IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-18

Idelalisib (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 *Idelalisib (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2016). 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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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
PRAC	Pharmacovigilance Risk Assessment Committee
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 idelalisib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 5 April 2016.

Research question

The aim of this report was to assess the added benefit of idelalisib compared with the appropriate comparator therapy (ACT) specified by the G-BA for adult patients with chronic lymphocytic leukaemia (CLL)

- who have received at least one prior therapy, or
- for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment.

According to the approval of idelalisib, the G-BA distinguished the 2 subindications within the therapeutic indication CLL mentioned above (research questions 1 and 2). The G-BA further distinguished the patient population with at least one previous treatment into 2 subpopulations (research questions 1a and 1b). Accordingly, the assessment was conducted for a total of 3 research questions. The research questions and the corresponding ACTs are shown in Table 2.

Table 2: Research questions of the benefit assessment of idelalisib

Research question	Subindication	Appropriate comparator therapy[a]
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
1b	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	Ibrutinib or best supportive care[b]
2	Continuation of treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment	Ibrutinib or best supportive care[b] (corresponding to the treatment already initiated)

a: Presentation of the respective ACT specified by the G-BA.
b: 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

For research question 1a, the company deviated from the ACT specified by the G-BA and defined individually optimized treatment specified by the physician and under consideration of the approval status as comparator therapy. The company itself included no relevant evidence for research question 1a in its assessment.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Note on research question 2

Following the decision of the European Commission from 23 March 2016, the approved therapeutic indication of idelalisib was changed. For this reason, the research question 2 considered in the present benefit assessment deviates from the research question 2 considered in the first assessment of idelalisib [3]. The change was based on a preliminary recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) issued in the framework of a European risk assessment procedure for idelalisib. With this change, idelalisib is no longer approved in first-line treatment, but only for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment.

Due to the ongoing risk assessment procedure, the company conducted no conclusive assessment of the added benefit of idelalisib for patients of research question 2.

Results

As in dossier assessment A14-35 of idelalisib for patients with relapsed or refractory CLL for whom chemotherapy is indicated (research question 1a) and for patients with relapsed or refractory CLL for whom chemotherapy is not indicated (research question 1b), no relevant studies were available.

Research question 1a: patients with relapsed or refractory CLL for whom chemotherapy is indicated

The company identified no relevant study for the assessment of the added benefit of idelalisib for patients with relapsed or refractory CLL for whom chemotherapy is indicated. This resulted in no hint of an added benefit of idelalisib in comparison with the ACT; an added benefit is therefore not proven.

Research question 1b: patients with relapsed or refractory CLL for whom chemotherapy is indicated

As in the first assessment of idelalisib (A14-35), the company identified study GS-US-312-0116 and the extension study GS-US-312-0117, the data of which were partly included in the analysis of study GS-US-312-0116. These studies were unsuitable for the assessment of the added benefit of idelalisib in comparison with the ACT specified by the

G-BA. The reasons for exclusion correspond to the reasons already mentioned in the first assessment of idelalisib and can be found in benefit assessment A14-35.

The company used the results of the second interim analysis of the GS-US-312-0116 study (last blinded data cut-off from 23 November 2013) for the derivation of the added benefit. The company had already used these data for the first assessment of idelalisib to derive the added benefit.

Newly presented data on the studies GS-US-312-0116 and GS-US-312-0117

Furthermore, the company additionally presented the new results of the final data cut-off from 20 April 2014 for the GS-US-312-0116 study. According to the company, the final data cut-off included all data of the patients collected until the end of the study (i.e. until their completion of the study or their first unblinded treatment in the framework of the extension study GS-US-312-0117). In addition, the company presented a current interim analysis of the extension study GS-US-312-0117 (data cut-off: 18 September 2015). The company did not use the results of both newly presented analyses in its assessment for the derivation of the added benefit because unblinded data were also included in the final data cut-off, and all patients were treated with idelalisib in the extension study. From the company's point of view, no treatment effects could therefore be derived from the extension study in the sense of a comparison of idelalisib with the comparator therapy according to the research question. For this reason, the company presented the results of both analyses only as additional information.

