Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V Venetoclax (Reassessment after cancellation of orphan drug status)

From 16. May 2019

Contents

1. Legal basis

According to Section 35a paragraph 1 Book V of the German Social Code (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 shall be carried out on the basis of evidence provided by the pharmaceutical manufacturer. This must be submitted to the G-BA electronically (including all clinical trials carried out or commissioned) at the latest by the time the medicinal product has been placed on the market for the first time and been authorised for a new therapeutic indication. It must contain the following information in particular:

1st Approved therapeutic indication

2nd medicinal benefits

3rd additional medical benefits in relation to appropriate comparator therapy

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

5th Therapy costs for statutory health insurance

6th Requirement for quality-assured application

The Federal Joint Committee may commission the Institute for Quality and Efficiency in Health Care (IQWiG) with 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 shall decide 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 decision

The medicinal product Venclyxto® with the active ingredient Venetoclax was initially authorised as an orphan drug under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999. This marketing authorisation as an orphan drug was granted for the following therapeutic indication

“Venclyxto is used as monotherapy to treat chronic lymphocytic leukaemia (CLL) in adults who have 17p deletion or TP53 mutation and who are not suitable for treatment with an inhibitor of the B-cell receptor signalling pathway or who have experienced therapeutic failure.

Venclyxto is used as monotherapy to treat CLL in adults without 17p deletion or TP53 mutation who have experienced therapy failure both with chemo-immunotherapy and an inhibitor of the B-cell receptor signalling pathway

For this therapeutic indication, the G-BA decided on 15. Juni 2017 on the benefit assessment of Venetoclax on the basis of the statutory regulations on the benefit assessment of orphan drugs (Section 35a paragraph 1 sentence 11 SGB V).

Because of the approval for further therapeutic indications, the orphan status for the marketing authorisation Venclyxto® was revoked. As a result of this, the pharmaceutical manufacturer was requested by the G-BA, by letter dated 9. November 2018 to submit proofs in accordance with Chapter 5, Section 5, paragraphs 1 to 6 VerfO and to prove the additional benefit compared with the appropriate comparator therapy.

On 22. November 2018, the pharmaceutical manufacturer submitted a dossier on the active ingredient Venetoclax in due time (i.e. within three months of receipt of the request of the G-BA) in corresponding application of Section 35a paragraph 1 sentence 10 SGB V in conjunction with Chapter 5 Section 8 paragraph 1 No. 6 and Section 12 No. 2 of the Rules of Procedure (VerfO) of the G-BA.

The G-BA commissioned the IQWiG with the assessment of the dossier. The benefit assessment was published on 1. März 2019 on the website of the G-BA (www.g-ba.de), thus initiating the written comments procedure. An oral hearing was also held.

The G-BA made its decision on the question whether an additional benefit of Venetoclax compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical manufacturer, the dossier evaluation prepared by the IQWiG, and the comments submitted in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA evaluated the data justifying the finding of an additional benefit with regard to 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 comments received and the oral hearing, the Federal Joint Committee 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 for Venetoclax (Venclyxto®) in accordance with the product information (last revised: December 2018)

Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia CLL:

- in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
- in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with CLL who have a 17p deletion or TP53 mutation and who are unsuitable for or have failed a B-cell receptor inhibitor

Ibrutinib

or

Idelalisib + rituximab

or

Best supportive care (only for patients for whom prior therapy with ibrutinib or idelalisib + rituximab failed)

Best supportive care is the therapy that ensures the best possible, individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

b) Adult CLL patients who do not exhibit 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor

Ibrutinib

or

Idelalisib + rituximab

or

Best supportive care

Best supportive care is the therapy that ensures the best possible, individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

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 guidelines pursuant to Section 92 paragraph 1 SGB V or the principle of economic efficiency contradict this.

