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
Ivosidenib (acute myeloid leukaemia with IDH1 R132 mutation, first-line, combination with azacitidine)

of 18 January 2024

At its session on 18 January 2024, 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 (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Ivosidenib as follows:

Ivosidenib

Resolution of: 18 January 2024
Entry into force on: 18 January 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 4 May 2023):

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

Therapeutic indication of the resolution (resolution of 18 January 2024):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Ivosidenib is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

Extent of the additional benefit and significance of the evidence of ivosidenib:

Indication of a major additional benefit

Study results according to endpoints:[1]

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↔	Overall, no relevant differences for the benefit assessment; advantage in the endpoint of constipation.
Health-related quality of life	↔	Overall, no relevant differences for the benefit assessment; advantage in the deterioration of emotional functioning.
Side effects	↔	Overall, no relevant differences for the benefit assessment; in detail, mostly advantages in some 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
∅: No data available.
n.a.: not assessable

AGILE study

- RCT, phase III, double-blind (early unblinding on 30.07.2021)
- Ivosidenib + azacitidine vs placebo + azacitidine
- Data cut-offs:
  - 30.06.2022 (mortality, side effects)
  - 18.03.2021 (morbidity, quality of life)

[1] Data from the dossier assessment of the G-BA (published on 16. Oktober 2023), and from the amendment to the dossier assessment from 20 December 2023, unless otherwise indicated.

Mortality

Endpoint	Ivosidenib + azacitidine		Placebo + 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 (HR) [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	73	29.3 [13.2; NE] *37 (50.7)*	75	7.9 [4.11; 11.3] *58 (77.3)*	0.42 [0.27; 0.65] < 0.0001 AD = + 21.4 months

Morbidity

Endpoint	Ivosidenib + azacitidine		Placebo + 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 (HR) [95% CI] p value Absolute difference (AD)[a]
EFS (presented additionally)[b]					
	72	0.03 [0.03; 11.01] *46 (63.9)*	74	0.03 [NE; NE] *62 (83.8)*	0.33 [0.16; 0.69] 0.0023
Transfusion independence ≥ 24 weeks[c] (presented additionally)					
	73	*34 (75.6)*	75	*16 (64.0)*	RR: 1.18 [0.84; 1.65] 0.31[d]
Symptomatology (EORTC QLQ-C30)[e,f] - time to first deterioration					
Fatigue	72	1.1 [0.7; 2.1] *42 (58.3)*	74	1.0 [0.7; 1.4] *46 (62.2)*	0.81 [0.51; 1.26] 0.34
Pain	72	2.3 [1.6; 10.1] *37 (51.4)*	74	1.9 [1.2, 4.3] *34 (45.9)*	0.91 [0.56; 1.47] 0.69
Nausea and vomiting	72	1.5 [1.0; 16.7] *37 (51.4)*	74	1.5 [1.0; 13.4] *33 (44.6)*	1.04 [0.64; 1.70] 0.88

Dyspnoea	72	21.5 [1.1; n.a.] *30 (41.7)*	74	2.2 [1.5; 5.6] *32 (43.2)*	0.91 [0.54; 1.54] 0.72
Insomnia	72	1.5 [1.0; 3.7] *42 (58.3)*	74	4.0 [1.6, 6.2] *33 (44.6)*	1.37 [0.85; 2.22) 0.20
Appetite loss	72	1.9 [1.0; n.a.] *36 (50.0)*	74	1.4 [1.0; 2.1] *39 (52.7)*	0.75 [0.46; 1.22] 0.24
Constipation	72	7.0 [1.6; 19.3] *32 (44.4)*	74	1.4 [0.6; 3.8] *37 (50.0)*	0.53 [0.31; 0.89] 0.016 AD = -5.6 months
Diarrhoea	72	20.4 [7.7; n.a.] *23 (31.9)*	74	6.2 [3.8; n.a.] *25 (33.8)*	0.69 [0.38; 1.25] 0.22
Health status (EQ-5D VAS)[g] - Time to first deterioration					
	72	n.a. [1.9; n.a.] *26 (36.1)*	74	1.7 [1.1; 8.4] *35 (47.3)*	0.60 [0.35; 1.02] 0.06