Overall, the company presented new data on the studies GS-US-312-0116 and GS-US-312-0117, but did not use them for the derivation of the added benefit. The conclusions on the added benefit of idelalisib drawn by the company were therefore based on the same data as in the first assessment. In addition, the company provided no additional arguments in the present dossier to justify an inclusion of the studies.

Research question 2: continuation of treatment with idelalisib in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy

The company identified no relevant data for the assessment of the added benefit of idelalisib for patients with relapsed or refractory CLL for whom chemotherapy is not indicated. Hence an added benefit of idelalisib is not proven for these patients.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Table 3: Idelalisib – extent and probability of added benefit

Research question		Appropriate comparator therapy[a]	Extent and probability of added benefit
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	Added benefit not proven
1b	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	**Ibrutinib** or **best supportive care**[b]	Added benefit not proven
2	Continuation of treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment[c]	Ibrutinib or best supportive care (corresponding to the treatment already initiated)[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: 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.
c: Due to the ongoing European risk assessment procedure and the changed approval status, the company conducted no conclusive assessment of the added benefit of idelalisib for patients of research question 2.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of idelalisib compared with the ACT specified by the G-BA for adult patients with CLL

- who have received at least one prior therapy, or

[4] 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, no added benefit, or less benefit). For further details see [1,2].

- for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment.

According to the approval of idelalisib, the G-BA distinguished the 2 subindications within the therapeutic indication CLL mentioned above (research questions 1 and 2). The G-BA further distinguished the patient population with at least one previous treatment into 2 subpopulations (research questions 1a and 1b). Accordingly, the assessment was conducted for a total of 3 research questions. The research questions and the corresponding ACTs are shown in Table 4.

Table 4: Research questions of the benefit assessment of idelalisib

Research question	Subindication	Appropriate comparator therapy[a]
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated
1b	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	Ibrutinib or best supportive care[b]
2	Continuation of treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment	Ibrutinib or best supportive care[b] (corresponding to the treatment already initiated)

a: Presentation of the respective ACT specified by the G-BA.
b: 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

For research question 1a, the company deviated from the ACT specified by the G-BA and defined individually optimized treatment specified by the physician and under consideration of the approval status as comparator therapy. The company itself included no relevant evidence for research question 1a in its assessment, which is why this deviation is not commented on.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Note on research question 2

Following the decision of the European Commission from 23 March 2016, the approved therapeutic indication of idelalisib was changed. For this reason, the research question 2 considered in the present benefit assessment deviates from the research question 2 considered in the first assessment of idelalisib [3]. The change was based on a preliminary recommendation by the PRAC at the EMA issued in the framework of a European risk

assessment procedure for idelalisib. With this change, idelalisib is no longer approved in first-line treatment, but only for continuing treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment.

Due to the ongoing risk assessment procedure, research question 2 reflects the currently valid approval status of idelalisib [4]. The assessment of the added benefit for the population that is currently approved due to the risk assessment procedure, and which only consists of patients currently treated with idelalisib, appears to be of only limited relevance.

Due to the ongoing risk assessment procedure, the company conducted no conclusive assessment of the added benefit of idelalisib for patients of research question 2.

2.3 Research question 1a: patients with relapsed or refractory CLL for whom chemotherapy is indicated

2.3.1 Information retrieval and study pool (research question 1a)

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

Sources of the company in the dossier:

- study lists on idelalisib (status: 18 March 2016)
- bibliographical literature search on idelalisib (last search on 18 March 2016)
- search in trial registries for studies on idelalisib (last search on 16 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on idelalisib (last search on 12 April 2016)

No relevant study was identified from the steps of information retrieval mentioned. This concurs with the company's approach, which also identified no relevant study for the present research question 1a.