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

1. To be considered as a comparator therapy, the drug must, in principle, have a marketing authorisation for the therapeutic indication.
2. If non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. Drug applications or non-drug treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee are preferred as comparator therapy.
4. According to the generally accepted state of medical knowledge, 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. The active ingredients bendamustine, chlorambucil, cyclophosphamide, fludarabine, ibrutinib (as a single substance or in combination with bendamustine and rituximab), idelalisib (in combination with rituximab or ofatumumab), venetoclax, obinutuzumab,

ofatumumab, rituximab (in combination with chemotherapy), prednisolone, and prednisone have been approved for the treatment of CLL. However, ofatumumab is no longer marketable in Germany.

Because CLL belongs to the group of non-Hodgkin's lymphomas, the active ingredients cytarabine, doxorubicin, trofosfamide, vinblastine, and vincristine are also approved in principle.

On 2. Allogenic stem cell transplantation represents a non-medicinal treatment option in the present therapeutic indication. However, this is only applicable in individual cases for a few patients and cannot be considered a standard therapy for the majority of patients in the therapeutic indication. It is assumed that allogenic stem cell transplantation is not indicated at the time of therapy.

On 3. The following decisions or guidelines of the G-BA are available for drugs or non-drug treatments:

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

- Idelalisib: Resolutions from 15 September 2016 and 16 March 2017
- Ibrutinib: Resolutions from 16 April 2015, 21 July 2016, 15 December 2016, and 16 March 2017
- Venetoclax: Resolution from 15 June 2017 (replaced by this resolution)
- Obinutuzumab: Resolution from 5 February 2015

On 4.

a) <u>Adult patients with CLL who have a 17p deletion or TP53 mutation and who are unsuitable for or have failed a B-cell receptor inhibitor</u>

With regard to the formulation of the therapeutic indication, it is assumed that the patients are not suitable for only one of the two inhibitors of the B-cell receptor signalling pathway (BCRi: idelalisib or ibrutinib) or showed therapeutic failure.

Patients with a 17p deletion or TP53 mutation respond significantly worse to chemo-immunotherapy; remission is usually only of short duration. Therefore, for patients with 17p deletion or TP53 mutation, chemo-immunotherapy is not usually considered to be an appropriate comparator therapy.

The therapeutic indication includes both patients who are not suitable for one of the two BCRi drugs and have not been pretreated as well as patients who have been pretreated and have experienced a therapeutic failure.

For the first-line treatment of patients with a 17p deletion or TP53 mutation several resolutions have been passed on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

For the active ingredient ibrutinib, an indication of an unquantifiable additional benefit was found compared with best supportive care for patients who are unsuitable for chemo-immunotherapy (resolution of 21 July 2016).

For idelalisib in combination with rituximab, an indication of an unquantifiable additional benefit was found compared with best supportive care for patients for whom no other therapies are suitable (resolution of 16 March 2017).

The resolution of 16 March 2017 found idelalisib in combination with ofatumumab was not certified as having any additional benefit for patients not suited to any other therapies.

Guidelines recommend treatment with ibrutinib or also idelalisib in combination with rituximab in the present therapeutic situation; however, the latter is recommended only if no other therapy options are suitable.

Should ibrutinib or idelalisib in combination with rituximab fail, there is no high-quality evidence that switching to the other B-cell receptor inhibitor will benefit patients. However, especially taking into account the healthcare prognosis of patients with a 17p deletion and/or TP53 mutation, follow-up therapy with ibrutinib or idelalisib in combination with rituximab, depending on which active ingredient was used in the previous therapy, is considered to be a possible therapy alternative to best supportive care.

b) Adult CLL patients who do not exhibit 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor

According to the guidelines, it may be recommended to switch to the other BCRi for patients who have experienced therapy failure both with chemo-immunotherapy and with a B-cell receptor inhibitor.

