Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V venetoclax (new therapeutic indication: acute myeloid leukaemia, combination therapy, first-line)

of 2 December 2021

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

On 19 May 2021, Venetoclax received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 11 June 2021, i.e. at the latest within four weeks of notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient venetoclax with the new therapeutic indication (acute myeloid leukaemia, first-line combination therapy).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 September 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of venetoclax compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure (as well as the addendum to the benefit assessment prepared by IQWiG). In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of venetoclax.

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

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

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

Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

Therapeutic indication of the resolution (resolution from 02.12.2021):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy

Appropriate comparator therapy:

- azacitidine
  or
- decitabine

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

or

– glasdegib in combination with low-dose cytarabine

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

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

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

1: To be considered as a comparator therapy, the medicinal product must principally have a marketing authorisation for the therapeutic indication.

2: If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.

3: As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.

4: According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. Besides venetoclax, medicinal products with the following active ingredients are approved for the present therapeutic indication:

azacitidine, cytarabine, daunorubicin, decitabine, doxorubicin, etoposide, glasdegib, histamine dihydrochloride, idarubicin, mitoxantrone, and tioguanine. In addition, hydroxycarbamide is prescribable for off-label use.

on 2. No non-medicinal treatment options can be considered for patients with AML who are ineligible for intensive induction chemotherapy.

on 3. Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- glasdegib - resolution of 9 February 2021
- decitabine - resolution of 2 May 2013

Annex VI to Section K of the Pharmaceuticals Directive (last revised: 18 August 2021) - Medicinal products that are prescribable for unapproved therapeutic indications (off-label use)

- hydroxycarbamide in chronic myelomonocytic leukemia (CMML) or in CMML after transition to acute myeloid leukaemia

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

In determining the appropriate comparator therapy, it is taken into account that patients with acute promyelocytic leukaemia are not included in the therapeutic indication. This patient population differs in aetiology and therapeutic approach.

In patients with AML, who are ineligible for intensive standard induction chemotherapy, the therapeutic goal is to prolong overall survival with the highest possible quality of life.

Guidelines recommend azacitidine, decitabine and cytarabine as monotherapy for the treatment of patients with AML, who are ineligible for standard intensive induction chemotherapy. In addition to the aforementioned monotherapies and the combination therapy of venetoclax in combination with hypomethylating agents (HMA), the current NCCN guideline also recommends the combination therapies venetoclax in combination with low-dose cytarabine and glasdegib in combination with low-dose cytarabine as well as the active ingredient gemtuzumab ozogamicin as monotherapy and best supportive care.

For decitabine, there is a resolution of the G-BA of 2 May 2013 on the benefit assessment, in which a minor additional benefit was identified compared to the therapy of choice of best supportive care or cytarabine. The available evidence based on systematic reviews and reviews of azacitidine and decitabine does not indicate that either of the two active ingredients is superior to the other in the treatment of patients with AML who are ineligible for intensive chemotherapy.

For glasdegib in combination with low-dose cytarabine, hint of a considerable additional benefit over low-dose cytarabine (LDAC) was identified in the benefit assessment resolution of 18 February 2021.

Both decitabine and glasdegib in combination with low-dose cytarabine show an advantage over cytarabine based on the respective marketing authorisation-related studies. In addition, due to the newly approved therapy options, in particular the combination therapy of glasdegib in combination with LDAC, cytarabine monotherapy has lost significance in the German health care context, so that monotherapy with cytarabine is not considered as an appropriate comparator therapy.

The combination of venetoclax with low-dose cytarabine is not approved in Europe, which is why this combination is not an appropriate comparator therapy.

According to the marketing authorisation, gemtuzumab ozogamicin should only be used in patients who are eligible for intensive induction chemotherapy, which is why gemtuzumab ozogamicin also does not represent an appropriate comparator therapy in the therapeutic indication.

For the present determination of the appropriate comparator therapy, it is taken into account that best supportive care alone is not an option for all patients in the therapeutic indication at the time of therapy with venetoclax in combination with HMA, and therefore, does not represent an appropriate comparator therapy. The possible implementation of accompanying supportive measures to alleviate symptoms and improve the quality of life remains unaffected.

