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)

Trifluridine/Tipiracil (new therapeutic indication: colorectal cancer, after 2 prior therapies, combination with bevacizumab)

of 15 February 2024

At its session on 15 February 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. 4 to the information on the benefit assessment of Trifluridine/ tipiracil in accordance with the resolution of 1 October 2020:

Trifluridine/tipiracil

Resolution of: 15 February 2024
Entry into force on: 15 February 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 July 2023):

Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

Therapeutic indication of the resolution (resolution of 15 February 2024):

See new therapeutic indication according to marketing authorisation.

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

Adults with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents

Appropriate comparator therapy:

- Trifluridine/tipiracil

Extent and probability of the additional benefit of trifluridine/tipiracil in combination with bevacizumab compared to trifluridine/tipiracil:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Adults with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↑	Advantage in health status.
Health-related quality of life	↔	Overall, no relevant differences for the benefit assessment; advantage in the physical functioning.
Side effects	↑	Advantage in the endpoint of serious adverse events.
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		

SUNLIGHT study:

Trifluridine/tipiracil in combination with bevacizumab vs trifluridine/tipiracil

Study design: RCT, open-label

Data cut-off: 19 July 2022

1 Data from the dossier assessment of the IQWiG (A23-85) and from the addendum (A24-09), unless otherwise indicated.

Mortality

Endpoint	Trifluridine/tipiracil + bevacizumab		Trifluridine/tipiracil		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 (%)*	Hazard ratio[a] [95% CI] p value Absolute difference (AD)[b]
Overall survival					
	246	10.8 [9.4; 11.8] *148 (60.2)*	246	7.5 [6.3; 8.6] *183 (74.4)*	0.61 [0.49; 0.77]; < 0.001 AD = + 3.3 months

Morbidity

Progression-free survival (PFS)[c]					
	264	5.6 [4.5; 5.9] *206 (83.7)*	246	2.4 [2.1; 3.2] *236 (95.9)*	0.44 [0.36; 0.54]; < 0.0001 AD = + 3.2 months
Symptomatology (EORTC QLQ-C30 – time to 1st Deterioration[d])					
Fatigue	246	3.3 [2.7; 4.5] *141 (57.3)*	246	2.3 [1.9; 3.0] *145 (58.9)*	0.79 [0.62; 1.01]; 0.060
Nausea and vomiting	246	6.5 [4.7; n.c.] *109 (44.3)*	246	6.9 [3.7; n.c.] *96 (39.0)*	0.95 [0.72; 1.26]; 0.724
Pain	246	4.6 [3.7; 6.0] *129 (52.4)*	246	3.3 [2.8; 5.1] *123 (50.0)*	0.87 [0.67; 1.12]; 0.285
Dyspnoea	246	n.r. [9.0; n.c.] *79 (32.1)*	246	9.7 [5.8; n.c.] *82 (33.3)*	0.76 [0.55; 1.04]; 0.087
Insomnia	246	10.6 [8.3; n.c.] *87 (35.4)*	246	8.1 [6.9; n.c.] *82 (33.3)*	0.88 [0.64; 1.20]; 0.408
Appetite loss	246	4.7 [3.8; 7.5] *125 (50.8)*	246	4.6 [3.7; 6.9] *105 (42.7)*	0.97 [0.74; 1.27]; 0.828
Constipation	246	n.r. [8.8; n.c.] *87 (35.4)*	246	n.r. [10.6; n.c.] *68 (27.6)*	1.13 [0.82; 1.56]; 0.459
Diarrhoea	246	n.r. [6.5; n.c.] *91 (37.0)*	246	n.r. [5.8; n.c.] *77 (31.3)*	1.03 [0.75; 1.40]; 0.858
Health status (EQ-5D VAS – time to 1st Deterioration[e])					
	246	n.r. [8.1; n.c.] *85 (34.6)*	246	7.8 [4.5; n.c.] *87 (35.4)*	0.70 [0.51; 0.95]; 0.023

(continuation)

Health-related quality of life

EORTC QLQ-C30 (time to 1st deterioration[f])					
Global health status	246	5.6 [4.2; 9.5] *120 (48.8)*	246	5.5 [3.7; 6.7] *109 (44.3)*	0.84 [0.64; 1.10]; 0.201
Physical functioning	246	6.9 [4.6; 11.3] *108 (43.9)*	246	5.0 [3.3; 6.1] *115 (46.7)*	0.73 [0.55; 0.95]; 0.020 AD = 1.9 months
Role functioning	246	5.0 [3.8; 8.8] *123 (50.0)*	246	4.4 [3.3; 6.5] *117 (47.6)*	0.80 [0.62; 1.05]; 0.107
Emotional functioning	246	n.r. [8.3; n.c.] *84 (34.1)*	246	7.9 [6.9; n.c.] *83 (33.7)*	0.83 [0.61; 1.14]; 0.252
Cognitive functioning	246	8.1 [5.5; n.c.] *101 (41.1)*	246	6.9 [4.7; n.c.] *87 (35.4)*	0.94 [0.70; 1.26]; 0.675
Social functioning	246	6.9 [4.8; 13.2] *107 (43.5)*	246	5.8 [4.4; 9.7] *102 (41.5)*	0.84 [0.63; 1.11]; 0.225

Side effects[g]

Endpoint	**Trifluridine/ tipiracil + bevacizumab**		**Trifluridine/ tipiracil**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio[h] [95% CI] p value
Serious adverse events (SAE)					
	246	n.r. *45 (18.3)*	246	11.1 [8.8; n.r.] *50 (20.3)*	0.59 [0.39; 0.89]; 0.012
Severe adverse events (CTCAE grade ≥ 3)					
	246	3.7 [2.8; 4.8] *144 (58.5)*	246	2.8 [2.1; 3.3] *133 (54.1)*	0.83 [0.65; 1.05]; 0.125
Therapy discontinuation due to adverse events					
	246	n.r. *22 (8.9)*	246	n.r. *7 (2.8)*	2.09 [0.87; 4.99]; 0.091

a Effect and CI: Cox proportional hazards model; p value: log-rank test. Each stratified by RAS status (mutated vs wild type), time since diagnosis of first metastasis (< 18 months vs ≥ 18 months) and region (North America vs European Union vs rest of the world).
b Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
c Data from the dossier of the pharmaceutical company (Module 4D) of 18 August 2023.
d An increase in the EORTC QLQ-C30 score by ≥ 10 points compared to baseline is considered a clinically relevant deterioration (scale range 0 to 100). Patients were censored at the time of death.
e The pharmaceutical company describes in Module 4 A that the original scale values were transformed for the present analyses so that the lowest scale value 0 represents the best health status and the highest scale value 100 represents the worst health status. An increase in the transformed score on the VAS by ≥

15 points compared to baseline is considered a clinically relevant deterioration (scale range 0 to 100). Patients were censored at the time of death.

f A decrease in the EORTC QLQ-C30 score by ≥ 10 points compared to baseline is considered a clinically relevant deterioration (scale range 0 to 100). Patients were censored at the time of death.

g Adverse events that, in the opinion of the principal investigator, were related to the progression of the underlying disease were not considered.

h Effect and CI: unstratified Cox proportional hazards model; p value: unstratified log-rank test

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; HR: hazard ratio; CI: confidence interval; n: number of patients with event; N: number of patients evaluated; n.c.: not calculable; n.r. = not reached; RAS: rat sarcoma viral oncogene homologue; RCT: randomised controlled trial; VAS: visual analogue scale; vs = versus

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

Adults with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents

approx. 3,530 – 6,230 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 Lonsurf (active ingredient: trifluridine/ tipiracil) at the following publicly accessible link (last access: 6 February 2024):

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

Treatment with trifluridine/ tipiracil should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with metastatic colorectal cancer.

4. Treatment costs

Annual treatment costs:

Adults with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Trifluridine/ tipiracil	€ 43,986.54
Bevacizumab	€ 38,260.25
Total:	€ 82,246.79
Appropriate comparator therapy:	
Trifluridine/ tipiracil	€ 43,986.54

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 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
Bevacizumab	Preparation of parenteral solutions with monoclonal antibodies	€ 100	1	26.1	€ 2,610

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 metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents

- No medicinal product with new active ingredients that can be used in a combination therapy that 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 15 February 2024.

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

Berlin, 15 February 2024

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

Prof. Hecken