However, there is no high-quality evidence for the benefit of switching to the other B-cell receptor inhibitor. Nevertheless, especially taking into account the healthcare prognosis of patients with therapy failure under chemo-immunotherapy and also under an inhibitor of the B-cell receptor signalling pathway, follow-up therapy with ibrutinib or idelalisib in combination with rituximab, depending on which active ingredient has been used in the previous therapy, is regarded as a possible therapy alternative to best supportive care.

For ibrutinib in combination with bendamustine and rituximab, a significant additional benefit over bendamustine in combination with rituximab was found in the benefit assessment for patients with at least two prior therapies for whom bendamustine in combination with rituximab represents the individually optimised therapy (resolution of 16 March 2017). However, according to the existing therapeutic indication, patients in whom both chemo-immunotherapy and an inhibitor of the B-cell receptor signalling pathway failed in therapy are not usually indicated for re-therapy with chemo-immunotherapy following treatment with an inhibitor of the B-cell receptor signalling pathway, which is why the additional benefit cannot easily be transferred to the existing therapeutic indication.

According to the resolution of 16 March 2017, there is no additional benefit for idelalisib in combination with ofatumumab for the treatment of patients with relapsed or refractory CLL for whom chemotherapy is not indicated.

In summary, the combinations ibrutinib and bendamustine and rituximab as well as idelalisib and ofatumumab are, therefore, currently not an appropriate comparator therapy in the therapeutic indication.

For both partial therapeutic indications, it was assumed in determining the appropriate comparator therapy that only patients in need of treatment (e.g. with Stage C according to Binet) were to be included.

The findings established in Annex XII should not be construed as constraining the scope of treatment available to medical practitioners tasked with treatment.

2.1.3 Extent and probability of additional benefit

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

a) Adult patients with CLL who have a 17p deletion or TP53 mutation and who are unsuitable for or have failed a B-cell receptor inhibitor

An additional benefit is not proven.

Justification

In order to demonstrate an additional benefit, the pharmaceutical manufacturer used the results of the corresponding sub-populations of the pivotal study M13-982 and the supportive study M14-032.

The pivotal M13-982 study is a single-arm, non-controlled phase II study to evaluate the efficacy and safety of venetoclax in CLL patients with 17p deletion. A total of 158 patients with relapsed or refractory CLL were examined as well as a small proportion of patients without prior CLL treatment. The study was conducted at a total of 40 centres in Europe, North America, and Australia.

The inclusion of the patients took place in two phases: first within the framework of the main cohort and later supplemented by a safety cohort. After initial titration, patients were treated with 400 mg of venetoclax once daily. The build-up dosing phase of the 107 patients in the main cohort was 4 weeks; solely for the 51 patients of the subsequently included safety cohort was build-up dosing performed according to the five-week scheme shown in the product information. The extension of the build-up dosing phase was introduced primarily with the aim of minimising the risk of tumour lysis syndrome. Otherwise, there were no significant differences in the inclusion and exclusion criteria between the main cohort and the safety cohort.

The primary endpoint of the study was the overall response rate according to criteria of the iwCLL working group of the National Cancer Institute[2]. In addition to other endpoints of therapy response, overall survival (OS), progression-free survival (PFS), the proportion of patients with allogenic stem cell transplantation, and adverse events were identified as secondary endpoints. The minimal residual disease (MRD), morbidity and quality of life endpoints were also assessed, the latter two using the MD Anderson Symptom Inventory (MDASI) and the patient-reported questionnaire EORTC-QLQ-C30 in conjunction with the supplementary module CLL16.

In the two-arm, non-controlled, M14-032 supportive phase II study, US CLL patients were examined at several centres after previous therapy with a B-cell receptor inhibitor (91 patients after ibrutinib therapy and 36 patients after idelalisib therapy). Patients were included regardless of 17p deletion status or TP53 mutation. The dosage received by the study patients was built up in accordance with the product information, eventually reaching a daily dosage of 400 mg venetoclax. The endpoints of response, overall survival, adverse events, morbidity, and quality of life were also evaluated in this study using the respective EORTC QLQ-C30 and EORTC QLQ-CLL16 scoring system.

