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 (cholangiocarcinoma with IDH1 R132 mutation, after at least 1 prior therapy)

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. **In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Ivosidenib in accordance with the resolution of 18 January 2024 for the therapeutic indication: "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":**

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 monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

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).

<u>Adults with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy</u>

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adults with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	Overall, no relevant differences for the benefit assessment; in detail, 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

ClarIDHy study

- RCT, double-blind, phase III
- Ivosidenib + BSC vs placebo + BSC
- Data cut-off from 31 May 2020

Mortality

Endpoint	Ivosidenib + BSC		Placebo + BSC		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	126	10.3 [7.8; 12.4] 100 (79.4)	61	7.5 [4.8; 11.1] 50 (82.0)	0.79 [0.56; 1.12] 0.19

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

Morbidity

Endpoint	Ivosidenib + BSC		Placebo + BSC		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
Data cut-off from 31 January 2019	124	2.7 [1.6; 4.2] 76 (61.3)	61	1.4 [1.4; 1.6] 50 (82.0)	0.37 [0.25; 0.54] < 0.0001 AD = +1.3 months
Symptomatology (EORTC QLQ-C30 and EORTC QLQ-BIL21)					
No usable data available					
General health status (EQ-5D VAS)					
No usable data available					

Health-related quality of life

Endpoint	Ivosidenib + BSC		Placebo + BSC		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Functional scales (EORTC QLQ-C30 and EORTC QLQ-BIL21)					
No usable data available					

Side effects[c]

Endpoint	Ivosidenib + BSC		Placebo + BSC		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	123	0.5 [0.3; 0.5] 120 (97.6)	59	0.4 [0.3; 0.5] 57 (96.6)	-
Serious adverse events (SAE)					
	123	18.8 [8.9; NE] 42 (34.1)	59	NE [NE; NE] 14 (23.7)	1.00 [0.54; 1.88] 0.99
Severe adverse events (CTCAE grade ≥ 3)					
	123	7.4 [3.0; 13.4] 62 (50.4)	59	6.5 [2.6; NE] 22 (37.3)	1.01 [0.61; 1.67] 0.97
Therapy discontinuation due to adverse events					
	123	NE [NE; NE] 9 (7.3)	59	6.9 [NE; NE] 5 (8.5)	0.47 [0.14; 1.53] 0.20
SAE with incidence ≥ 5% or ≥ 10 events and ≥ 1% of patients in at least one study arm (SOC) and preferred term (PT) [PT only with statistically significant difference]					
Gastrointestinal disorders (SOC)	123	NE [NE; NE] 13 (10.6)	59	NE [NE; NE] 4 (6.8)	1.08 [0.34; 3.47] 0.89
Infections and infestations (SOC)	123	NE [NE; NE] 12 (9.8)	59	NE [NE; NE] 5 (8.5)	0.61 [0.20; 1.89] 0.39
Hepatobiliary disorders (SOC)	123	NE [NE; NE] 13 (10.6)	59	NE [NE; NE] 1 (1.7)	3.61 [0.45; 28.66] 0.19
Metabolism and nutrition disorders (SOC)	123	NE [NE; NE] 3 (2.4)	59	NE [NE; NE] 4 (6.8)	0.33 [0.07; 1.47] 0.12
Severe adverse events (CTCAE grade ≥ 3) with incidence ≥ 5% or ≥ 10 events and ≥ 1% of patients in at least one study arm (SOC) and preferred term (PT) [PT only with statistically significant difference]					

Endpoint	Ivosidenib + BSC		Placebo + BSC		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
General disorders and administration site conditions (SOC)	123	NE [21.5; NE] 8 (6.5)	59	NE [NE; NE] 3 (5.1)	0.74 [0.19; 2.96] 0.67
Blood and lymphatic system disorders (SOC)	123	NE [NE; NE] 9 (7.3)	59	NE [NE; NE] 0 (0)	n.a. [n.c.; n.c.] -
Gastrointestinal disorders (SOC)	123	NE [NE; NE] 23 (18.7)	59	NE [NE; NE] 5 (8.5)	1.53 [0.56; 4.13] 0.40
Infections and infestations (SOC)	123	NE [16.1; NE] 15 (12.2)	59	NE [NE; NE] 4 (6.8)	0.96 [0.30; 3.08] 0.95
Hepatobiliary disorders (SOC)	123	NE [24.7; NE] 15 (12.2)	59	6.9 [NE; NE] 2 (3.4)	1.82 [0.39; 8.49] 0.44
Metabolism and nutrition disorders (SOC)	123	NE [NE; NE] 15 (12.2)	59	6.5 [6.5; NE] 10 (16.9)	0.47 [0.20; 1.10] 0.07
Investigations (SOC)	123	NE [NE; NE] 16 (13.0)	59	NE [4.8; NE] 8 (13.6)	0.63 [0.26; 1.54] 0.31
AEs with incidence ≥ 10% in the placebo arm or ≥ 10 and ≥ 1% in the ivosidenib arm and statistically significant difference between the treatment arms according to SOC and PT					
Dyspnoea (PT)	123	NE [NE; NE] 13 (10.6)	59	NE [NE; NE] 10 (16.9)	0.28 [0.11; 0.70] 0.003
Hypercalcaemia (PT)	123	NE [NE; NE] 3 (2.4)	59	NE [NE; NE] 7 (11.9)	0.17 [0.04; 0.67] 0.004

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] For the placebo arm, the evaluation includes all events prior to a possible treatment switch to ivosidenib, which was only permitted after disease progression. The analysis is based on all randomised patients at the 1st data cut-off from 31.01.2019. This does not correspond to the ITT population of the study, as 2 additional subjects were randomised after this data cut-off.
[c] The safety analyses were performed on the basis of the safety population. For the placebo arm, censoring was performed at treatment change.

Abbreviations used:
AD = absolute difference; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-BIL21 = European Organisation for Research and Treatment of Cancer – Quality of Life

Endpoint	Ivosidenib + BSC		Placebo + BSC		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 (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Questionnaire – Cholangiocarcinoma and Gallbladder Cancer Module; 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.c. = not calculable; NE = not estimable; PT = preferred term; SOC = MedDRA system organ class; vs = versus					

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

Adults with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy

approx. 80 – 160 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: 5 October 2023):

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, internal medicine and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with cholangiocarcinoma.

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 locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Ivosidenib	€ 211,017.69

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

Costs for additionally required SHI services: not applicable

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 locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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