Health-related quality of life

Endpoint	**Ivosidenib + azacitidine**		**Placebo + 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 (HR) [95% CI] p value Absolute difference (AD)[a]
Functional scales (EORTC QLQ-C30)[h,i] - Time to first deterioration					
Physical functioning	72	1.0 [0.6; 1.9] *45 (62.5)*	74	1.4 [1.0; 2.2] *44 (59.5)*	1.13 [0.72; 1.77] 0.60
Role functioning	72	1.1 [1.0; 1.6] *43 (59.7)*	74	1.4 [1.1; 2.0] *43 (58.1)*	1.05 [0.67; 1.63] 0.84
Emotional functioning	72	9.9 [1.4; 15.7] *33 (45.8)*	74	1.4 [1.0; 3.7] *42 (56.8)*	0.58 [0.35; 0.96] 0.03 AD = -7.5 months
Cognitive functioning	72	1.4 [0.7; 7.0] *40 (55.6)*	74	1.4 [1.0; 1.9] *43 (58.1)*	0.84 [0.53; 1.34] 0.47
Social functioning	72	1.0 [0.6; 1.5] *44 (61.1)*	74	1.2 [0.7; 1.4] *44 (59.5)*	1.11 [0.71; 1.73] 0.65
General health status/ quality of life	72	1.3 [0.9; 2.1] *42 (58.3)*	74	1.5 [1.0; 7.5] *36 (48.6)*	1.11 [0.69; 1.78] 0.66

Side effects

Endpoint	Ivosidenib + azacitidine		Placebo + azacitidine		Intervention vs control
	N	Median in months [95% CI][j] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator (HR) [95% CI] p value[k,l] Absolute difference (AD)[a]
Total adverse events (presented additionally)	72	0.1 [0.0; 0.1] *71 (98.6)*	74	0.1 [0.0; 0.1] *74 (100)*	-
Serious adverse events (SAE)	72	1.6 [0.7; 3.2] *51 (70.8)*	74	1.4 [1.0; 1.7] *62 (83.8)*	0.72 [0.48; 1.06] 0.095
Severe adverse events (CTCAE grade ≥ 3)	72	0.5 [0.4; 0.7] *66 (91.7)*	74	0.5 [0.3; 0.8] *71 (95.9)*	0.81 [0.56; 1.17] 0.26
Therapy discontinuation due to adverse events	72	NE [19.2; NE] *26 (36.1)*	74	NE [10.8; NE] *21 (28.4)*	0.90 [0.48; 1.67] 0.73
SAEs with incidence ≥ 5% of patients in at least one study arm by system organ class (SOC) and preferred term (PT) [PT only with statistically significant difference]					
Infections and infestations (SOC)	72	19.7 [7.1; NE] *30 (41.7)*	74	2.7 [1.5; 8.8] *42 (56.8)*	0.54 [0.33; 0.87] 0.01
Blood and lymphatic system disorders (SOC)	72	NE [NE; NE] *21 (29.2)*	74	NE [5.8; NE] *22 (29.7)*	0.71 [0.38; 1.33] 0.29
Benign, malignant and unspecified neoplasms (including cysts and polyps)(SOC)	72	NE [NE; NE] *9 (12.5)*	74	NE [NE; NE] *2 (2.7)*	3.02 [0.61; 14.82] 0.15
General disorders and administration site conditions (SOC)	72	NE [NE; NE] *8 (11.1)*	74	NE [NE; NE] *8 (10.8)*	0.91 [0.33; 2.53] 0.85
Nervous system disorders (SOC)	72	NE [NE; NE] *7 (9.7)*	74	NE [NE; NE] *3 (4.1)*	1.85 [0.47; 7.28] 0.37
Respiratory, thoracic and mediastinal disorders (SOC)	72	NE [NE; NE] *7 (9.7)*	74	NE [NE; NE] *9 (12.2)*	0.67 [0.23; 1.97] 0.47
Gastrointestinal disorders (SOC)	72	NE [32.0; NE] *5 (6.9)*	74	NE [NE; NE] *8 (10.8)*	0.40 [0.12; 1.34] 0.13
Renal and urinary disorders (SOC)	72	NE [NE; NE] *4 (5.6)*	74	NE [NE; NE] *2 (2.7)*	1.08 [0.18; 6.68] 0.93
Severe adverse events (CTCAE grade ≥ 3) with incidence ≥ 5% of patients in at least one study arm by system organ class (SOC) and preferred term (PT) [PT only with statistically significant difference]					
Blood and lymphatic system disorders (SOC)	72	1.7 [0.8; 2.8] *51 (70.8)*	74	1.5 [1.0; 2.4] *49 (66.2)*	0.84 [0.55; 1.28] 0.42