The pharmaceutical company specified that the sub-population relevant to their analysis should comprise patients with 17p deletion or TP53 mutation. These received doses in accordance with the product information, both in the build-up dosage phase and over the subsequent course of the study. In the case of the M14-032 study, this applied to more than 80% of the patients, which is why the total study population was used as a proxy. This percentage was lower for the M13-982 study, and, as a result, the pharmaceutical company instead established a sub-population that had received venetoclax in accordance with the approval specifications. In total, the results of 131 patients from both studies are presented.

In the summary, the pharmaceutical manufacturer compares individual results of this patient pool descriptively with results from various ibrutinib studies (RESONATE-17, NCT01105247, NCT01109069).

However, on the basis of the present unadjusted historical comparison, no additional benefit can be determined for adult CLL patients with a 17p deletion or TP53 mutation and who are

[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 leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008; 111(12): 5446–56.

unsuitable for treatment with an inhibitor of the B-cell receptor signalling pathway or who experienced therapy failure. The additional benefit for this patient population is not proven.

Even taking into account the small number of patients and in particular the extent of the treatment effects described in the historical comparison to the appropriate comparator therapy, it would be impossible to definitively exclude the possibility that the potential differences are mainly due to systematic bias (e.g. due to relevant differences between the compared populations).

In the case of the present patients with 17p deletion or TP53 mutation who are not suitable for treatment with a B-cell receptor signalling pathway inhibitor or who showed therapy failure, taking into account the particular prognosis of CLL patients with 17p deletion or TP53 mutation, treatment with venetoclax in accordance with the product information may be a relevant therapy option for individual patients.

b) Adult CLL patients who do not exhibit 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor An additional benefit is not proven.

Justification

In order to demonstrate an additional benefit in sub-population b, the pharmaceutical manufacturer also relied on the results of the corresponding patients of the M14-032 study.

Only those patients from study M14-032 without 17p deletion or TP53 mutation are relevant for the analysis; this excludes all patients from the M13-982 study, as these were all without a 17p deletion. The sub-population formed by the pharmaceutical company on the basis of the total study population of M14-032 comprises only 14 patients.

The pharmaceutical company selectively compares the results of the very small sub-population identified from the M14-032 study with the results of patients from different ibrutinib studies (RESONATE-17, NCT01105247, NCT01109069). This is an unadjusted historical comparison.

In the present case, such an approach is in general unsuitable for establishing the additional benefit of venetoclax compared with the appropriate comparator therapy. Conclusions on the extent to which overall survival under treatment with venetoclax is similar to that under treatment with ibrutinib are not valid on the basis of the available results.

Overall, the additional benefit for adult CLL patients with a 17p deletion or TP53 mutation in whom both chemo-immunotherapy and a B-cell receptor signalling pathway inhibitor have failed is not proven.

For patients without 17p deletion or TP53 mutation who experienced therapy failure under chemo-immunotherapy and after receiving a B-cell receptor signalling pathway inhibitor, taking into account the prognosis of these patients, treatment with venetoclax in accordance with the product information may, however, be a relevant therapy option for individual patients.

2.1.4 Summary of the assessment

The present assessment concerns the re-assessment of Venclyxto® with the active ingredient venetoclax in the following therapeutic indication following the withdrawal of orphan drug status:

Venclyxto monotherapy is indicated for the treatment of CLL:

- in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
- in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor

In the benefit assessment, two patient groups were distinguished:

a) Adult patients with CLL who have a 17p deletion or TP53 mutation and who are unsuitable for or have failed a B-cell receptor inhibitor

b) Adult CLL patients who do not exhibit 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor

Patient group a)

Ibrutinib or idelalisib in combination with rituximab or best supportive care were determined as appropriate comparator therapy. The latter only for patients after previous therapy with a BCRi.