Overall, based on the available data, the monotherapies with azacitidine or decitabine and the combination therapy of glassdegib and low-dose cytarabine are considered equally appropriate comparator therapies for patients with AML, who are ineligible for intensive induction chemotherapy.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of venetoclax in combination with hypomethlyating agents (HMA) is assessed as follows:

There is a hint of a considerable additional benefit for venetoclax in combination with HMA for the treatment of acute myeloid leukaemia in adult patients who are ineligible for intensive chemotherapy.

Justification:

The benefit assessment of venetoclax in combination with HMA is based on the ongoing pivotal Viale-A study. This is a double-blind, randomised, controlled, multicentre phase III study, comparing the combination therapy of venetoclax and azacitidine with placebo + azacitidine. No data are available comparing the combination of venetoclax with another HMA (decitabine) versus the appropriate comparator therapy.

The study includes adult patients with previously untreated AML (according to WHO criteria[2]) who are ineligible for standard induction therapy with cytarabine and an anthracycline. Here, patients ≥ 75 years of age had an ECOG-PS of 0-2 while those ≥ 18 to 74 years of age had an ECOG-PS of 0-3. In addition, only patients with intermediate or poor cytogenetic risk (according to the National Comprehensive Cancer Network [NCCN] classification) were included, and not patients with low risk.

Of a total of 433 patients, 287 were assigned to the intervention arm (venetoclax + azacitidine) and 146 to the control arm (placebo + azacitidine). Randomisation was stratified by age (≥ 18 to < 75 years; ≥ 75 years), region (European Union; Japan, USA; rest of the world; China), and

[2] Arber DA et al. The 2016 revision to the World Health Organisation classification of myeloid neoplasms and acute leukaemia. Blood 2016; 127(20): 2391-2405.

cytogenetic risk (intermediate; poor). Patients were on average 78 years old, about 65% had intermediate risk and 35% poor risk, and about 40% were included in the study in Europe.

In the Viale-A study, treatment with venetoclax and azacitidine was carried out according to the specifications in the product information. Study treatment was generally given until disease progression (according to the European LeukaemiaNET (ELN) criteria[3]), until the occurrence of unacceptable toxicity, or until the principal investigator or patient made a decision.

The study was launched in February 2017 and is ongoing. A total of 134 centres across Europe (including Germany), America, Asia and the rest of the world were involved.

For the Viale-A study, 3 data cut-offs are available. According to the information provided by the pharmaceutical company, the first two data cut-offs of 1 October 2018 and 4 January 2020 are a priori planned interim data cut-offs, and the 3rd data cut-off of 4 July 2020 is a follow-up data cut-off requested by the Food and Drug Administration (FDA). For the present benefit assessment, the results of the 3rd data cut-off was used. Results are available for the co-primary endpoints of overall survival and composite complete remission, and for additional endpoints of morbidity, health-related quality of life, and adverse events (AEs).

Relevant sub-population of the Viale-A study

The Viale-A study included patients who were ineligible for standard intensive induction therapy.

The pharmaceutical company submitted a sub-population in the dossier for the benefit assessment, based on consultations with the G-BA, according to which the inclusion and exclusion criteria applied in the Viale-A study are not fully suitable for identifying patients who are ineligible for intensive chemotherapy.

To form the sub-population, the pharmaceutical company applies narrower criteria to define lack of eligibility for treatment with intensive chemotherapy, compared to the inclusion criteria of the study. Only the following patients were included in the relevant sub-population: patients ≥ 75 years of age with at least one other previous disease, patients < 75 years of age with ECOG PS 2 and at least one other previous disease, and patients < 75 years of age with ECOG PS 3, regardless of other previous diseases.

The sub-population included 313 patients (72.3% of the total population), of whom 210 were treated with venetoclax + azacitidine and 103 with placebo + azacitidine.

In light of the current guideline recommendations[4], according to which intensive chemotherapy can also be considered for patients with an ECOG-PS = 2 and without comorbidities, this approach is considered appropriate.

[3] Döhner H et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017; 129(4): 424-447.

[4] According to recommendations of the German Society of Haematology and Medical Oncology (Röllig et al., Akute Myeloische Leukämie (AML: acute myeloid leukaemia): guideline; recommendations of the scientific-medical society for the diagnosis and therapy of haematological and oncological diseases. 2021), European Society For Medical Oncology (Heuser et al., Acute Myeloid Leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020) and European LeukaemiaNet (Döhner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017; 129(4): 424-447).

