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 (New therapeutic indication: chronic lymphocytic leukaemia, combination with rituximab)

From 16. May 2019

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 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 at the time of the first placing on the market and the marketing authorisation of new therapeutic indication for the medicinal product. 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 G-BA 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

On 1. Januar 2017, the active ingredient Venetoclax was listed for the first time in the “Große Deutsche Spezialitäten-Taxe” (Lauer-Taxe®).

On 29. Oktober 2018, Venetoclax received marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 No. 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of changes to marketing authorisations for medicinal products for human and veterinary use (OJ L 334, 12 December 2008, pg. 7).

The pharmaceutical manufacturer has submitted a dossier in accordance with Section 4 paragraph 3 No. 2 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 on 22. November 2018 in due time (i.e. at the latest within four weeks after informing the pharmaceutical manufacturer 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 1. März 2019 on the website of the G-BA (www.g-ba.de), thus initiating the written statement 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 assessment prepared by the IQWiG, the statements submitted in the written and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. 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 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 for Venetoclax (Venclyxto®) according to marketing authorisation dated 29 October 2018

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

A patient individualized chemo-immunotherapy with selection of bendamustine, chlorambucil, fludarabine with cyclophosphamide, and ibrutinib with bendamustine, each in combination with rituximab, taking into account the general condition as well as the success and tolerability of the previous therapy.

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

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 the 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

[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. 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 are 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 counted as one of the standard therapies 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 drug applications 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
- Obinutuzumab: Resolution from 5 February 2015

On 4.

Based on the evidence available, the G-BA considers it appropriate to divide patients with chronic lymphocytic leukaemia who have received at least one prior therapy into two relevant sub-populations.

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

Patients without 17p deletion or TP53 mutation can also benefit from the combination of a chemotherapeutic agent with rituximab in the second line of therapy. A therapy decision should be made taking into account the general condition as well as the success and tolerability of the prior therapy. Re-therapy with the active ingredients of the previous therapy is also possible. Under these conditions, rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR), and rituximab in combination with chlorambucil (ClbR) represent possible treatment options included in the appropriate comparator therapy.

An additional benefit of idelalisib (in combination with rituximab or ofatumumab) and ibrutinib as a single substance has not yet been demonstrated for this sub-population in the approved

therapeutic indication (see resolutions on the benefit assessment of medicinal products with new active ingredients of 21 July 2016, 15 September 2016, and 16 March 2017).

For patients in the present sub-population with at least two prior therapies and without 17p deletion, the combination of ibrutinib, bendamustine, and rituximab is included in the appropriate comparator therapy. For this patient group, the G-BA found evidence of a considerable additional benefit compared to bendamustine with rituximab (resolution of 16 March 2017).

The G-BA has therefore determined a patient individualized chemo-immunotherapy according to the physician's requirements for pre-treated patients without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated, taking into account the general condition as well as the success and tolerability of the pre-treatment, to be an appropriate comparator therapy.

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

Patients with a 17p deletion or TP53 mutation respond significantly worse to chemo-immunotherapy; remission is usually only of short duration. Guidelines recommend treatment with ibrutinib or idelalisib/rituximab in this therapeutic situation.

The G-BA has found an indication of a non-quantifiable additional benefit for both ibrutinib and idelalisib with rituximab within the framework of the benefit assessment for patients with relapsed or refractory CLL for whom chemotherapy is not indicated. Particularly in patients with 17p deletion or TP53 mutation, clinically relevant advantages were shown. However, the evaluations focused on patients for whom chemotherapy was not indicated because of poor general condition, the number of prior therapies, or existing contraindications. However, despite the limited evidence, it can be assumed that even in patients who were refractory to prior chemo-immunotherapies or showed only a short relapse-free interval, treatment with ibrutinib or idelalisib with rituximab would be preferable, even if these patients (based on their general condition) would in principle be eligible for renewed chemo-immunotherapy.

After the failure of ibrutinib or idelalisib/rituximab in the primary treatment of CLL, there is no high-quality evidence of the benefit of switching to the other B-cell receptor inhibitor. However, especially taking into account the care situation of patients with a 17p deletion or TP53 mutation, follow-up therapy with ibrutinib or idelalisib and rituximab, depending on which active ingredient was used in the previous therapy, is considered to be a possible therapy alternative to best support care. Best supportive care is only part of the appropriate comparator therapy for patients for whom prior therapy with ibrutinib or idelalisib and rituximab has failed.

With venetoclax as monotherapy, there is another treatment option available that has been approved in this therapeutic indication. However, the therapeutic significance of this cannot currently be conclusively assessed on the basis of the evidence on which the resolution of 15 June 2017 was based. The resolution of 15 June 2017 was limited until June 2022 because the limited database. It was also combined with the requirement to generate further study evidence for venetoclax as a monotherapy.

For both partial application areas, it was assumed for the determination of the appropriate comparator therapy that only patients in need of treatment (e.g. with Stage C according to Binet) were included.

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 additional benefit

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

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

a1) Patients for whom bendamustine in combination with rituximab is the patient-individually most suitable therapy

Indication of a minor additional benefit.

Justification

In order to demonstrate an additional benefit, the pharmaceutical manufacturer used the results of the pivotal MURANO study.

A total of 391 adult patients with relapsed or refractory CLL according to iwCLL criteria[2] were enrolled in the randomised, open-label phase III study. Patients had to have at least one but no more than three pre-therapies. At the beginning of the study, patients were randomized 1:1 to receive either a treatment with venetoclax in combination or a treatment with rituximab or bendamustine in combination with rituximab. Treatment with the respective combination therapy was carried out for a maximum of six cycles or until disease progression or the occurrence of intolerable toxicities. If no progression or toxicity occurred, subsequent monotherapy with venetoclax was possible in the intervention arm for a total of up to 2 years. The dosage of the medicinal products used corresponded to the specifications of the respective product information, also with regard to the dosage of venetoclax, both in the intervention arm and in the comparison arm.

Patients with good general condition (ECOG PS 0 to 1) after relapsed or refractory disease were enrolled. By definition, a refractory disease was present if a patient did not respond to the previous therapy or if the disease progressed after less than six months. Relapsed patients responded at least partially to pre-treatment and showed disease progression after 6 months at the earliest. Pre-treatment with bendamustine was only permitted if the response to the therapy had been at least 24 months. Patients who had previously undergone allogenic stem cell transplantation were excluded from the study.

The inclusion of the patients in the MURANO study was independent of the presence of a 17p deletion or TP53 mutation. To demonstrate the additional benefit for sub-population a, the pharmaceutical manufacturer presented the results of the subgroup in patients who did not show a 17p deletion or TP53 mutation and also responded to the previos therapy (relapse after more than 12 months after chemotherapy or 24 months after chemo-immunotherapy). 74 patients remained in the intervention arm for the corresponding evaluation and 66 patients in the comparison arm. The average age of the patients was 63 and 65 years, respectively.

The primary endpoint of the study was progression-free survival as documented by the investigator. The endpoint was also assessed for interim analysis by an Independent Review Committee. Other secondary endpoints were overall survival, percentage of patients with complete response, event-free survival, and time to next treatment. As part of the study, patient health was assessed using the visual analogue scale of EQ-5D; patient reported symptoms and quality of life were assessed using EORTC QLQ-C30. The proportion of patients with minimal residual disease was also explored. Side effects analysis included all adverse events that occurred at the beginning of the study and up to 28 days after the last treatment with study therapy or 90 days after the last dose of rituximab, whichever was longer.

At the time the resolution was passed, the MURANO study had not yet been completed. In the dossier, results were presented for the data cut-offs of 8 May 2017 and, if available, 8 May 2018.

The operationalization of the CIT population in the dossier of the pharmaceutical manufacturer (patients without 17p deletion or TP53 mutation with relapse after more than 12 months after

[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.

chemotherapy or 24 months after chemo-immunotherapy) is considered adequate and representative of care practice for patients for whom chemo-immunotherapy is indicated.

In accordance with the assessments of the professional societies within the framework of the statements procedure, it is assumed that bendamustine in combination with rituximab represents the primary therapy option for a large number of patients in the partial therapeutic indication in question. In principle, however, the partial therapeutic indication also includes patients for whom other therapy options (e.g. therapy with FCR) would have been more suitable. Nevertheless, the G-BA assumes that bendamustine in combination with rituximab represents an adequate implementation of the appropriate comparator therapy for the majority of patients in the present case.

