Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure is the first placing on the (German) market of the active ingredient fruquintinib on 15 July 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 28 June 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 October 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of fruquintinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of

the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of fruquintinib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Fruquintinib (Fruzaqla) in accordance with the product information

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 16.01.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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[2]

Appropriate comparator therapy for fruquintinib as monotherapy:

– Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.
[2] not sold in Germany

its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. In the present therapeutic indication, in addition to fruquintinib, the cytostatic agents 5-fluorouracil, calcium folinate, capecitabine, irinotecan, mitomycin, oxaliplatin, tegafur/ gimeracil/ oteracil and trifluridine/ tipiracil, the antibodies bevacizumab, cetuximab, ipilimumab, nivolumab, panitumumab, pembrolizumab and ramucirumab, the protein kinase inhibitors encorafenib and regorafenib as well as the active ingredient aflibercept are approved.

Medicinal products with explicit marketing authorisation for first-line treatment were not taken into account in accordance with the present therapeutic indication.

On 2. Non-medicinal treatment is not considered.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Trifluridine/ tipiracil (combination with bevacizumab): resolution of 15 February 2024
- Pembrolizumab: resolution of 19 January 2023
- Nivolumab: resolution of 20 January 2022
- Encorafenib: resolution of 17 December 2020
- Trifluridine/ tipiracil: resolution of 1 October 2020
- Ramucirumab: resolution of 1 September 2016
- Regorafenib: resolution of 17 March 2016
- Aflibercept: resolution of 15 August 2013

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V (see "Information on appropriate comparator therapy"). There is no written feedback from the scientific-medical societies or AkdÄ on the question of comparator therapy.

The treatment concept of metastatic colorectal cancer in the palliative treatment setting is characterised by the sequence of different lines of therapy. For first- and second-line therapy, guidelines provide for defined therapies that include fluoropyrimidine, oxaliplatin- or irinotecan-containing chemotherapy regimens and that can be combined with anti-vascular endothelial growth factor (VEGF) substances (bevacizumab, aflibercept and ramucirumab) and anti-epidermal growth factor receptor (EGFR) substances (cetuximab, panitumumab) in accordance with the respective marketing authorisation.

According to the treatment sequence recommended in the guidelines, it is assumed that patients with a BRAF V600E mutation or high-frequency microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) have already been treated with corresponding targeted active ingredients.

The therapeutic indication for fruquintinib describes a treatment stage of metastatic colorectal cancer in which patients must have already been treated with available standard therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, anti-EGFR therapy (for wild-type RAS), and trifluridine/ tipiracil or regorafenib.

For the treatment of patients whose cancer progresses after previous therapy with trifluridine/ tipiracil or regorafenib, no specific therapy recommendation for further antineoplastic therapy can be derived from the guidelines. Further treatment therefore

generally addresses the alleviation of symptoms and improvement of the quality of life, which is why best supportive care is a suitable appropriate comparator therapy.

According to the joint statement by the Working Group for Internal Oncology of the German Cancer Society (AIO), the German Society of Haematology and Medical Oncology (DGHO) and the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS), best supportive care at this stage of the disease is in line with current recommendations.

As a result, a best supportive care is determined as the appropriate comparator therapy in the present therapeutic indication.

"Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of fruquintinib is assessed as follows:

Hint for a minor additional benefit

Justification:

The benefit assessment of fruquintinib for the treatment of adults with metastatic colorectal cancer who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/ tipiracil or regorafenib, will be based on the results of the FRESCO-2 study.

FRESCO-2 is a double-blind, randomised, multicentre phase III study comparing fruquintinib + BSC (hereinafter: fruquintinib) with BSC.

A total of 691 adults with histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum were enrolled in the study. 461 patients were randomised to the intervention arm and 230 patients to the control arm in a 2:1 ratio. All patients had to have received a pretreatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, as well as an anti-VEGF therapy. In the case of wild-type RAS, patients also had to be pretreated with an anti-EGFR therapy, in the case of tumours with MSI-H or dMMR with checkpoint inhibitors, and in the case of tumours with BRAF mutation with a BRAF inhibitor. Furthermore, progression on or intolerance to trifluridine/ tipiracil and/or regorafenib had to be present. Further requirements for enrolment in the study were an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 and an expected survival time > 12 weeks.

The FRESCO-2 study was conducted at 124 study sites in Asia, Australia, Europe and North America from 2020 to 2022.

The present benefit assessment is based on the results for the 2nd data cut-off (final analysis) from 24 June 2022.

Limitations of the study and transferability to the German healthcare context

Only patients with adenocarcinoma were enrolled in the FRESCO-2 study, with this histological type accounting for the majority of metastatic colorectal cancer (over 95%).

At 62 years, the average age of the study population in the FRESCO-2 study is well below the mean age of onset of pretreated metastatic colorectal cancer in Germany, which is why it can be assumed that the patients in the therapeutic indication are older on average than the patients examined in the study. In addition, patients with an ECOG-PS > 1 were excluded.

Conduct of the study (protocol violations)

During the FRESCO-2 study, at least one major protocol violation occurred in 89% of the study participants. Deviations related to omitted study procedures (53% of patients in the intervention arm versus 44% in the comparator arm), the dosage of the study medication (51% versus 40%), and the inclusion and exclusion criteria (36% versus 35%) occurred most frequently.

No information on the protocol deviations in the FRESCO-2 study was provided by the pharmaceutical company in the dossier. With their statement, the pharmaceutical company subsequently submitted information on the definition and classification of protocol deviations. With the statement, missing data were only presented on omitted study procedures, while analyses on the dosage of the study medication or inclusion and exclusion criteria are still missing. The available documents therefore do not clarify the deviations from the study planning in detail. There are also differences between the study arms with regard to deviations in omitted study procedures and dosage of the study medication. Overall, it remains unclear how the protocol deviations affect the available results of the FRESCO-2 study.

Extent and probability of the additional benefit

Mortality

The overall survival is defined in the FRESCO-2 study as the time from randomisation to death from any cause.

For the endpoint of overall survival, there was a statistically significant extension in survival time in favour of fruquintinib compared to BSC. Taking into account the advanced stage of the disease and treatment, the extension in survival time achieved is assessed as a relevant improvement to not more than a minor extent.

Morbidity

Progression-free survival (PFS)

PFS is operationalised in the FRESCO-2 study as the time from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first. The occurrence of disease progression was assessed using RECIST criteria (version 1.1).

For the PFS, there is a statistically significant difference between the treatment groups to the advantage of fruquintinib.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST version 1.1 criteria).

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Symptomatology (assessed using EORTC QLQ-C30) and health status (assessed using EQ-5D VAS)

Patients' symptomatology was assessed in the FRESCO-2 study using the EORTC QLQ-C30. The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

With their dossier, the pharmaceutical company presented both responder analyses, operationalised as the time to first improvement or deterioration, and continuous evaluations for the EORTC QLQ-C30 and the EQ-5D VAS.

There was a sharp decline in the number of questionnaires returned early on in the course of the study. In addition, there were significant differences in return rates between the treatment arms. Due to the small percentage of patients for whom data was collected, no valid statements can therefore be made. As a result, the data presented are unusable for the benefit assessment.

Quality of life

Patients' quality of life was assessed in the FRESCO-2 study using the EORTC QLQ-C30.

With their dossier, the pharmaceutical company presented both responder analyses, operationalised as the time to first improvement or deterioration, and continuous evaluations for the EORTC QLQ-C30.

There was a sharp decline in the number of questionnaires returned early on in the course of the study. In addition, there were significant differences in return rates between the treatment arms. Due to the small percentage of patients for whom data was collected, no valid statements can therefore be made. As a result, the data presented are unusable for the benefit assessment.

Side effects

Adverse events in total

Adverse events occurred in 98.7% of patients in the fruquintinib arm and in 91.7% of patients in the BSC arm. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Specific AEs

Abnormal liver function (SMQ, SAE)

For the endpoint of abnormal liver function (SMQ, SAE), fruquintinib showed an advantage over the control arm.

Gastrointestinal perforation (SMQ, AE) and bleeding (SMQ, AE, severe AE)

There were no statistically significant differences between the treatment groups for the endpoints of gastrointestinal perforation (SMQ], AE) and bleeding (SMQ, AE, severe AE).

Diarrhoea (TT, AE), hand-foot syndrome (PT, severe AE), hypertension (SMQ, severe AE), mucosal inflammation (PT, AE), stomatitis (PT, AE) and dysphonia (PT, AE)

For the endpoints of diarrhoea (TT, AE), hand-foot syndrome (PT, severe AE), hypertension (SMQ, severe AE), mucosal inflammation (PT, AE), stomatitis (PT, AE) and dysphonia (PT, AE), fruquintinib showed a disadvantage over BSC in each case.

In terms of side effects, the overall analysis showed no relevant difference. In detail, there were disadvantages and one advantage for specific AEs.

Overall assessment

Data from the double-blind, randomised FRESCO-2 study on mortality, morbidity, quality of life and side effects compared to BSC are available for the benefit assessment of fruquintinib for the treatment of adults with metastatic colorectal cancer 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.

For the endpoint of overall survival, there was a statistically significant prolongation in survival time in favour of fruquintinib, which was assessed as a relevant improvement, but no more than a minor improvement.

No assessable data are available for the endpoints of symptomatology (assessed by EORTC QLQ-C30) and health status (assessed by EQ-5D VAS). Likewise, no assessable data are available on health-related quality of life. This is based on the fact that there was a sharp decline in the number of questionnaires returned early on in the course of the study, with clear differences between the treatment arms as well. Consequently, data was only collected for a small percentage of patients, which is why no valid statements can be made for the respective endpoints. Statements on symptomatology and quality of life are given a particularly high significance in the present advanced, palliative treatment setting.

In terms of side effects, the overall analysis showed no relevant difference. In detail, there were disadvantages and one advantage for specific AEs.

In the overall assessment, a minor additional benefit of fruquintinib over best supportive care was identified.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the double-blind, randomised, phase III FRESCO-2 study.

With regard to the transferability of the study results to the German healthcare context, there are relevant uncertainties resulting in particular from the significantly lower age of the patients in the study compared to the reality of care.

Following the FRESCO-2 study, a relevant percentage of both patients who had been treated with fruquintinib (29.4%) and patients who received best supportive care (34.3%) received at least one antineoplastic subsequent therapy, so that uncertainties exist as to whether only BSC was a therapy option for the patients in the study population and to what extent they had already been pretreated with all of the (then) available therapies in accordance with the marketing authorisation text, thus corresponding to the target population according to the therapeutic indication.

In addition, uncertainties remain due to a high number of important protocol violations in the study, the extent of which they influence the results of the FRESCO-2 study remaining unclear.

Overall, the available data basis is subject to relevant uncertainties. Thus, the reliability of data for the additional benefit identified is classified in the "hint" category.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Fruzaqla with the active ingredient fruquintinib.

The therapeutic indication assessed here is as follows:

"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".

The G-BA determined Best Supportive Care to be the appropriate comparator therapy.

For the assessment, the pharmaceutical company presented the double-blind, randomised phase III FRESCO-2 study comparing fruquintinib with BSC.

For overall survival, there was a statistically significant advantage for treatment with fruquintinib. Although the prolongation of survival time achieved is assessed as a relevant improvement, its extent is minimal.

No assessable data are available for the endpoints of symptomatology (assessed by EORTC QLQ-C30) and health status (assessed by EQ-5D VAS). Likewise, no assessable data are available on health-related quality of life. This is based on the fact that there was a sharp decline in the number of questionnaires returned early on in the course of the study, with clear differences between the treatment arms as well. Consequently, data was only collected for a small percentage of patients, which is why no valid statements can be made for the respective endpoints. Statements on symptomatology and quality of life are given a particularly high significance in the present advanced, palliative treatment setting.

In terms of side effects, the overall analysis showed no relevant difference. In detail, there were disadvantages and one advantage for specific AEs.

In the overall assessment, a minor additional benefit of fruquintinib over best supportive care was identified.

Due to relevant uncertainties with regard to the conduct of the study and the transferability of the study results to the reality of care, the reliability of data for the additional benefit identified is classified as a "hint" overall.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are however underestimated due to the lack of consideration of patients with a first diagnosis in the previous year and an outpatient diagnosis in the following year and the lack of consideration of percentages of patients for who are eligible for subsequent therapy. In addition, there are uncertainties due to an unclear description of the methodological approach in several steps.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 December 2024).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Fruquintinib	1 x on day 1-21 of a 28-day cycle	13.0	21	273.0
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Fruquintinib	5 mg	5 mg	1 x 5 mg	273.0	273 x 5 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction

of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Fruquintinib 5 mg	21 HC	€ 7,020.37	€ 2.00	€ 397.64	€ 6,620.73
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: HC = hard capsules					

LAUER-TAXE® last revised: 15 December 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to

Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

References:

Product information for fruquintinib (Fruzaqla); Takeda Fruzaqla hard capsules; last revised: June 2024

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 6 June 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 June 2024, the pharmaceutical company submitted a dossier for the benefit assessment of fruquintinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 10 July 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient fruquintinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 October 2024. The deadline for submitting statements was 5 November 2024.

The oral hearing was held on 25 November 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 January 2025, and the proposed draft resolution was approved.

At its session on 16 January 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 June 2023	Determination of the appropriate comparator therapy
Working group Section 35a	19 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 November 2024	Conduct of the oral hearing
Working group Section 35a	03.12.2024; 17.12.2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 January 2025	Concluding discussion of the draft resolution
Plenum	16 January 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 January 2025

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

Prof. Hecken