Limitation of the Viale-A study

The marketing authorisation underlying the resolution is based on the combination therapy of venetoclax with a hypomethylating agent (HMA). From this group of active ingredients, both azacitidine and decitabine are approved by the European Medicines Agency (EMA) as monotherapy for the present indication.

In the dossier for the benefit assessment, the pharmaceutical company presents the Viale-A study, in which venetoclax is investigated in combination with azacitidine. No data are presented regarding the combination of venetoclax with decitabine[5]. The dossier points out that the two active ingredients azacitidine and decitabine, as representatives of the group of HMAs, are to be regarded as equivalent in terms of efficacy and tolerability. In addition, it is pointed out that the transferability of the results was also confirmed during the marketing authorisation process. In the context of the marketing authorisation, the effect of venetoclax in combination with azacitidine was extrapolated to venetoclax in combination with decitabine on the basis of the comparable mechanism of action[6].

Neither the dossier nor the written statement procedure provides any further information on the transferability of the effects of venetoclax in combination with azacitidine to the combination of venetoclax with decitabine. Thus, a relevant uncertainty remains with regard to the benefit assessment's question of the extent of transfer of the results - on which the present assessment is based - from the Viale-A study on patient-relevant therapeutic effects to the combination venetoclax + decitabine, in particular also with regard to the quantification of the extent of the additional benefit.

Taking this uncertainty into account in the present assessment, the G-BA nevertheless considers it appropriate to assess the extent and probability of additional benefit beyond venetoclax in combination with azacitidine, i.e. in combination with HMA, on the basis of the Viale-A study.

Extent and probability of the additional benefit

Mortality

In the Viale-A study, overall survival was assessed as the co-primary endpoint. Treatment with venetoclax + azacitidine results in a statistically significant benefit in overall survival compared to placebo + azacitidine.

The extent of this advantage is also assessed as a significant improvement in overall survival against the background of the known poor prognosis for patients in the therapeutic indication.

Morbidity

Remission

The remission endpoint was the co-primary endpoint in the Viale-A study. The endpoint was operationalised as the occurrence of a complete remission (CR) or a complete remission with

[5] IQWiG dossier assessment (A21-82)

[6] Venclyxto - European Public Assessment Report (EPAR) - EMEA/H/C/004106/II/0030: https://www.ema.europa.eu/en/documents/variation-report/venclyxto-h-c-4106-ii-0030-epar-assessment-report-variation_en.pdf

incomplete regeneration of the blood count (CRi). CR was defined by an absolute neutrophil count > 103/µl, platelet count > 105/µl, erythrocyte transfusion independence, bone marrow with < 5% blasts, absence of circulating blasts and blasts with Auer rods, and absence of extramedullary disease. CRi was defined by the criteria of a CR, allowing a neutrophil count ≤ 103/µl and/or a platelet count ≤ 105/µl and/or erthyrocyte transfusion dependency.

For the present assessment, the analyses according to the principal investigator's estimation are available, since no further evaluations by an independent review committee (IRC) were performed after the primary endpoint was reached.

The endpoint of complete remission (CR) is an important prognostic factor and relevant for the treatment decision. A CR associated with a noticeable reduction in disease symptomatology for the patient is generally patient-relevant for the benefit assessment.

In the present study, CR/CRi was predominantly assessed by blood and bone marrow examinations according to the above criteria. Thus, endpoints were not assessed based on symptoms but on laboratory tests. A validation of CR as a surrogate parameter for patient-relevant endpoints, e.g. mortality, is not available. Furthermore, it is unclear whether the achievement of CRi has a comparable clinical relevance as the achievement of CR.

Therefore, the endpoint CR/CRi is classified as endpoint of unclear relevance in the present assessment and is only presented additionally.

Transfusion independence

In the Viale-A study, the endpoint of transfusion independence is defined as the percentage of patients with transfusion independence (no transfusions of either platelets or erythrocytes) of ≥ 8 weeks during the treatment phase, i.e. between first study medication and one of the following events: last administration of study medication + 30 days, death, or initiation of subsequent therapy (whichever occurs first). In the Viale-A study, transfusions are administered on a patient-individual basis and are based on local guidelines.

