B surface antigen status (fee schedule number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (fee schedule number 32614)	€ 5.90	1	€ 5.90
	Pre-medication Corticosteroid e.g. dexamethasone 20 mg Antihistamines e.g. dimetindene i.v. 4 mg Antipyretics e.g. Paracetamol 2 x 500 mg	€ 29.56[9] € 14.46 € 1.33[6]	9 9 9	€ 29.56 € 28.92 € 1.33

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*) (status: 11th Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit 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 sales price and the maximum surcharge for

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

[9] Based on a fixed reimbursement rate.

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 according to the regulations in Annex 3 of the *Hilfstaxe*.

3. Bureaucratic costs

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

4. Process sequence

At its session on 8 January 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy established by the G-BA was reviewed. At its session on 26 June 2019, the Subcommittee on Medicinal Products redefined the appropriate comparator therapy.

On 3 April 2020, the pharmaceutical company submitted a dossier for the benefit assessment of venetoclax to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 3 April 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient venetoclax.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 July 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 July 2020. The deadline for submitting written statements was 5 August 2020.

The oral hearing was held on 24 August 2020.

By letter dated 24 August 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 25 September 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 October 2020, and the proposed resolution was approved.

At its session on 15 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 January 2019	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	26 June 2019	Redefinition of the appropriate comparator therapy
Working group Section 35a	18 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	24 August 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 September 2020 29 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 October 2020	Concluding discussion of the draft resolution
Plenum	15 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 15 October 2020

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

Prof. Hecken