The pharmaceutical company draws on results from sub-populations from the non-comparative studies M13-982 and M14-032 to demonstrate the additional benefit and compares these in an unadjusted manner with results from studies in which ibrutinib was investigated.

The evidence presented is of limited significance and, therefore, not suitable for assessing the additional benefit of venetoclax. Overall, the additional benefit for sub-population a) is not proven.

Patient group b)

To demonstrate the additional benefit in patient group b), the pharmaceutical manufacturer also draws on the results of a sub-population from the non-comparative study M14-032 and compares these with the results of studies in which ibrutinib was investigated.

Overall, the evidence presented is of limited significance and, therefore, not suitable for assessing the additional benefit of venetoclax. Thus, an additional benefit for patient group b) is not proven.

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

The G-BA bases its resolution on the patient numbers stated by the pharmaceutical manufacturer in the dossier, taking the analyses of the IQWiG into account. The patient numbers submitted by the pharmaceutical manufacturer are taken from the previous resolution on venetoclax in the indication under evaluation. The ranges used here take into account uncertainties in the data basis and reflect the minimum and maximum values obtained when deriving the patient numbers. The proportions for subdivision into sub-populations with and without 17p deletion or TP53 mutation as well as the proportions for patients suitable or unsuitable for BCRi should be regarded as uncertain.

2.3 Requirements for quality-assured application

The requirements of the product information must be taken into account. The European Medicines Agency (EMA) makes the contents of the summary of product characteristics on Venclyxto® (active ingredient: Venetoclax) freely available under the following link (last access: 2. April 2019):

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

Treatment with venetoclax 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.

Patients who are unsuitable for treatment with a B-cell receptor inhibitor because of a pertinent cardiovascular disease were not investigated in the M13-982 study.

2.4 Treatment costs

a) Adult patients with CLL who have a 17p deletion or TP53 mutation and who are unsuitable for or have failed a B-cell receptor inhibitor

and

b) Adult CLL patients who do not exhibit 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor

The treatment costs are based on the information provided in the product information and the LAUER-TAXE® (last revised: 15. April 2019).

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and the price less statutory discounts in accordance with Sections 130 and 130a SGB V. To calculate the annual costs of treatment, the required number of packs of a particular potency was first determined on the basis of consumption. After determining the number of packs of a particular potency, the pharmaceutical costs were then calculated on the basis of the costs per pack less the statutory discounts.

Only standard doses were considered in calculating costs. Patient-specific dose adjustments (e.g. because of side effects or comorbidities) were not taken into account when calculating annual treatment costs.

Treatment period:

If no maximum therapy duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual therapy duration varies from patient to patient and/or is shorter on average.

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	continuously 1 × daily	365	1	365
Appropriate comparator therapy				
Ibrutinib				
Ibrutinib	continuously 1 × daily	365	1	365
Idelalisib + rituximab[3]				
Idelalisib	continuously 2 × daily	365	1	365

[3] Dosage of Idelalisib in combination with Rituximab according to the schedule in the GS-US-312-0116 study.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Rituximab	once at Week 1, 2, 4, 6, 8, 12, 16, and 20	8 cycles	1	8
Best supportive care (BSC)[4]				
BSC	patient- individualized			

Usage:

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

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/day of treatment	Treatment days/ Patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Venetoclax[5]	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	365	14 × 10 mg 7 × 50 mg 1 369 × 100 mg
Appropriate comparator therapy					
Ibrutinib					
Ibrutinib	420 mg	420 mg	3 × 140 mg	365	1 095 × 140 mg
Idelalisib + rituximab					
Idelalisib	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Rituximab	Cycle 1: 375 mg/m^2 Cycle 2–8: 500 mg/m^2	Cycle 1: 712.5 mg Cycle 2–8: 950 mg	Cycle 1: 3 × 100 mg 1 × 500 mg Cycle 2–8: 2 × 500 mg	8	3 × 100 mg 15 × 500 mg
Best supportive care (BSC)					

[4] In a comparison with BSC, this should also be used in addition to the medicinal product to be assessed.
[5] Calculation for the first year of treatment. In the following year, the average annual consumption was 1460 tablets of 100 mg each.