Patients in the present therapeutic indication require frequent and lifelong transfusions. A long-term or sustainable avoidance of transfusions (transfusion independence) while maintaining a defined minimum value of haemoglobin represents a relevant therapeutic objective in the present therapeutic indication, with which a control of anaemia and anaemia-related symptoms is achieved, while avoiding transfusions.

With regard to the evaluations of the different transfusion-free periods, the G-BA considers a transfusion-free period of ≥ 24 weeks to be the relevant period for assuming long-term avoidance of transfusions (transfusion independence). Thus, transfusion independence of ≥ 24 weeks may represent a patient-relevant endpoint in the present therapeutic indication.

The present assessment is based on evaluations from the written statement procedure. These are time-to-event analyses over a transfusion-free period ≥ 24 weeks based on a joint consideration of platelet and erythrocyte transfusions.

These analyses are considered sufficiently adequate with respect to the joint evaluation of platelet and erythrocyte transfusions and on the basis of time-to-event analyses. However, a high risk of bias can still be assumed due to the considerable differences in the median observation periods of the treatment arms. In addition, uncertainties arise because the median observation period in the comparator arm is shorter than 24 weeks. However, a consistent effect to the advantage of venetoclax + azacitidine can be seen, based on all time-to-event analyses for complete transfusion-free periods (over ≥ 8, ≥ 16 and ≥ 24 weeks) submitted by the pharmaceutical company; therefore, it can be assumed that the risk of bias

of the results is not further increased by the longer observation period. In addition, the clinical experts stated in the written statement procedure that a relevant percentage of patients in the intervention arm already achieved a CR after one therapy cycle, but only a small percentage in the comparator arm. It was therefore unlikely that patients in the comparator arm would have achieved a higher rate of transfusion independence, even with a longer observation period.

Uncertainties also remain regarding the validity of the endpoint. In the written statement procedure, no new information is provided on the criteria according to which transfusions were administered in the Viale-A study. According to the statements of the clinical experts during the written statement procedure, the patient-individual procedure for the administration of transfusions corresponds to the reality of care. According to this, the need for transfusion in patients is not only based on laboratory-chemical parameters (e.g. Hb value), but is very much oriented towards patient-individual factors such as the patient's symptoms, age and concomitant diseases. However, information on reasons for transfusion administration was not presented by the pharmaceutical company. The lack of information results in uncertainty about the extent to which transfusions were administered under comparable conditions in different study centres and whether this corresponds to the German health care context.

Based on time-to-event analysis for complete transfusion-free period (erythrocyte and platelet transfusions) over ≥ 24 weeks, there is a statistically significant advantage for venetoclax in combination with azacitidine over placebo + azacitidine.

Against the background that palliative, strongly individualised therapy goals are pursued with the administration of erythrocyte and platelet transfusions in the present therapeutic indication, the positive effect of venetoclax in combination with azacitidine, taking into account the magnitude of the effect as well as the explanations of the clinical experts in the written statement procedure, is taken as a relevant result for the present assessment despite the uncertainties described above.

Symptomatology (EORTC QLQ-C30)

Disease symptomatology will be assessed in the Viale-A study using the cancer-specific questionnaire EORTC QLQ-C30. The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the time to 1st deterioration. In addition, the pharmaceutical company submits supplementary evaluations of the mean change from the start of study (MMRM analyses).

The assessment of patient-reported endpoints in the Viale-A study is welcomed. However, due to the low return rates in the two treatment arms as early as cycle 3, which is the first survey time point during treatment with the study medication, the evaluations submitted by the pharmaceutical company are not considered usable and are not used for the present benefit assessment.

Health status (EQ-5D VAS)

Health status is assessed in the Viale-A study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company submitted responder analysis, operationalised as time to 1st deterioration with a change of ≥ 7 points as well as supplementary evaluations of the mean change compared to the start of study (MMRM analyses).

Taking into account the comments in the "Symptomatology" section on the low return rates, the evaluations on health status submitted by the pharmaceutical company are not used for the present benefit assessment.

Overall, for the endpoint category of morbidity, there is an advantage of venetoclax in combination with HMA for the endpoint of transfusion independence. This is used in the present therapeutic indication, in which palliative, strongly individualised therapy goals are pursued with the administration of erythrocyte and platelet transfusions, taking into account the magnitude of the effect as well as the explanations of the clinical experts in the written statement procedure for the present evaluation despite uncertainties.

Quality of life

In the Viale-A study, health-related quality of life was assessed using the functional scales and the global health status scale (overall assessment) of the cancer-specific questionnaire EORTC QLQ-C30. The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the time to 1st deterioration. In addition, the pharmaceutical company submits supplementary evaluations of the mean change from the start of study (MMRM analyses).

Taking into account the comments in the "Symptomatology" section on the low return rates, the evaluations on the quality of life submitted by the pharmaceutical company are not used for the present benefit assessment.

For the endpoint category quality of life, no advantages or disadvantages of venetoclax + azacitidine versus placebo + azacitidine can be derived.

Side effects

In addition to treatment-related adverse events (AEs), the presented overall rates of side effects also include AEs that may be due to progression of the underlying disease. In the dossier for the benefit assessment, the pharmaceutical company refers to the difficult specific demarcation between AEs and progression events in this therapeutic indication, which is why it refrains from an analysis of the endpoints of tolerability without the possible, but not clearly assignable disease-related preferred terms (PTs). The overall rates of the endpoints of the category side effects only include a few events that can represent a progression of the underlying disease (e.g. the system organ class (SOC) Neoplasms benign, malignant and unspecified), so that the overall rates are used without limitations for the benefit assessment. However, the named endpoint "Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)" cannot be interpreted as a specific AE in the present data situation and is not used for the benefit assessment.

Adverse events (AEs) in total

AEs occurred in all study participants. The results were only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AE

There were no statistically significant differences between treatment arms for SAEs, severe AEs (CTCAE grade ≥ 3), and therapy discontinuations due to AE.

With regard to therapy discontinuations due to AE, evaluations of the time to discontinuation of any active ingredient component were presented in the dossier for the benefit assessment. It remains unclear whether both active ingredient components should be discontinued or whether the treatment with 1 active ingredient component could be continued. In principle, the evaluation of the time to discontinuation of at least one active ingredient component is considered appropriate for the benefit assessment. Results from the 2nd data cut-off on the therapy discontinuation of venetoclax and/or azacitidine indicate that both active ingredient

components were usually discontinued together, so that the discontinuations due to AE can be used in the present assessment to derive an additional benefit despite the uncertainty mentioned above.

Specific AEs

For the specific AEs of contusion (AE) and injury, poisoning and procedural complications (severe AEs), there was a statistically significant difference in the advantage of venetoclax + azacitidine compared to placebo + azacitidine. For the endpoint of neutropenia (composed of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, neutropenic sepsis [severe AEs]), there is a statistically significant difference to the disadvantage of venetoclax + azacitidine compared to placebo + azacitidine.

In the overall analysis of the results on side effects, there were no benefit-assessment-related differences between the treatment arms in terms of the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, there are advantages for the specific adverse events of contusion (AE) and injury, poisoning and procedural complications (severe AEs) and a disadvantage for the neutropenia endpoint for treatment with venetoclax + azacitidine.

Overall assessment

For the assessment of the additional benefit of venetoclax in combination with hypomethylating agents (HMA), results from the double-blind, randomised, controlled study Viale-A are available for the endpoint categories of mortality, morbidity, quality of life, and side effects. The ongoing study compares venetoclax in combination with azacitidine to placebo in combination with azacitidine. Data comparing venetoclax in combination with another HMA (decitabine) to the appropriate comparator therapy are not available.

For overall survival, there is a statistically significant difference between the treatment arms, which is assessed as a clear advantage for venetoclax in combination with HMA. In light of the known poor prognosis for patients in the therapeutic indication, this is considered a significant improvement.

In the overall analysis of the morbidity results, there is an advantage of venetoclax in combination with HMA for the endpoint of transfusion independence. This is used in the present therapeutic indication, in which palliative, strongly individualised therapy goals are pursued with the administration of erythrocyte and platelet transfusions, taking into account the magnitude of the effect as well as the explanations of the clinical experts in the written statement procedure for the present evaluation despite uncertainties.

No usable data are available for the endpoint category of quality of life.

Based on the results on side effects, there were no benefit-assessment-related differences between the treatment arms in terms of the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, there are advantages for the specific adverse events of contusion (AE) and injury, poisoning and procedural complications (severe AEs) and a disadvantage for the neutropenia endpoint.