Endpoint	Ivosidenib + azacitidine		Placebo + azacitidine		Intervention vs control
	N	Median in months [95% CI][j] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator (HR) [95% CI] p value[k,l] Absolute difference (AD)[a]
Infections and infestations (SOC)	72	7.1 [1.8; NE] *37 (51.4)*	74	2.3 [1.3; 4.4] *47 (63.5)*	0.69 [0.45; 1.08] 0.10
Investigations (SOC)	72	27.2 [18.3; NE] *25 (34.7)*	74	n.r. [8.3; NE] *19 (25.7)*	0.93 [0.50; 1.74] 0.83
Gastrointestinal disorders (SOC)	72	NE [32.0; NE] *9 (12.5)*	74	NE [NE; NE] *15 (20.3)*	0.50 [0.21; 1.19] 0.11
Metabolism and nutrition disorders (SOC)	72	NE [NE; NE] *9 (12.5)*	74	NE [4.5; NE] *25 (33.8)*	0.32 [0.15; 0.68] 0.0020
Loss of appetite (PT)	72	NE [NE; NE] *1 (1.4)*	74	NE [NE; NE] *6 (8.1)*	0.13 [0.02; 1.08] 0.026
Nervous system disorders (SOC)	72	NE [NE; NE] *8 (11.1)*	74	NE [NE; NE] *6 (8.1)*	1.01 [0.34; 2.96] 0.99
Respiratory, thoracic and mediastinal disorders (SOC)	72	NE [NE; NE] *8 (11.1)*	74	NE [NE; NE] *14 (18.9)*	0.39 [0.15; 1.03] 0.051
Cardiac disorders (SOC)	72	NE [NE; NE] *6 (8.3)*	74	NE [NE; NE] *6 (8.1)*	0.72 [0.22; 2.41] 0.60
General disorders and administration site conditions (SOC)	72	NE [NE; NE] *6 (8.3)*	74	NE [NE; NE] *13 (17.6)*	0.44 [0.16; 1.19] 0.097
Asthenia (PT)	72	NE [NE; NE] *0*	74	NE [NE; NE] *6 (8.1)*	0.00 [0.00, NE] 0.0094
Benign, malignant and unspecified neoplasms (including cysts and polyps) (SOC)	72	NE [NE; NE] *6 (8.3)*	74	NE [NE; NE] *4 (5.4)*	0.76 [0.18; 3.10] 0.70
Injury, poisoning and procedural complications (SOC)	72	NE [NE; NE] *4 (5.6)*	74	NE [18.7; NE] *3 (4.1)*	0.82 [0.17; 3.94] 0.80
Musculoskeletal and connective tissue disorders (SOC)	72	NE [NE; NE] *4 (5.6)*	74	NE [NE; NE] *3 (4.1)*	1.24 [0.27; 5.65] 0.78
Renal and urinary disorders (SOC)	72	NE [NE; NE] *4 (5.6)*	74	NE [NE; NE] *5 (6.8)*	0.46 [0.11; 1.98] 0.29
Vascular disorders (SOC)	72	NE [NE; NE] *5 (6.9)*	74	NE [NE; NE] *8 (10.8)*	0.35 [0.09; 1.33] 0.11