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/day of treatment	Treatment days/ Patient/ year	Average annual consumption by potency
BSC	patient- individualized				
<> <> *TBL: Tablets*					

Costs:

Costs of the medicinal product:

Designation of the therapy	Package sizes	Costs (pharmacy selling price)	Sales discount Section 130 SGB V	Sales discount Section 130a SGB V	Costs after deduction of statutory discounts
Venetoclax	10 mg 14 TBL	€ 94.36	€ 1.77	-	€ 92.59
	50 mg, 7 TBL	€ 219.40	€ 1.77	-	€ 217.63
	100 mg, 112 TBL	€ 6,523.13	€ 1.77	-	€ 6,521.36
Rituximab	100 mg, 2 vials	€ 716.88	€ 1.77	€ 39.08	€ 676.03
	500 mg, 1 vial	€ 1,777.00	€ 1.77	€ 98.21	€ 1,677.02
Ibrutinib	140 mg, 120 TBL	€ 8,516.41	€ 1.77	-	€ 8,514.64
Idelalisib	150 mg, 60 TBL	€ 4,534.74	€ 1.77	€ 255.71	€ 4,277.26
<> <> *TBL: Tablets*					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15. April 2019

Costs for additional SHI services required:

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 additional SHI services required.

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 usual expenditure in the course of the treatment are not shown.

Designation of the therapy	Type of service	Cost per package	Treatment days per year	Annual costs per patient
Rituximab	HBV test	Hepatitis B surface antigen status: € 5.50[6]		

[6] Fee schedule number 32781.

		Hepatitis B antibody status: € 5.90[7]		
	Pre-medication Antihistamines e.g. dimetinden i.v. Antipyretics e.g. paracetamol	€ 14.76 € 1.36[8]	8 8	€ 29.52 € 1.36

Other services covered by SHI funds:

The special agreement 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 retail 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"] (last revised: Arbitral award to determine the mg prices for parenteral preparations of proprietary medicinal products in oncology in the auxiliary tax according to Section 129 paragraph 5c sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatics 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 shall be payable for the production of parenteral solutions containing monoclonal antibodies. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating stipulated in the *Hilfstaxe*. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts 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

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

By letter dated 21. Dezember 2017, received on 21. Dezember 2017, the pharmaceutical manufacturer requested consultation in accordance with Section 8 AM-NutzenV, among other things, on the question of appropriate comparator therapy. The sub-committee on medicinal products determined the appropriate comparator therapy at its meeting on 20. Februar 2018. The consultation took place on 9. März 2018 .

On 22. November 2018, the pharmaceutical manufacturer 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, No. 6 VerfO.

By letter dated 22. November 2018 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

[7] Fee schedule number 32614.

[8] Non-prescription drugs 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 drug) are not subject to the current drug price regulation. Instead, 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 manufacturer – plus the surcharges pursuant to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

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 IQWiG's evaluation of the dossier was submitted to the G-BA on 27. Februar 2019, and with its publication on 1. März 2019 on the G-BA website, the written statement procedure was initiated. The deadline for submitting written statements was 22. März 2019.

The oral hearing was held on 8. April 2019.

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 meetings.

The evaluation of the comments received and the oral hearing were discussed at the meeting of the subcommittee on 7. Mai 2019 , and the proposed resolution was approved.

At its meeting on 16. Mai 2019, the plenum decided to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	20. Februar 2018	Determination of the appropriate comparator therapy
Working group Section 35a	2. April 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8. April 2019	Conduct of the oral hearing
Working group Section 35a	16. April 2019 29. April 2019	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7. Mai 2019	Concluding discussion of the proposed resolution
Plenum	16. Mai 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16. May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken