IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A18-82

Venetoclax (chronic lymphocytic leukaemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Venetoclax (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment:

- Anne Hüning
- Christiane Balg
- Wolfram Groß
- Charlotte Guddat
- Christopher Kunigkeit
- Regine Potthast
- Dorothea Sow
- Volker Vervölgyi

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CLL	chronic lymphocytic leukaemia
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug venetoclax. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 22 November 2018.

Research question

The aim of this report was to assess the added benefit of venetoclax as monotherapy compared with the appropriate comparator therapy (ACT) in adult patients with chronic lymphocytic leukaemia (CLL)

- with 17p deletion or TP53 mutation who are unsuitable for treatment with an inhibitor of the B-cell receptor signal pathway or who showed treatment failure, or
- without 17p deletion or TP53 mutation who experienced treatment failure both under chemoimmunotherapy and under an inhibitor of the B-cell receptor signal pathway.

The research questions presented in Table 2 resulted in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of venetoclax

Research question	Subindication	ACT[a]
1	Adult patients with CLL and 17p deletion or TP53 mutation for whom treatment with an inhibitor of the B-cell receptor signal pathway is unsuitable or who experienced treatment failure[b]	Ibrutinib or Idelalisib + rituximab or Best supportive Care[c] (only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab)
2	Adult patients with CLL and without 17p deletion or TP53 mutation who experienced treatment failure both under chemoimmunotherapy and under an inhibitor of the B-cell receptor signal pathway	Ibrutinib or Idelalisib + rituximab or Best supportive care[c]

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment. Moreover, it is assumed that chemoimmunotherapy is not suitable for patients with 17p deletion or TP53 mutation.
c: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The company assessed the added benefit of venetoclax under consideration of the results of the non-controlled approval studies M13-982 and M14-032. Since the company presented no results on venetoclax in comparison with the ACT, derivation of an added benefit of venetoclax versus the ACT is impossible.

This resulted in no hint of an added benefit of venetoclax in comparison with the ACT for neither of the two studies; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of venetoclax.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Venetoclax – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with CLL and 17p deletion or TP53 mutation for whom treatment with an inhibitor of the B-cell receptor signal pathway is unsuitable or who experienced treatment failure[b]	Ibrutinib or Idelalisib + rituximab or Best supportive Care[c] (only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab)	Added benefit not proven
2	Adult patients with CLL and without 17p deletion or TP53 mutation who experienced treatment failure both under chemoimmunotherapy and under an inhibitor of the B-cell receptor signal pathway	Ibrutinib or Idelalisib + rituximab or Best supportive care[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment. Moreover, it is assumed that chemoimmunotherapy is not suitable for patients with 17p deletion or TP53 mutation.
c: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2016. In this assessment, the G-BA had determined a non-quantifiable added benefit of venetoclax for both research questions. However, in this assessment, the added benefit had been regarded as proven by the approval because of the special situation for orphan drugs, irrespective of the underlying data.

2.2 Research question

The aim of this report was to assess the added benefit of venetoclax as monotherapy compared with the ACT in adult patients with CLL

- with 17p deletion or TP53 mutation who are unsuitable for treatment with an inhibitor of the B-cell receptor signal pathway or who showed treatment failure, or
- without 17p deletion or TP53 mutation who experienced treatment failure both under chemoimmunotherapy and under an inhibitor of the B-cell receptor signal pathway.

The research questions presented in Table 4 resulted in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of venetoclax

Research question	**Subindication**	**ACT[a]**
1	Adult patients with CLL and 17p deletion or TP53 mutation for whom treatment with an inhibitor of the B-cell receptor signal pathway is unsuitable or who experienced treatment failure[b]	Ibrutinib or Idelalisib + rituximab or Best supportive Care[c] (only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab)
2	Adult patients with CLL and without 17p deletion or TP53 mutation who experienced treatment failure both under chemoimmunotherapy and under an inhibitor of the B-cell receptor signal pathway	Ibrutinib or Idelalisib + rituximab or Best supportive care[c]

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment. Moreover, it is assumed that chemoimmunotherapy is not suitable for patients with 17p deletion or TP53 mutation.
c: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

Assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on venetoclax (status: 14 September 2018)
- bibliographical literature search on venetoclax (last search on 12 September 2018)
- search in trial registries for studies on venetoclax (last search on 14 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax (last search on 11 December 2018)

The check of the completeness of the study pool produced no relevant randomized controlled trials (RCTs), neither for research question 1 (adults with 17p deletion or TP53 mutation) nor for research question 2 (adults without 17p deletion or TP53 mutation).

The company also identified no relevant RCTs. However, among the further studies (Module 4 B, Section 4.3.2.3), the company presented 2 non-controlled venetoclax studies (M13-982 [3-9] and M14-032 [10-13]) for the derivation of an added benefit.

The company presented no suitable data enabling a comparison of venetoclax with the ACT. The derivation of an added benefit of venetoclax in comparison with the ACT is therefore impossible in the present benefit assessment. The studies M13-982 and M14-032 as well as the company's approach are described below as additional information.

Study M13-982

The study M13-98 is an ongoing multicentre, non-controlled and open-label phase II study. The statutory approval of venetoclax was based on this study as pivotal study. The study included a total of 158 adult patients with relapsed or refractory CLL or without prior CLL-targeted treatment. All patients had 17p deletion. After a 4 to 5-week up-titration phase of venetoclax, 400 mg venetoclax were administered daily in compliance with the approval [14] for at most 2 years. Primary outcome of the study was the overall response rate.

Study M14-032

The study M14-032 is a multicentre, non-controlled and open label 2-arm phase II study exclusively conducted in the USA, which served as supportive study for the approval of venetoclax. 127 adult patients who had experienced relapses or who were refractory to treatment with ibrutinib (arm A) or idelalisib (arm B) were included in the study independent of their 17p deletion or TP53 mutation status. A 5-week up-titration phase of venetoclax was followed by further administration for at most 2 years. The study is presently ongoing. Primary outcomes were "overall response rate" and "adverse events" (AEs).

Approach of the company

For the derivation of the added benefit, the company used subpopulations of the two studies M13-982 and M14-032 for research question 1 and 2.

For research question 1, the company considered patients with 17p deletion and/or TP53 mutation from both studies. It stated that the application of venetoclax was to be in compliance with the Summary of Product Characteristics (SPC) both in the up-titration phase and in the further course of the study. Since more than 80% of the patients with 17p deletion and/or TP53 mutation received venetoclax in accordance with the approval in study M14-032, the company did not further limit the patient population with regard to the intervention. In the M13-982 study, less than 80% of the patients received venetoclax in accordance with the approval; therefore, the company only considered those patients who had received venetoclax in

accordance with the approval. The subpopulation created by the company comprised 131 patients from both studies.

For research question 2, the company only considered study M14-032, because study M13-982 only included patients with 17p deletion. From the study M14-032, the company used data of those patients without 17p deletion and/or TP53 mutation. It stated venetoclax dosage in compliance with the approval as further criterion. The subpopulation created by the company comprised 14 patients.

The company presented the results of venetoclax on the outcomes it deemed relevant for the patients of research question 1 and 2 of the present benefit assessment. For the outcome "overall survival", for instance, the company additionally compared the results with the results of a patient population it considered to be similar from various ibrutinib studies (RESONATE-17 [NCT01744691], NCT01105247, NCT01109069 [15-17]). In the company's assessment, these results imply a comparable result for the outcome "survival".

Neither of the studies enabled a comparison with the ACT, in the present benefit assessment, they are therefore not used for the assessment of the added benefit of venetoclax in comparison with the ACT.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of venetoclax versus the ACT, neither for research question 1 nor for research question 2. This resulted in no hint of an added benefit of venetoclax in comparison with the ACT for none of the research questions; an added benefit is therefore not proven.

This deviates from the company's approach, which derived a hint of an added benefit on the basis of the two non-controlled venetoclax studies M13-982 and M14-032.

2.5 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of venetoclax. An added benefit of venetoclax versus the ACT is thus neither proven for patients with CLL and 17p deletion or TP53 mutation who are unsuitable for treatment with an inhibitor of the B-cell receptor signal pathway or who experienced treatment failure, nor for patients without 17p deletion or TP53 mutation and who experienced treatment failure both under a chemo-immunotherapy and under an inhibitor of the B-cell receptor signal pathway.

This assessment deviates from the company's approach, which derived a hint of a non-quantifiable added benefit each.

The result of the assessment of the added benefit of venetoclax in comparison with the ACT is summarized in Table 5.

Table 5: Venetoclax – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with CLL and 17p deletion or TP53 mutation for whom treatment with an inhibitor of the B-cell receptor signal pathway is unsuitable or who experienced treatment failure[b]	Ibrutinib or Idelalisib + rituximab or Best supportive Care[c] (only for patients with failure of a previous therapy with ibrutinib or idelalisib + rituximab)	Added benefit not proven
2	Adult patients with CLL and without 17p deletion or TP53 mutation who experienced treatment failure both under chemoimmunotherapy and under an inhibitor of the B-cell receptor signal pathway	Ibrutinib or Idelalisib + rituximab or Best supportive care[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: As specified by the G-BA, the present therapeutic indication refers to patients requiring treatment (e.g. stage C according to Binet) for whom allogeneic stem cell transplantation is not indicated at the time point of treatment. Moreover, it is assumed that chemoimmunotherapy is not suitable for patients with 17p deletion or TP53 mutation.
c: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2016. In this assessment, the G-BA had determined a non-quantifiable added benefit of venetoclax for both research questions. However, in this assessment, the added benefit had been regarded as proven by the approval because of the special situation for orphan drugs, irrespective of the underlying data.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016; 17(6): 768-778.

4. Stilgenbauer S, Eichhorst B, Schetelig J, Hillmen P, Seymour JF, Coutre S et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. J Clin Oncol 2018; 36(19): 1973-1980.

5. A study of the efficacy of ABT-199 in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia with the 17p deletion [online]. In: ClinicalTrials.gov. 2018 [Accessed: 12.09.2018]. URL: https://clinicaltrials.gov/show/NCT01889186.

6. A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harboring the 17p deletion [online]. In: EU Clinical Trials Register. [Accessed: 13.09.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004027-20/DE.

7. A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed or refractory chronic lymphocytic leukemia harboring the 17p deletion [online]. In: International Clinical Trials Registry Platform. 2018 [Accessed: 13.09.2018]. URL: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00005494.

8. A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harboring the 17p deletion [online]. In: International Clinical Trials Registry Platform. 2018 [Accessed: 13.09.2018]. URL: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01889186.

9. A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed / refractory or previously untreated chronic lymphocytic leukemia harboring the 17p deletion [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 14.09.2018]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

10. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol 2018; 19(1): 65-75.

11. Coutre S, Choi M, Furman RR, Eradat H, Heffner L, Jones JA et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood 2018; 131(15): 1704-1711.

12. A phase 2 open-label study of the efficacy and safety of ABT-199 (GDC-0199) in chronic lymphocytic leukemia (CLL) subjects with relapse or refractory to B-cell receptor signaling pathway inhibitor therapy [online]. In: ClinicalTrials.gov. 2018 [Accessed: 12.09.2018]. URL: https://ClinicalTrials.gov/show/NCT02141282.

13. A phase 2 open-label study of the efficacy and safety of ABT-199 (GDC-0199) in chronic lymphocytic leukemia subjects with relapse or refractory to B-cell receptor signaling pathway inhibitor therapy [online]. In: International Clinical Trials Registry Platform. 2018 [Accessed: 13.09.2018]. URL: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02141282.

14. AbbVie. Venclyxto 10 mg/50 mg/100 mg Filmtabletten: Fachinformation [online]. 12.2018 [Accessed: 22.01.2019]. URL: http://www.fachinfo.de.

15. O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol 2016; 17(10): 1409-1418.

16. O'Brien S, Furman RR, Coutre S, Flinn IW, Burger JA, Blum K et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood 2018; 131(17): 1910-1919.

17. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013; 369(1): 32-42.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-82-venetoclax-chronic-lymphocytic-leukaemia-benefit-assessment-according-to-35a-social-code-book-v.11004.html