2.3.2 Results on added benefit (research question 1a)

The company presented no relevant data for the assessment of the added benefit of idelalisib for research question 1a. This resulted in no hint of an added benefit of idelalisib in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question 1a)

The company presented no relevant data for the assessment of the added benefit of idelalisib for patients with relapsed or refractory CLL for whom chemotherapy is indicated. Hence an added benefit of idelalisib is not proven for these patients. This concurs with the company's assessment.

The G-BA decides on the added benefit.

2.3.4 List of included studies (research question 1a)

Not applicable as no studies for research question 1a were included in the benefit assessment.

2.4 Research question 1b: patients with relapsed or refractory CLL for whom chemotherapy is not indicated

2.4.1 Information retrieval and study pool (research question 1b)

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

Sources of the company in the dossier:

- study lists on idelalisib (status: 18 March 2016)
- bibliographical literature search on idelalisib (last search on 18 March 2016)
- search in trial registries for studies on idelalisib (last search on 16 March 2016)
- bibliographical literature search on ACTs (last search on 18 March 2016)
- search in trial registries for studies on ACTs (last search on 16 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on idelalisib (last search on 12 April 2016)

No relevant study was identified from the check. This deviates from the company's approach, which identified study GS-US-312-0116 and the extension study GS-US-312-0117, the data of which were partly included in the analysis of study GS-US-312-0116. The company had already presented both studies for the first assessment of idelalisib [3]. These studies were unsuitable for the assessment of the added benefit of idelalisib in comparison with the ACT specified by the G-BA.

Description of the studies GS-US-312-0116 and GS-US-312-0117

GS-US-312-0116

Study GS-US-312-0116 was a company-sponsored, randomized, active-controlled, double-blind approval study. 220 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms idelalisib + rituximab and placebo + rituximab. Patients of both treatment arms received drugs as needed to alleviate symptoms and for accompanying diseases. Pretreated patients with CLL that had progressed within 24 months after their last prior therapy were included. Both patients with relapsed and with refractory CLL were included in the study population. Further information on the study design can be found in benefit assessment A14-35 [3].

GS-US-312-0117

Study GS-US-312-0117 was a company-sponsored, 2-arm extension study of the GS-US-312-0116 study. The patients in the GS-US-312-0116 study who had tolerated the study medication but had progressed could be enrolled in this study. The patients from the previous verum arm received (still blinded) idelalisib at twice the daily dosage (600 mg), and the patients from the previous control arm received (still blinded) 300 mg idelalisib daily. After the premature completion of the GS-US-312-0116 study, all patients could be included in the GS-US-312-0117 study, which was then continued unblinded.

Newly presented data on the studies GS-US-312-0116 and GS-US-312-0117

The company presented the results of the second interim analysis of the GS-US-312-0116 study (last blinded data cut-off from 23 November 2013) for the present benefit assessment and used these results for the derivation of the added benefit. The company had already used these data for the first assessment of idelalisib to derive the added benefit [3].

Furthermore, the company additionally presented the new results of the final data cut-off from 20 April 2014 for the GS-US-312-0116 study. According to the company, the final data cut-off included all data of the patients collected until the end of the study (i.e. until their completion of the study or their first unblinded treatment in the framework of the extension study GS-US-312-0117). In addition, the company presented a current interim analysis of the extension study GS-US-312-0117 (data cut-off: 18 September 2015).

The company did not use the results of both newly presented analyses in its assessment for the derivation of the added benefit because unblinded data were also included in the final data cut-off, and all patients were treated with idelalisib in the extension study. From the company's point of view, no treatment effects could therefore be derived from the extension study in the sense of a comparison of idelalisib with the comparator therapy according to the research question. For this reason, the company presented the results of both analyses only as additional information.

Overall, the company presented new data on the studies GS-US-312-0116 and GS-US-312-0117, but did not use them for the derivation of the added benefit. The conclusions on the added benefit of idelalisib drawn by the company were therefore based on the same data as in the first assessment [3].

Relevance of the studies GS-US-312-0116 and GS-US-312-0117

The studies GS-US-312-0116 and GS-US-312-0117 were not relevant for the present assessment. The reasons for exclusion correspond to the reasons already mentioned in the first assessment of idelalisib and can be found in benefit assessment A14-35 [3].

The company provided no additional arguments in the present dossier to justify an inclusion of the studies. The GS-US-312-0116 study still allowed no comparison of idelalisib with the

ACT specified by the G-BA (see also the justification on the decision of the first assessment of idelalisib [5]).

2.4.2 Results on added benefit (research question 1b)

The company presented no relevant data for the assessment of the added benefit of idelalisib for research question 1b. This resulted in no hint of an added benefit of idelalisib in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question 1b)

The company presented no relevant data for the assessment of the added benefit of idelalisib for patients with relapsed or refractory CLL for whom chemotherapy is not indicated. Hence an added benefit of idelalisib is not proven for these patients. This deviates from the assessment of the company, which saw proof of major added benefit for patients with 17p deletion and/or TP53 mutation and an indication of major added benefit for patients without 17p deletion and TP53 mutation.

The G-BA decides on the added benefit.

2.4.4 List of included studies (research question 1b)

Not applicable as no studies were included in the benefit assessment.

2.5 Research question 2: continuation of treatment with idelalisib in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy

2.5.1 Information retrieval and study pool (research question 2)

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

Sources of the company in the dossier:

- study lists on idelalisib (status: 18 March 2016)
- bibliographical literature search on idelalisib (last search on 18 March 2016)
- search in trial registries for studies on idelalisib (last search on 16 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on idelalisib (last search on 12 April 2016)

No relevant study was identified from the steps of information retrieval mentioned. This concurs with the company’s approach, which also identified no relevant study for the present research question 2.

2.5.2 Results on added benefit (research question 2)

The company presented no relevant data for the assessment of the added benefit of idelalisib for research question 2. This resulted in no hint of an added benefit of idelalisib in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit (research question 2)

The company presented no relevant data for the assessment of the added benefit of idelalisib for patients with relapsed or refractory CLL for whom chemotherapy is not indicated. Hence an added benefit of idelalisib is not proven for these patients. This concurs with the company's assessment.

The G-BA decides on the added benefit.

2.5.4 List of included studies (research question 2)

Not applicable as no studies were included in the benefit assessment.

2.6 Extent and probability of added benefit – summary

Table 5 presents a summary of the extent and probability of the added benefit of idelalisib.

Table 5: Idelalisib – extent and probability of added benefit

Research question		**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
1a	Patients with relapsed or refractory CLL for whom chemotherapy is indicated	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	Added benefit not proven
1b	Patients with relapsed or refractory CLL for whom chemotherapy is not indicated	**Ibrutinib** or **best supportive care**[b]	Added benefit not proven
2	Continuation of treatment in patients with 17p deletion or TP53 mutation who were unsuitable for chemo-immunotherapy and who had already initiated idelalisib as first-line treatment[c]	Ibrutinib or best supportive care (corresponding to the treatment already initiated)[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: 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.
c: Due to the ongoing European risk assessment procedure and the changed approval status, the company conducted no conclusive assessment of the added benefit of idelalisib for patients of research question 2.
ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; G-BA: Federal Joint Committee

An added benefit of idelalisib is not proven for any of the 3 research questions because the company presented no suitable data for any of the research questions of the present benefit assessment in the therapeutic indication of CLL.

This deviates from the assessment of the company, which for research question 1b saw proof of major added benefit for patients with 17p deletion and/or TP53 mutation and an indication of major added benefit for patients without 17p deletion and TP53 mutation.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a16-18-idelalisib-nutzenbewertung-gemaess-35a-sgb-v.7368.html.