A selection of the therapy by the investigator was nevertheless not possible within the scope of the MURANO study. In this respect, the further therapy options of the appropriate comparator therapy were not shown here.

Consequently, the results of the MURANO study cannot be used to derive an additional benefit in the entire sub-population a). The division of the population into patients for whom bendamustine in combination with rituximab is the patient-individually most suitable therapy (a1) and patients for whom a therapy other than bendamustine in combination with rituximab is the patient-individually most suitable therapy (a2) is therefore appropriate.

Extent and probability of additional benefit

Mortality

Overall survival

Overall survival differed significantly between study arms in terms of the p value based on the pre-specified log-rank test (hazard ratio (HR): 0.32 [95% confidence interval (CI): 0.10; 1.02]; p value 0.043). The median time to the event has not yet been reached in both study arms for the available data cut-off of 8 May 2018. The evaluation is based on very low event numbers with only four deaths in the intervention arm (5.4%) and 10 deaths in the comparison arm (15.2%).

Because of the small number of cases included in the evaluation of overall survival to date, taking into account the broad confidence interval of the effect estimator, which includes 1, the advantage of venetoclax in combination with rituximab over the appropriate comparator therapy in terms of overall survival cannot currently be quantified.

Morbidity

Progression-free survival

In the MURANO study, the endpoint PFS is operationalised as the time from first use of the study medication to disease progression or death regardless of cause of death.

Progression-free survival was statistically significantly different in both study arms in favour of intervention (HR: 0.11 [95% CI: 0.05; 0.25]; p value < 0.001). The median time to event was not yet reached in the intervention arm at the data cut-off of 8 May 2017; for only 9.5% of patients was an event recorded. In the comparison arm, the median time to event was 22.8 months.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively by means of imaging procedures. Taking into account the aforementioned aspects, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

EQ-5D visual analogue scale

Results of the visual analogue scale of the EQ-5D are available for the assessment of the health status of the study patients.

For the benefit assessment, the pharmaceutical manufacturer presented evaluations of the mean change in the VAS score and also responder analyses for the time until the change by ≥ 7 and by ≥ 12 points compared with the baseline value.

In addition to the responder analyses, the IQWIG addendum presents the evaluation of the mean change compared to the baseline value.

The IQWiG classifies the study on which the derivation of the MID for the responder analyses is based (Pickard et al., 2007) as unsuitable to prove the validity of the MID. This is justified on the one hand by the fact that the work mentioned does not contain a longitudinal study for the determination of MID, which is assumed in the current scientific discussion for the derivation of a valid MID. In addition, the IQWiG does not consider the ECOG-PS and FACT-G anchors used in the study to be suitable for the derivation of MID.

Against the background that responder analyses based on a MID for a clinical assessment of effects have general advantages compared with an analysis of standardized mean value differences and taking into account that the validation study in question has already been used in previous evaluations, the responder analyses are nevertheless used by the G-BA in the present assessment to assess the effects on the symptoms.

The difference between the study arms is not statistically significant for any of the evaluations presented.

Symptom scales EORTC QLQ-C30

In the MURANO study, the symptomatology of the patients was measured using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30.

The pharmaceutical manufacturer submits MMRM evaluations (mixed model with repeated measurements) and additional responder analyses in the dossier. However, in the present case, the responder analyses for the time until the change by ≥ 10 points cannot be used. This is mainly due to the fact that a high proportion of patients, especially from the intervention arm, were not included in the assessments. Because of a protocol error, only 40.5% of the patients in the intervention arm received a baseline value at the beginning of the study (comparison arm 93.9%). In addition, at the time the baseline value was collected, patients were already aware of the allocation of therapy. In the comparison between intervention and control arms, there is a relevant difference between the baseline values.

However, it seems plausible that the subset of patients recruited later (for which a survey was available at the beginning of the study) is structurally identical with the control group so that the results are nevertheless used differently by the pharmaceutical manufacturer. The MMRM evaluations could include at most patients with baseline values. In addition, at least one value after at the beginning of each study was presumably required for consideration in the evaluation. In addition, the baseline value was adjusted. Nevertheless, considerable uncertainties remain regarding the evaluation of this endpoint.

With regard to the mean difference, there was a statistically significant difference for the diarrhoea symptom scale alone – to the detriment of the intervention (mean difference (MD): 10.74 [95% CI: 1.37; 20.10]). However, taking the Hedges' g into account, it cannot be assumed that this difference is clinically relevant (0.50 [95 % CI: 0.05; 0.94]). With regard to all other symptom scales, there were no statistically significant differences.

B symptoms

In the context of the endpoint B symptoms, unexplained weight loss (>10% in no more than 6 months), night sweats, and unexplained fever were recorded. The components of the endpoint are generally patient-relevant.

On the one hand, patients who had at least one B-symptom at the beginning of the study that reappeared after a period of symptom-free treatment were evaluated. Patients without interim symptom relief were therefore not included in the analysis. The assessment of this evaluation also lacks information on the time after which freedom from symptoms occurred in the course

of treatment. This time of the first symptom relief marks the starting point for the analysis. Overall, it is unclear to what extent the randomisation for this evaluation was maintained.

On the other hand, patients without B symptoms at the beginning of the study were examined with respect to the time until the first occurrence of a corresponding symptomatology. Because this is only given for a part of the patients (68% vs 64%), no statements can be derived for the total population.

Overall, there are neither advantages nor disadvantages of venetoclax in combination with rituximab in the endpoint category morbidity.

Health-related quality of life

Global Health Status & Functional Scales EORTC QLQ-C30

The explanations on the symptom scales of the EORTC QLQ-C30 apply equally to the evaluation of the associated function scales of the instrument. Taking into account the aforementioned limitation, the MMRM evaluations showed no significant difference for either the global health status or for any of the functional scales.

There is no additional benefit in the endpoint category quality of life.

Side effects

Almost all patients in both study arms had an adverse event in the course of the respective treatment (100 % vs 97.0%).

With almost identical overall rates (37.8% vs 37.9%) there is a significant difference in favour of venetoclax with rituximab in terms of time to the occurrence of the first serious adverse event (SAE; HR 0.39 [95% CI: 0.20; 0.76]; p value 0.005). The median time to an SAE was 8.8 months in the comparison arm; in the intervention arm, the median time was not yet reached.

Severe adverse events (CTCAE grade ≥ 3) were observed in 79.7% of patients in the intervention arm and in 65.2% of patients in the comparison arm after a median of 3.1 and 3.7 months, respectively. The difference is not statistically significant.

In the intervention arm, 16.2% of the patients discontinued treatment because of an adverse event; in the comparison arm, 10.6% of the patients withdrew from treatment. The difference is also not statistically significant.

When considering specific adverse events, the event time analyses only showed advantages of intervention with regard to PTs (Preferred term) of any severity to nausea, vomiting, infusion reactions, reduced appetite, dyspnoea, and rash. With regard to SOCs (system organ class) infections and parasitic diseases, there was also a statistically significant difference at the level of the SAEs in favour of venetoclax in combination with rituximab (HR: 0.33 [95% CI: 0.12; 0.94]; p value 0.038).

Overall, in the endpoint category side effects only effects in favour of venetoclax in combination with rituximab are present. The extent of the improvements is assessed as moderate in the overall view.

At the level of specific adverse events, advantages were found to be significant in the case of adverse events that are considered controllable and sufficiently treatable in the care system.

In the overall view, there is a minor additional benefit in the endpoint category side effects.

<u>Overall assessment</u>

For the benefit assessment of venetoclax in combination with rituximab, results on overall survival, morbidity, health-related quality of life, and side effects from the MURANO study are available for the sub-population under consideration.

Venetoclax in combination with rituximab significantly prolongs overall survival compared with bendamustine in combination with rituximab; however, this is based on only a few events to date.

With regard to the endpoint categories morbidity and health related quality of life, there are no differences between the interventions under consideration.

In the endpoint category side effects only positive effects of the medicinal product combination under evaluation can be observed.

Taking into account the severity of the disease, a minor additional benefit of venetoclax in combination with rituximab in sub-population a1) is determined on the basis of the positive effects. A moderate and not only slight improvement of the therapy-relevant benefit has not been achieved so far, especially with regard to a moderate avoidance of serious side effects.

Statement reliability (probability of additional benefit)

The present assessment is based on the results of a randomised controlled trial. The risk of bias at the study level is classified as low.

The risk of bias at the endpoint level is estimated to be low for the overall survival endpoint.

On the other hand, the risk of bias for the endpoints symptomatology, health-related quality of life, and health status is considered potentially high based on the limitations identified.

In the assessment of the results on adverse events, it should also be noted that the observation period between the treatment arms differs significantly. The survey was carried out in both arms until 28 days after the last study treatment. However, the treatment duration in the comparator arm is limited to six cycles of 28 days each, whereas in the intervention arm, treatment could be continued for up to 2 years. Because only a few censorings took place before the end of treatment in the comparator arm, it can be assumed that a relevant bias by potentially informative censoring is unlikely, which is why the risk of bias with regard to the SAE and the severe AE is assessed as low (CTCAE grade ≥ 3). On the other hand, the endpoint treatment withdrawals because of AE can be regarded as potentially highly biased because of the open study design.

Despite the limitation described above, an indication of an additional benefit can be derived on the basis of the MURANO randomised, controlled pivotal study.

a2) *Patients for whom a therapy other than bendamustine in combination with rituximab is the patient-individually most suitable therapy*An additional benefit is not proven.

Justification

For the sub-population of patients for whom a therapy other than bendamustine in combination with rituximab is the patient-individually most suitable therapy, no statements on the additional benefit can be made in consideration of the MURANO study. Because only results with a comparison to bendamustine in combination with rituximab were presented for the benefit assessment, there is no usable data.

The additional benefit of venetoclax in combination with rituximab is therefore not proven for sub-population a2).

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

An additional benefit is not proven.

Justification

In order to demonstrate the additional benefit in sub-population b, the pharmaceutical company also used the results of the pivotal MURANO study described above. In the dossier, the results of a high-risk population (patients with known 17p deletion or TP53 mutation, refractory patients and patients with relapse after less than 12 months) defined by the company were presented in addition to the results of the overall study population of the MURANO study.

An assessment of the additional benefit on the basis of the data submitted is not possible because from the comparison of venetoclax with rituximab versus bendamustine and rituximab, no conclusions can be drawn about the results in comparison to the appropriate comparator therapy in the sub-population in question.

In addition, the pharmaceutical company descriptively compares individual results on OS, PFS, and response from various studies investigating ibrutinib (RESONATE, RESONATE-17, CLL3002, NCT01500733, Compassionate Use Programme of the Polish Adult Leukaemia Group, PCYC-1102-CA) with the results on venetoclax with rituximab from the MURANO study.

However, the pharmaceutical company does not use any adjustment procedures and does not sufficiently discuss the comparability of the respective populations. The comparison also does not include all endpoint categories relevant for the benefit assessment. This approach is generally not suitable for generating comparative results to be taken into account for the benefit assessment in order to demonstrate an additional benefit of venetoclax in combination with rituximab compared to the appropriate comparator therapy.

The additional benefit for adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the re-evaluation of Venclyxto® with the active ingredient venetoclax in the following therapeutic indication:

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

In the benefit assessment, two patient groups were distinguished:

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

and

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

Patient group a)

Patient-specific chemo-immunotherapy with selection of bendamustine, chlorambucil, fludarabine with cyclophosphamide, and ibrutinib with bendamustine, each in combination with rituximab, taking into account the general condition as well as the success and tolerability of the previous therapy was determined as appropriate comparator therapy.

To demonstrate the additional benefit, the pharmaceutical commpany presents the results of a sub-population from the MURANO study in which the combinations venetoclax and rituximab as well as bendamustine and rituximab were compared.

The evidence presented is suitable for demonstrating an additional benefit for some of the patients in the present patient group.

Patients for whom bendamustine in combination with rituximab is the patient-individually most suitable therapy are found to have a significant additional benefit with respect to overall survival and side effects.

Because of the small number of cases considered in the evaluation of the overall survival, the significance of the results for this endpoint is limited. Nevertheless, in combination with the moderate avoidance of serious side effects, a minor overall additional benefit is found.

The probability of the additional benefit is classified in the category “indication”, taking into account the present individual clinical study.

However, there is no usable data for patients for whom a therapy other than bendamustine in combination with rituximab is the patient-individually most suitable therapy. The additional benefit is not proven for these patients.

Patient group b)

Ibrutinib or idelalisib in combination with rituximab or best supportive care were determined as appropriate comparator therapy in the present sub-population, the latter only after prior treatment with ibrutinib or idelalisib.

In order to demonstrate the additional benefit in sub-population b, the pharmaceutical company also used the results of the MURANO study. However, based on a comparison with bendamustine in combination with rituximab, the additional benefit compared with the above options of appropriate comparator therapy cannot be assessed.

The other evidence presented, which is based on non-adjusted historical comparisons, is also unsuitable because of its low significance. 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 presented by the pharmaceutical manufacturer are taken from previous resolution on ibrutinib and idelalisib 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 proportional values for subdivision into sub-populations are to be understood as an approximation.

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.

2.4 Treatment costs

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

a) Adult patients with CLL without 17p deletion or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy.

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 is different for each individual patient or is shorter on average. The use of venetoclax in combination with rituximab is limited to 2 years.

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
Rituximab	every 28 days on Day 1	6 cycles	1	6
Appropriate comparator therapy				
Bendamustine + rituximab (BR)[3]				
Bendamustine	every 28 days on Day 1 and 2	6 cycles	2	12
Rituximab	every 28 days on Day 1	6 cycles	1	6
Chlorambucil + rituximab (ClbR)[4]				

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

[4] 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.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Chlorambucil	every 28 days on Day 1 and 15	6 cycles	2	12
Rituximab	every 28 days on Day 1	6 cycles	1	6
Fludarabine + cyclophosphamide + rituximab (FCR)[5]				
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
Ibrutinib + bendamustine + rituximab (IbrBR)				
Ibrutinib	continuously 1 × daily	365	1	365
Bendamustine	every 28 days on Day 2 and 3 (1st cycle) or Day 1 and 2 (subsequent cycles)	6 cycles	2	12
Rituximab	every 28 days on Day 1	6 cycles	1	6

Usage:

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

For dosages depending on body weight (BW) or body surface, the average body measurements were used as a basis (average body size: 1.72 m, average body weight: 77

[5] Robak T et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukaemia. J Clin Oncol. 2010 Apr 1; 28 (10): 1756–65.

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	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[7]	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5ff: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5ff: 400 mg	Week 1: 2 × 10 mg Week 2: 1 × 50 mg Week 3: 1 × 100 mg Week 4: 2 × 100 mg Week 5ff: 4 × 100 mg	365	14 × 10 mg 7 × 50 mg 1 369 × 100 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
Appropriate comparator therapy					
Bendamustine + rituximab (BR)					
Bendamustine	70 mg/m²	133 mg	6 × 25 mg	12	72 × 25 mg
Rituximab	Cycle 1: 375 mg/m² Cycle 2–6: 500 mg/m²	Cycle 1: 712.5 mg Cycle 2–6: 950 mg	Cycle 1: 3 × 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
Fludarabine + cyclophosphamide + rituximab (FCR)[8]					
Fludarabine	25 mg/m²	47.5 mg	1 × 50 mg	18	18 × 50 mg

German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

[7] Calculation for the first year of treatment. In the following year, the average annual consumption was 1460 tablets of 100 mg each.

[8] The basis for the calculation is the total consumption for a complete treatment over 6 cycles.

Designation of the therapy	Dosage	Dosage/patient/treatment days	Consumption by potency/day of treatment	Treatment days/ Patient/ year	Average annual consumption by potency
Cyclophosphamide	250 mg/m²	475 mg	1 × 500 mg	18	18 × 500 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
Ibrutinib + bendamustine + rituximab (IbrBR)					
Ibrutinib	420 mg	420 mg	3 × 140 mg	365	1 095 × 140 mg
Bendamustine	70 mg/m²	133 mg	6 × 25 mg	12	72 × 25 mg
Rituximab	Cycle 1: 375 mg/m² Cycle 2–6: 500 mg/m²	Cycle 1: 712.5 mg Cycle 2–6: 950 mg	Cycle 1: 3 × 100 mg 1 × 500 mg Cycle 2–6: 2 × 500 mg	6	3 × 100 mg 11 × 500 mg

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 TAB	€ 94.36	€ 1.77	-	€ 92.59
	50 mg, 7 TAB	€ 219.40	€ 1.77	-	€ 217.63
	100 mg, 112 TAB	€ 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
Chlorambucil	2 mg, 50 TAB	€ 137.42	€ 1.77	€ 68.23	€ 67.42
Fludarabine	2 ml, 1 vial	€ 118.20	€ 1.77	€ 5.09	€ 111.34
	2 ml, 5 vials	€ 546.52	€ 1.77	€ 25.41	€ 519.34
Cyclophosphamide	500 mg, 6 vials	€ 81.92	€ 1.77	€ 8.98	€ 71.17
Bendamustine	25 mg, 5 vials	€ 374.48	€ 1.77	€ 17.25	€ 355.46

Ibrutinib	140 mg, 120 TAB	€ 8,516.41	€ 1.77	-	€ 8,514.64
Vial: Vial; TAB: 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.

Because there are no 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, no costs for additional SHI services required had to be taken into account.

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 from finished 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 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 to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"].

b) Adult patients with CLL with 17p deletion or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy

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 is different for each individual patient or is shorter on average. The use of venetoclax in combination with rituximab is limited to 2 years.

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
Rituximab	every 28 days on Day 1	6 cycles	1	6
Appropriate comparator therapy				
Ibrutinib				
Ibrutinib	continuously 1 × daily	365	1	365
Idelalisib + rituximab[9]				
Idelalisib	continuously 2 × daily	365	1	365
Rituximab	once at Week 1, 2, 4, 6, 8, 12, 16, and 20	8 cycles	1	8
Best supportive care (BSC)[10]				
BSC	Different for each individual patient			

Usage:

The (daily) doses recommended in the product information or the identified 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[11]	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

[9] Dosage of idelalisib in combination with rituximab according to the schedule in the 312-0116 study.
[10] In a comparison with BSC, this should also be used in addition to medicinal product to be assessed.
[11] 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
Rituximab	Cycle 1: 375 mg/m^2 Cycle 2–6: 500 mg/m^2	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
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)					
BSC	Different for each individual patient				

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 TAB	€ 94.36	€ 1.77	-	€ 92.59
	50 mg, 7 TAB	€ 219.40	€ 1.77	-	€ 217.63
	100 mg, 112 TAB	€ 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 TAB	€ 8,516.41	€ 1.77	-	€ 8,514.64
Idelalisib	150 mg, 60 TAB	€ 4,534.74	€ 1.77	€ 255.71	€ 4,277.26
Vial: Vial; TAB: Tablets					

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[12] Hepatitis B antibody status: € 5.90[13]		
	Pre-medication Antihistamines e.g. dimetinden i.v. Antipyretics e.g. paracetamol	€ 14.76 € 1.36[14]	6-8 6-8	€ 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 from finished 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 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 to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"].

[12] GOP number 32781.
[13] GOP number 32614.
[14] 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 of the German Social Code, Book V, (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 Regulation in the 31 December 2003 version – shall apply

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 16. August 2017, received on 16. August 2017, the pharmaceutical manufacturer requested consultation in accordance with Section 8 AM-NutzenV on the question of the appropriate comparator therapy, among other things. The sub-committee on medicinal products determined the appropriate comparator therapy at its meeting on 24. Oktober 2017. The consultation took place on 25. Oktober 2017 .

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. 2 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 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 27. Februar 2019, and the written statement procedure was initiated with publication on the G-BA website on 1. März 2019. The deadline for submitting written statements was 22. März 2019.

The oral hearing was held on 8. April 2019.

By letter dated 9. April 2019, the IQWiG was commissioned to carry out a supplementary assessment of data submitted in the statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 26. 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 statements 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	24. Oktober 2017	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 The IQWiG is commissioned to carry out a supplementary assessment of documents
Working group Section 35a	16. April 2019 29. April 2019	Consultation on the dossier assessment by the IQWiG and the 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