Endpoint	Ivosidenib + azacitidine		Placebo + azacitidine		Intervention vs control
	N	Median in months [95% CI][j] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator (HR) [95% CI] p value[k,l] Absolute difference (AD)[a]
Hypotension (PT)	72	NE [NE; NE] *0*	74	NE [NE; NE] *4 (5.4)*	0.00 [0.00, NE] 0.042
Psychiatric disorders (SOC)	72	NE [NE; NE] *2 (2.8)*	74	NE [NE; NE] *4 (5.4)*	0.21 [0.02; 1.87] 0.12
AEs with incidence ≥ 10% and statistically significant difference between the treatment arms by system organ class (SOC) and preferred term (PT)					
Constipation (PT)	72	NE [14.0; NE] *24 (33.3)*	74	2.3 [1.1; 13.4] *39 (52.7)*	0.38 [0.22; 0.66] 0.0004
Infections and infestations (SOC)	72	1.8 [0.9; 4.9] *53 (73.6)*	74	1.1 [0.7; 1.5] *59 (79.7)*	0.68 [0.46; 0.99] 0.045
General disorders and administration site conditions (SOC)	72	1.8 [0.8; 7.4] *48 (66.7)*	74	0.9 [0.5; 1.1] *60 (81.1)*	0.63 [0.42; 0.94] 0.02
Asthenia (PT)	72	NE [28.7; NE] *12 (16.7)*	74	9.8 [4.9; NE] *25 (33.8)*	0.35 [0.17; 0.73] 0.0034
Oedema, peripheral (PT)	72	NE [NE; NE] *9 (12.5)*	74	NE [8.6; NE] *17 (23.0)*	0.36 [0.15; 0.84] 0.015
Electrocardiogram QT-prolonged (PT)	72	NE [27.2; NE] *16 (22.2)*	74	NE [NE; NE] *5 (6.8)*	2.87 [1.04; 7.94] 0.034
Weight loss (PT)	72	NE [NE; NE] *4 (5.6)*	74	NE [NE; NE] *12 (16.2)*	0.26 [0.08; 0.81] 0.013
Metabolism and nutrition disorders (SOC)	72	12.6 [1.5; 32.2] *37 (51.4)*	74	1.2 [0.7; 1.9] *51 (68.9)*	0.54 [0.34; 0.85] 0.0070
Loss of appetite (PT)	72	NE [32.2; NE] *13 (18.1)*	74	NE [8.8; NE] *21 (28.4)*	0.44 [0.21; 0.93] 0.028
Hypokalaemia (PT)	72	NE [NE; NE] *11 (15.3)*	74	NE [5.6; NE] *21 (28.4)*	0.47 [0.22; 0.98] 0.039
Cough (PT)	72	NE [NE; NE] *6 (8.3)*	74	NE [10.8; NE] *13 (17.6)*	0.31 [0.11; 0.85] 0.017
Haematoma (PT)	72	NE [NE; NE] *10 (13.9)*	74	NE [NE; NE] *1 (1.4)*	8.49 [1.08; 66.62] 0.015
Renal and urinary disorders (SOC)	72	NE [NE; NE] *12 (16.7)*	74	NE [5.3; NE] *20 (27.0)*	0.47 [0.23; 0.98] 0.039

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation

Endpoint	Ivosidenib + azacitidine		Placebo + azacitidine		Intervention vs control
	N	Median in months [95% CI][j] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator (HR) [95% CI] p value[k,l] Absolute difference (AD)[a]

[b] Primary endpoint of the AGILE study
[c] Transfusion independence after baseline is defined as a period of at least 24 weeks without erythrocyte and platelet transfusion after the start of study treatment and on or before the end of study treatment + 28 days or disease progression, confirmed relapse, death or the cut-off date, whichever occurs earlier.
[d] Own calculation by the medical counselling service
[e] Deterioration ≥ 10 points
[f] After the end of treatment, the test subjects were followed up for a further 4 weeks. Subjects without deterioration of the PRO are censored at the time of the last PRO collection. Subjects without PRO measurement at the start of study will be censored at the time of randomisation. Subjects without a PRO measurement after the baseline are censored at the time of the baseline.
[g] Deterioration ≥ 15 points
[h] Deterioration ≥ 10 points
[i] After the end of treatment, the test subjects were followed up for a further 4 weeks. Subjects without deterioration of the PRO are censored at the time of the last PRO collection. Subjects without PRO measurement at the start of study will be censored at the time of randomisation. Subjects without a PRO measurement after the baseline are censored at the time of the baseline.
[j] The median time to event with 95% CI was analysed by the Kaplan-Meier method using the Brookmeyer and Crowley method with log-log transformation.
[k] All events after switching treatment from placebo to ivosidenib were censored. No other reasons for censorship are listed.
[l] HR based on Cox proportional hazards model, stratified by randomisation stratification factors ("de novo status" and "geographic region"). p value based on stratified two-sided log-rank test stratified by the randomisation stratification factors.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Core Quality of Life Questionnaire; 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.a. = not applicable; n.c. = not calculable; NE = not estimable; PT = preferred term; RR = relative risk; SOC = MedDRA system organ class; vs = versus

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

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

approx. 45 - 125 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 Tibsovo (active ingredient: ivosidenib) at the following publicly accessible link (last access: 8 January 2024):

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

Treatment with ivosidenib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with acute myeloid leukaemia.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about differentiation syndrome.

An electrocardiogram (ECG) must be performed before start of treatment and at least once a week during the first 3 weeks of therapy.

4. Treatment costs

Annual treatment costs:

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ivosidenib	€ 211,017.69
Azacitidine	€ 45,434.48
Total	€ 256,452.17

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2024

Costs for additionally required SHI services: not applicable

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	€ 100	7	91	€ 9,100

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 18 January 2024.

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

Berlin, 18 January 2024

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

Prof. Hecken