Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
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

At its session on 2 December 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D. month YYYY (BAnz AT TT.MM.JJJJ BX), as follows:

I. In Annex XII, the following information is added after No 4 to the information on the benefit assessment of venetoclax in accordance with the decision of 15 October 2020:

Venetoclax

Resolution of: 2 December 2021
Entry into force on: 2 December 2021
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 19 May 2021):

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 of 2 December 2021):

See new therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

- azacitidine
  or
- decitabine
  or
- glasdegib in combination with low-dose cytarabine

Extent and probability of additional benefit of venetoclax in combination with a hypomethylating agent compared with azacitidine:

Hint of a considerable additional benefit

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantage in the endpoint of transfusion independence
Health-related quality of life	n.a.	There are no usable data for the benefit assessment
Side effects	↔	No relevant difference for the benefit assessment, advantages and disadvantages in detail in the case of specific AEs
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

Viale-A study:

Study design: double-blind, multicentre, RCT

Comparison: venetoclax + azacitidine versus azacitidine

Data cut-off: 3: data cut-off of 04.07.2020

Relevant sub-population: more narrowly defined criteria for patients who are ineligible for treatment with intensive chemotherapy[2]

[1] Data from the dossier assessment of the IQWiG (A21-82) and from the addendum (A21-138), unless otherwise indicated.

[2] 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 - accessed: 17.06.2021) and 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 - accessed: 17.06.2021)

Mortality

Endpoint	Venetoclax + azacitidine		Azacitidine		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI][a] p-value[b] Absolute difference (AD)[c]
Overall survival					
	210	12.6 [9.9; 17.6] *138 (65.7)*	103	9.1 [6.6; 11.9] *90 (87.4)*	0.61 [0.46; 0.80] < 0.001 AD: 3.5 months

Morbidity

Endpoint	Venetoclax + azacitidine		Azacitidine		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI][a] p-value[b] Absolute difference (AD)[c]
Remission - presented additionally					
Rate of CR + CRi (by principal investigator)	210	138 (65.7)	103	26 (25.2)	2.60 [1.83; 3.70] < 0.001
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI][a] p-value[b] Absolute difference (AD)[c]
Freedom from transfusion (≥ 24 weeks)					
Freedom from transfusion (≥ 24 weeks)	210	n.d. *74 (35.2)*	103	n.d. *18 (17.5)*	1.95 [1.16; 3.27] 0.010
Symptomatology (EORTC QLQ-C30)					
No usable data available					

(continuation)

Health status (EQ-5D VAS)
No usable data available

Health-related quality of life

Global health status and functional scales (EORTC QLQ-C30)
No usable data available

Side effects

Endpoint	**Venetoclax + azacitidine**		**Azacitidine**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value Absolute difference (AD)[a]
Adverse events in total					
	207	0.1 [0.0; 0.1] *207 (100.0)*	102	0.1 [0.1; 0.1] *102 (100.0)*	-
Serious adverse events (SAE)					
	207	1.3 [0.9; 1.7] *175 (84.5)*	102	1.6 [1.0; 2.6] *77 (75.5)*	1.12 [0.85; 1.47] 0.429
Severe adverse events (CTCAE grade ≥ 3)					
	207	0.2 [0.1; 0.4] *204 (98.6)*	102	0.5 [0.2; 0.6] *97 (95.1)*	1.28 [1.00; 1.64] 0.061
Therapy discontinuation due to adverse events					
	207	n.a. *58 (28.0)*	102	n.a. [22.2; n.c.] *23 (22.5)*	1.08 [0.66; 1.76] 0.767

(continuation)

Specific adverse events					
Contusion[d] (PT, AEs)	207	n.a. *9 (4.3)*	102	n.a. *11 (10.8)*	0.31 [0.13; 0.77] 0.008 AD: n.a.
Injury, poisoning and procedural complications (SOC, severe AEs (CTCAE grade ≥ 3))	207	n.a. *11 (5.3)*	102	n.a. [20.7; n.c.] *10 (9.8)*	0.40 [0.16; 1.00] 0.043 AD: n.a.
Neutropenia[e] (PTs, severe AEs (CTCAE grade ≥ 3))	207	1.8 [1.0; 2.5] *141 (68.1)*	102	7.5 [3.1; n.c.] *40 (39.2)*	2.04 [1.43; 2.91] < 0.001 AD: 5.7 months

[a] Effect and CI: Cox proportional hazards model, stratified by age (18-74 years, ≥ 75 years) and cytogenetic risk (intermediate, poor); no information on stratification factors for the endpoint of freedom from transfusion

[b] p-value from log-rank test, stratified by age (18-74 years, ≥ 75 years) and cytogenetic risk (intermediate, poor); no information on stratification factors for the endpoint of freedom from transfusion

[c] Information on absolute difference (AD) only in case of statistically significant difference; own calculation.

[d] Possibly includes events that may be both side effects and symptomatology of the disease

[e] Predefined endpoint presented in Module 4 A as an AE of special interest. Composed of the following CTCAE grade ≥ 3 events (coded according to MedDRA): Neutropenia (PT), neutrophil count decreased (PT), febrile neutropenia (PT), agranuloscytosis (PT), neutropenic infection (PT), neutropenic sepsis (PT).

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS = visual analogue scale of the European Quality of Life - 5 Dimensions; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; SOC = system organ class; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 560 – 840 patients

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 who are 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[3].

4. Treatment costs

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

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Venetoclax	€ 76,962.48
in combination with	
Azacitidine	€ 56,918.68
or	
Decitabine	€ 80,622.10
Total:	€ 133,881.16 - € 157,584.58

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

Designation of the therapy	Annual treatment costs/ patient
Appropriate comparator therapy:	
azacitidine	€ 56,918.68
decitabine	€ 80,622.10
glasdegib in combination with low-dose cytarabine	
glasdegib	€ 158,061.55
cytarabine	€ 418.08
Total:	€ 158,479.63

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 November 2021)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
azacitidine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	7	91	€ 7,371
decitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	65	€ 5,265
cytarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	10	130	€ 10,530

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 December 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 2 December 2021

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

Prof. Hecken