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
Fruquintinib (metastatic colorectal cancer, pretreated patients)

of 16 January 2025

At its session on 16 January 2025, 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 Fruquintinib as follows:

Fruquintinib

Resolution of: 16 January 2025
Entry into force on: 16 January 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 20 June 2024):

Fruzaqla as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib.

Therapeutic indication of the resolution (resolution of 16 January 2025):

See 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 (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib[1]

Appropriate comparator therapy:

– Best supportive care

Extent and probability of the additional benefit of fruquintinib compared to best supportive care:

Hint for a minor additional benefit

[1] not sold in Germany

Study results according to endpoints:[2]

Adults with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant difference for the benefit assessment; in detail, disadvantages and one advantage for 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		

FRESCO-2 study

Comparison: Fruquintinib versus Best Supportive Care (BSC)

Study design: RCT, double-blind

Data cut-off: 24 June 2022

[2] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-74) unless otherwise indicated.

Mortality

Endpoint	**Fruquintinib**		**BSC**		Fruquinitinib versus BSC
	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] p value[a] Absolute difference (AD)[b]
Overall survival					
	461	7.4 [6.7; 8.2] *317 (68.8)*	230	4.8 [4.0; 5.8] *173 (75.2)*	0.66 [0.55; 0.80] < 0.001[c] AD = + 2.6 months

Morbidity

Endpoint	**Fruquintinib**		**BSC**		Fruquinitinib versus BSC
	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] p value[a] Absolute difference (AD)[b]
Progression-free survival (PFS)[d]					
	461	3.7 [3.5; 3.8] *392 (85.0)*	230	1.8 [1.8; 1.9] *213 (92.6)*	0.32 [0.27; 0.39] < 0.001[c] AD = + 1.9 months
Symptomatology (EORTC QLQ-C30)					
No suitable data available.					
Health status (EQ-5D VAS)					
No suitable data available.					

Health-related quality of life

Endpoint	Fruquintinib		BSC		Fruquinitinib versus BSC
	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] p value[a]
EORTC QLQ-C30					
No suitable data available.					

Side effects

Endpoint	Fruquintinib		BSC		Fruquinitinib versus BSC
	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] p value[a]
Adverse events (presented additionally)[e]					
	456	0.3 [0.2; 0.3] *450 (98.7)*	230	0.5 [0.4; 0.6] *211 (91.7)*	-
Serious adverse events (SAE)[e]					
	456	11.0 [7.8; n.c.] *154 (33.8)*	230	n.r. [5.4; n.c.] *72 (31.3)*	0.77 [0.58; 1.03] 0.102
Severe adverse events (CTCAE grade ≥ 3)[e]					
	456	2.9 [2.5; 3.7] *277 (60.7)*	230	4.1 [3.4; 5.6] *103 (44.8)*	1.20 [0.96; 1.51] 0.078
Therapy discontinuations due to adverse events[e]					
	456	n.r. 85 (18.6)	230	n.r. *40 (17.4)*	0.70 [0.47; 1.03] 0.083

(continuation)

Specific adverse events
Gastrointestinal perforation (SMQ, AE)

	456	n.r. *16 (3.5)*	230	n.r. *1 (0.4)*	4.71 [0.61; 36.47] 0.094
Diarrhoea (PT; AE)					
	456	n.r. [10.9; n.c.] *110 (24.1)*	230	n.r. *24 (10.4)*	2.05 [1.31; 3.20] 0.001
Hand-foot syndrome (PT, severe AE (CTCAE grade ≥ 3))[f]					
	456	n.r. *29 (6.4)*	230	n.r. *0 (0)*	n.c.[g] < 0.001
Bleeding (SMQ, AE)					
	456	n.r. *65 (14.3)*	230	n.r. [5.7; n.c.] *22 (9.6)*	1.18 [0.72; 1.92] 0.507
Bleeding (SMQ, severe AE (CTCAE grade ≥ 3))					
	456	n.r. *8 (1.8)*	230	n.r. *4 (1.7)*	0.49 [0.14; 1.73] 0.309
Hypertension (SMQ, severe AE (CTCAE grade ≥ 3))					
	456	n.r. *64 (14.0)*	230	n.r. 2 (0.9)	16.62 [4.07; 67.94] < 0.001
Mucosal inflammation (PT, AE)					
	456	n.r. [13.2; n.c.] *62 (13.6)*	230	n.r. *6 (2.6)*	4.91 [2.12; 11.38] < 0.001
Stomatitis (PT, AE)					
	456	n.r. [18.0; n.c.] *67 (14.7)*	230	n.r. *8 (3.5)*	4.09 [1.96; 8.53] < 0.001
Dysphonia (PT, AE)					
	456	n.r. *74 (16.2)*	230	n.r. *12 (5.2)*	3.32 [1.80; 6.13] < 0.001
Abnormal liver function (SMQ; SAE)[h]					
	456	n.r. *11 (2.4)*	230	n.r. *11 (4.8)*	0.43 [0.18; 0.99] 0.041

a. HR and CI were calculated using an unstratified Cox regression model with the stratification factors and the treatment group as covariates. The p value was calculated using a stratified log-rank test. The stratification factors "previous therapy" (trifluridine/ tipiracil versus reografenib versus trifluridine/ tipiracil and regorafenib), "RAS status" (wild type versus mutation) and "duration of metastatic disease" (≤ 18 months versus > 18 months) were used.

b. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
c. HR and CI were calculated using a stratified Cox regression model and the p value was calculated using a stratified log-rank test. The stratification factors "previous therapy" (trifluridine/ tipiracil versus reografenib versus trifluridine/ tipiracil and regorafenib), "RAS status" (wild type versus mutation) and "duration of metastatic disease" (≤ 18 months versus > 18 months) were used.
d. Data from the dossier of the pharmaceutical company (Module 4 A) of 27 June 2024
e. Presentation without consideration of disease-related events (the PTs disease progression, malignant neoplastic progression, neoplastic progression, metastatic colorectal cancer, tumour pain, tumour invasion, metastasis, neoplastic meningitis, liver metastases, CNS metastases, cancer pain and metastatic lung cancer were not considered)
f. Operationalised via severe AEs (CTCAE grade ≥ 3) of the PT palmar-plantar erythrodysaesthesia syndrome (coded according to MedDRA)
g. An effect estimate was not calculable using the Cox regression model presented by the pharmaceutical company. For severe AEs of the higher-level SOC "Skin and subcutaneous tissue disorders", which predominantly comprise the PT "Palmar-plantar erythrodysaesthesia syndrome", the result is as follows: 31 (6.8%) vs 1 (0.4%); HR: 11.78 [1.60; 86.84]; p = 0.002.
h. Operationalised via SAE of the SMQ "Drug-induced liver diseases – comprehensive search" (coded according to MedDRA)

Abbreviations used:
AD = absolute difference; BSC = Best Supportive Care; 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 = European Quality of Life-5 Dimensions – visual analogue scale; HR = hazard ratio; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire – Core 30; RAS = Rat Sarcoma viral oncogene homologue; SMQ = standardised MedDRA query; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale

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

Adults with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib

Approx. 645 to 2,180 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 Fruzaqla (active ingredient: fruquintinib) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 7 January 2025):

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

Treatment with fruquintinib 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 (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Fruquintinib	€ 86,069.49
Best supportive care[3]	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care[3]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 December 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 metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib

– 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

[3] When comparing fruquintinib versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product to be assessed.

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 16 January 2025.

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

Berlin, 16 January 2025

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

Prof. Hecken