In the overall assessment, the G-BA concludes that venetoclax in combination with HMA is identified as having a considerable additional benefit in the treatment of adult patients with

newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the double-blind, randomised, controlled phase III Viale-A study comparing venetoclax + azacitidine to placebo + azacitidine. The sub-population of patients who were are ineligible for intensive chemotherapy is relevant for the benefit assessment.

Since the benefit assessment is based on the results of only one study, only indications of an additional benefit can be derived with regard to the reliability of data of the results.

The risk of bias at the study level is rated as low.

A high certainty of results can be assumed for the endpoints of overall survival.

No usable data on patient-reported endpoints are available for the endpoint categories of morbidity and health-related quality of life. Uncertainties regarding the validity of the results and the operationalisation of the endpoint in the present study arise for the morbidity endpoint of transfusion independence.

The risk of bias in the results of the endpoints of SAEs, severe AEs and specific AEs is rated as high. However, a high certainty of results can be assumed for the endpoint of severe AEs due to the early occurrence of events, compared to the median duration of observation. Limited certainty of results can be assumed for the endpoint of discontinuation due to AE.

There is a relevant uncertainty as to the extent to which the available results from the Viale-A study on patient-relevant therapeutic effects of venetoclax + azacitidine can also be transferred to the combination venetoclax + decitabine, particularly with regard to the quantification of the extent of the additional benefit.

Furthermore, there is a limitation in the representativeness of the Viale-A study for the patient population according to the approved therapeutic indication, as no data are available for patients with low cytogenetic risk.

Despite the overall low risk of bias at the study and endpoint level, these limitations lead to the fact that the reliability of data of the additional benefit identified is classified as a hint.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Venclyxto with the active ingredient venetoclax: "Venclyxto in combination with a hypomethylating agent (HMA) is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy."

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

- azacitidine

  or
- decitabine

  or
- glasdegib in combination with low-dose cytarabine

Results are available from the double-blind, randomised, controlled Viale-A study, comparing venetoclax in combination with azacitidine versus placebo in combination with azacitidine. Data comparing venetoclax in combination with another HMA (e.g. decitabine) to the appropriate comparator therapy are not available. Likewise, no data are available for low-risk patients.

For overall survival, there is a clear advantage of venetoclax in combination with azacitidine, which is considered a significant improvement in light of the known poor prognosis for patients in the therapeutic indication.

For the endpoint category of morbidity, there is an advantage of venetoclax in combination with azacitidine for the endpoint of transfusion independence. In view of the fact that palliative, strongly individualised therapy goals are pursued in the present therapeutic indication with the administration of erythrocyte and platelet transfusions, this advantage is used despite uncertainties.

No usable data are available for the endpoint category of quality of life.

For the side effects, there are no relevant differences for the benefit assessment. However, in detail, there are advantages for the specific adverse events of contusion (AE) and injury, poisoning and procedural complications (severe AEs) and a disadvantage for the neutropenia endpoint for venetoclax + azacitidine.

Relevant uncertainties arise with regard to the extent to which the patient-relevant advantages shown in the Viale-A study can also be transferred to the combination of venetoclax + decitabine.

In the overall assessment, the G-BA concludes that a hint of a considerable additional benefit of venetoclax in combination with HMA is identified in the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.

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

Adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy

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

For the lower limit of the number of patients with AML who are ineligible for standard induction therapy, the G-BA bases its decision on the number of patients specified by the pharmaceutical company in the dossier. The upper limit assessed by the pharmaceutical company tends to be an overestimate, as the more recent registry data tend to be in the range of the lower limit. Therefore, the patient numbers from the last resolution in the therapeutic indication (glasdegib, resolution of 18 February 2021) are used as the basis for the upper limit.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Venclyxto (active ingredient: venetoclax) at the following publicly accessible link (last access: 20 September 2021):

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

Initiation and monitoring of treatment with venetoclax in combination with azacitidine should only be carried out by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with acute myeloid leukaemia.
In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient card. The training material for medical professionals includes instructions on how to manage the risks of Tumour Lysis Syndrome (TLS) associated with venetoclax, as well as information on strict adherence to the dose titration regimen and risk minimisation measures for venetoclax in the updated product information. The patient card contains a list of symptoms of a TLS to prompt patient action, including immediate medical care if it occurs, and patient behaviour to prevent TLS; therefore, medical professionals should advise patients to carry their patient card with them at all times.

No data are available for patients with low cytogenetic risk according to the NCCN classification[7].

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The annual treatment costs shown refer to the first year of treatment.

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

[7] NCCN Guidelines Version 2, 2016 for Acute Myeloid Leukaemia

Treatment period:

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	1 x daily	365	1	365
in combination with				
azacitidine	on day 1-7 of a 28 day cycle	13	7	91
or				
decitabine	on day 1-5 of a 28 day cycle	13	5	65
Appropriate comparator therapy				
azacitidine	on day 1-7 of a 28 day cycle	13	7	91
decitabine	on day 1-5 of a 28 day cycle	13	5	65
glasdegib in combination with low-dose cytarabine				
glasdegib	1 x daily	365	1	365
cytarabine	on day 1-10, 2 x daily of a 28 day cycle	13	10	130

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[8]

[8] Statistisches Bundesamt (Federal Statistic Office). (2018). Microcensus 2017 - Questions on health - Body measurements of the population https://www.destatis.de/DE/Methoden/Qualitaet/Qualitaetsberichte/Bevoelkerung/mikrozensus-2017.pdf;jsessionid=B922CBC0E7D233E5ACE6BA7FAD0CC37A.internet8731?__blob=publicationFile (English translation not available; closest link: https://www.destatis.de/EN/Methods/Quality/QualityReports/Population/einfuehrung.html)

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
venetoclax	Day 1: 100 mg Day 2: 200 mg Afterwards: 400 mg	Day 1: 100 mg Day 2: 200 mg Afterwards: 400 mg	1 x 100 mg 2 x 100 mg 4 x 100 mg	365	1,455 x 100 mg
in combination with					
azacitidine	75 mg/m2 = 142.5 mg	142.5 mg	1 x 150 mg	91	91 x 150 mg
or					
decitabine	20 mg/m2 = 38 mg	38 mg	1 x 50 mg	65	65 x 50 mg
Appropriate comparator therapy					
azacitidine	75 mg/m2 = 142.5 mg	142.5 mg	1 x 150 mg	91	91 x 150 mg
decitabine	20 mg/m2 = 38 mg	38 mg	1 x 50 mg	65	65 x 50 mg
glasdegib in combination with low-dose cytarabine					
glasdegib	100 mg	100 mg	1 x 100 mg	365	365 x 100 mg
cytarabine	20 mg	40 mg	1 x 40 mg	130	130 x 40 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130 a SGB V. The required number of packs of a particular potency was first determined based on consumption to calculate the annual

treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Venetoclax 100 mg	112 FCT	€ 5,926.03	€ 1.77	€ 0.00	€ 5,924.26
Azacitidine 150 mg	1 PIS	€ 716.53	€ 1.77	€ 89.28	€ 625.48
Decitabine 50 mg	1 PCI	€ 1,242.11	€ 1.77	€ 0.00	€ 1,240.34
Appropriate comparator therapy					
Azacitidine 150 mg	1 PIS	€ 716.53	€ 1.77	€ 89.28	€ 625.48
Decitabine 50 mg	1 PCI	€ 1,242.11	€ 1.77	€ 0.00	€ 1,240.34
Glasdegib maleate 100 mg	30 FCT	€ 13,776.64	€ 1.77	€ 783.51	€ 12,991.36
Cytarabine 40 mg	10 SFI	€ 35.07	€ 1.77	€ 1.14	€ 32.16
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; PIS = powder for the preparation of an infusion suspension; PCI = powder for a concentrate for the preparation of a solution for infusion					

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<u>Costs for additionally required SHI services:</u>

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 additionally required SHI services.

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

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 assessed and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy sales price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 08 September 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 7 September 2021.

On 11 June 2021, the pharmaceutical company submitted a dossier for the benefit assessment of venetoclax to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 15 June 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient venetoclax.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 September 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 September 2021. The deadline for submitting written statements was 6 October 2021.

The oral hearing was held on 25 October 2021.

By letter dated 26 October 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 12 November 2021.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 23 November 2021, and the proposed resolution was approved.

At its session on 2 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	8 September 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	18 May 2021	New determination of the appropriate comparator therapy
Working group Section 35a	20 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	25 October 2021/ 26 October 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 November 2021; 17: November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	23 November 2021	Concluding discussion of the draft resolution
Plenum	2 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 December 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken