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

of 15 February 2024

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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 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 combination of active ingredients trifluridine/tipiracil (Lonsurf) was listed for the first time on 15 August 2016 in the "LAUER-TAXE®", the extensive German registry of available medicinal products and their prices.

On 26 July 2023, trifluridine/tipiracil received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 14 August 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of

Procedure (VerfO) of the G-BA on the active ingredient combination of active ingredients trifluridine/tipiracil with the new therapeutic indication:

"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."

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 November 2023 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 trifluridine/tipiracil 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 trifluridine/tipiracil.

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 trifluridine/tipiracil (Lonsurf) in accordance with the product information

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 15.02.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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 for trifluridine/tipiracil in combination with bevacizumab:

- Trifluridine/tipiracil

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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 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.

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

on 1. In the planned therapeutic indication, 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.

on 2. It is assumed that there is no indication for curative treatment or for primary or secondary resectability. Non-medicinal treatment is therefore not considered.

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

- 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 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-VEGF substances (bevacizumab, aflibercept and ramucirumab) and anti-EGFR substances (cetuximab, panitumumab) in accordance with the respective marketing authorisation. Furthermore, in the presence of a BRAF V600E mutation, the use of encorafenib in combination with cetuximab is possible for patients who have received prior systemic therapy.

The written statements of the scientific-medical societies show that there is no uniform therapy standard for the treatment setting in consultation, i.e. after multiple prior systemic therapies (fluoropyrimidine, oxaliplatin and irinotecan therapy, anti-VEGF antibodies, anti-EGFR antibodies, BRAF inhibitors). According to the scientific-medical societies, therapy is individualised according to the treating physicians. Therapy options include trifluridine/tipiracil, regorafenib, targeted therapy (checkpoint inhibitor(s) for MSI-H/dMMR, anti-HER2 antibodies, NTRK inhibitors for NTRK mutations, TKI in combination with an antibody for BRAF V600E mutations), repetition or resumption of a successful prior therapy and best supportive care.

The evidence shows that trifluridine/tipiracil or regorafenib is recommended for the present treatment setting.

In the benefit assessment for trifluridine/tipiracil for adults with metastatic colorectal cancer who have already been treated with available therapies or who are ineligible for them, a hint for a minor additional benefit over best supportive care was identified (resolution of 1 October 2020).

The active ingredient regorafenib has been off-label in Germany for a long time now and does not represent a therapy option in the context of the appropriate comparator therapy at this time. On the one hand, this is due to the fact that a regular supply is not

guaranteed in Germany; on the other, the benefit assessment did not identify any additional benefit compared to best supportive care (resolution of 17 March 2016).

In the overall assessment, trifluridine/tipiracil is therefore determined as the appropriate comparator therapy in the present therapeutic indication.

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 trifluridine/tipiracil is assessed as follows:

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

Hint for a considerable additional benefit

Justification:

The pharmaceutical company has presented the results of the SUNLIGHT study to demonstrate an additional benefit of trifluridine/tipiracil for the treatment of adult patients with metastatic colorectal cancer who have already received two prior anticancer therapies.

SUNLIGHT is a randomised, multicentre, open-label, controlled phase III study comparing trifluridine/tipiracil in combination with bevacizumab with trifluridine/tipiracil. The study commenced in November 2020 and was completed in September 2023. It was conducted in 99 study sites and 13 countries (North and South America as well as Europe).

Adults with metastatic colorectal cancer were enrolled in the study. Patients had to have been pretreated with ≤ 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and have shown progression or intolerance after the last chemotherapy regimen. Prior therapies had to include fluoropyrimidine-, oxaliplatin-, irinotecan-based chemotherapies, anti-VEGF and/or anti-EGFR substances in the presence of wild-type RAS colorectal cancer.

The 492 patients enrolled were randomised 1:1 to the trifluridine/tipiracil + bevacizumab arm (N = 246) and the trifluridine/tipiracil arm (N = 246). Stratification was based on RAS mutational status (wild type vs mutation), time since diagnosis of 1st metastasis (< 18 months vs ≥ 18 months) as well as geographic region (North America vs European Union vs rest of the world).

The mean age of the study population, which has already received two anticancer therapies, is 61 years in the trifluridine/tipiracil + bevacizumab arm and 62 years in the trifluridine/tipiracil arm, which is significantly below the mean age of 71 - 75 years marking the onset of colorectal cancer in Germany[2], which is why it can be assumed that the patients in the therapeutic indication are older on average than the SUNLIGHT study population. Patients with an Eastern Cooperative Oncology Group performance status of > 1 were excluded from the study.

2 https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Darmkrebs/darmkrebs_node.html

In addition to the primary endpoint of overall survival, endpoints in the categories of morbidity, health-related quality of life and adverse events were collected.

The pharmaceutical company presents the results of the data cut-offs from 5 July 2022 and 19 July 2022 in the dossier. The data cut-off from 19 July 2022 is used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival was operationalised in the SUNLIGHT study as the time from randomisation to death, regardless of the underlying cause.

For the overall survival endpoint, there is a statistically significant difference in favour of trifluridine/tipiracil + bevacizumab, which is assessed as a significant improvement in view of the advanced treatment setting with a poor prognosis.

Morbidity

Progression-free survival (PFS)

In the SUNLIGHT study, PFS was operationalised as the time between randomisation and radiologically confirmed disease progression (as assessed by the principal investigator according to RECIST version 1.1) or death, regardless of the underlying cause.

For the PFS, there is a statistically significant difference to the advantage of trifluridine/tipiracil + bevacizumab.

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 SUNLIGHT 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

Symptomatology was assessed in the SUNLIGHT study using the symptom scales of the cancer-specific EORTC QLQ-C30 questionnaire.

The pharmaceutical company submits responder analyses for the percentage of patients for the time to first deterioration and for the time to confirmed deterioration.

Due to the large differences in the treatment duration between the two treatment arms, the time to first deterioration was used for the present assessment.

There is no statistically significant difference between the treatment arms. For the endpoints of nausea and vomiting as well as pain, however, there is an effect modification for the sex characteristic. Accordingly, there is a statistically significant difference in favour of trifluridine/tipiracil + bevacizumab for men for both endpoints, whereas there was no statistically significant difference for women.

The scientific-medical societies stated in their statements on the present benefit assessment that no generally valid statements regarding a benefit for men can be derived from this.

For the endpoints nausea and vomiting as well as pain, no separate statement on the additional benefit according to the sex characteristic was made and no overall additional benefit was identified.

Health status (EQ-5D VAS)

The endpoint health status was assessed using the EQ-5D visual analogue scale (VAS).

The pharmaceutical company shall submit responder analyses for the endpoint of health status operationalised as time to first deterioration or to confirmed deterioration. The analyses of time to first deterioration are used for the present assessment.

For health status (EQ-5D VAS), there was a statistically significant difference to the advantage of trifluridine/tipiracil + bevacizumab. There is an effect modification for the sex characteristic, according to which there is a statistically significant difference in favour of trifluridine/tipiracil + bevacizumab for men and no statistically significant difference for women.

However, as the scientific-medical societies pointed out in their statements, no generally valid statements regarding an advantage for men can be derived from this. For the endpoint "health status" (EQ-5D VAS), no separate statement on the additional benefit according to the sex characteristic was therefore made.

In summary, an advantage was found for the endpoint category of morbidity for the endpoint of health status on the basis of the total population.

Quality of life

Health-related quality of life was assessed in the SUNLIGHT study using the functional scales of the EORTC QLQ-C30 questionnaire.

The pharmaceutical company shall submit evaluations for the time to first deterioration and for the time to multiple confirmed deterioration.

For the endpoint of health-related quality of life, the analyses of the time to first deterioration are also used in accordance with the above comments on symptomatology.

For the endpoint of physical functioning, there is a statistically significant difference in favour of trifluridine/tipiracil + bevacizumab. However, this advantage is not reflected in any other subscale of the EORTC QLQ-C30.

In the overall assessment of the endpoint category of quality of life, no relevant difference for the benefit assessment was derived against the background of the multimodal quality of life concept.

Side effects

In the dossier for the benefit assessment, the pharmaceutical company presented evaluations on adverse events (AEs), which revealed, among other things, ambiguities regarding the consideration of disease-related events in the overall AE rates.

If adverse events that represent disease-related events (e.g. progression) are included in the assessment and thus, also in the evaluation, additional AE analyses should be conducted for the overall rates (AEs, severe AEs and serious adverse events (SAEs)) in which these events are not taken into account.

A pre-definition (study protocol) of which events are categorised as disease-related events was not available in the SUNLIGHT study.

As part of the written statement procedure, the pharmaceutical company submitted additional analyses on the overall rates of adverse events, in which events that were related to the progression of the underlying disease according to the individual estimate of the principal investigator were not taken into account.

However, even when considering the overall AE rates without events that, according to the principal investigator's estimate, were related to the progression of the underlying disease, it is noticeable that in the present add-on situation, fewer serious adverse events (SAEs) occurred in the intervention arm, in which the patients received bevacizumab in addition to treatment with trifluridine/tipiracil, than in the control arm, in which the patients received trifluridine/tipiracil without the additional administration of bevacizumab. The results on drug safety are therefore still to be interpreted as a mixture of progression of the underlying disease/ symptomatology and side effects.

Irrespective of this, with regard to the existing data basis, the G-BA takes into account that, particularly in the present indication, a separation of drug-related adverse events and disease-related events is particularly difficult, which is why the subsequently submitted evaluations on adverse events are used as the basis for the present assessment.

Serious adverse events (SAE)

For the endpoint of SAEs, there is a statistically significant difference in favour of trifluridine/tipiracil + bevacizumab.

Severe adverse events (CTCAE grade ≥ 3)

For the endpoint of severe AEs, there is no statistically significant difference between the treatment arms.

Discontinuation due to AEs

For discontinuation due to AEs, no statistically significant difference was detected between the treatment arms.

The overall assessment of the results on side effects shows an advantage of trifluridine/tipiracil + bevacizumab with regard to serious adverse events.

Overall assessment

For the benefit assessment of trifluridine/tipiracil + bevacizumab for the treatment of adults with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens, whereby these therapies include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents, results are available from the SUNLIGHT study on mortality, morbidity (symptomatology and health status), health-related quality of life and side effects.

The results for the endpoint of overall survival show that treatment with trifluridine/tipiracil + bevacizumab achieved a prolongation of overall survival compared to trifluridine/tipiracil, which is assessed as a significant improvement against the background of the advanced treatment setting with a poor prognosis.

In the endpoint category of morbidity (assessed using EORTC QLQ-C30 and EQ-5D VAS), there is an advantage of trifluridine/tipiracil + bevacizumab in terms of health status.

Overall, no relevant difference for the benefit assessment is derived for the endpoint category of quality of life.

With regard to the evaluations submitted on side effects, the G-BA takes into account that it is particularly difficult to separate drug-related adverse events from disease-related events in

the present indication. Based on the available evaluations, there is an advantage of trifluridine/tipiracil + bevacizumab compared to trifluridine/tipiracil in terms of serious adverse events.

In the overall analysis, the G-BA comes to the conclusion that, in particular due to the advantages in overall survival associated with the advantages in health status and the avoidance of serious adverse events, there is a significant improvement in the treatment-relevant benefit overall.

As a result, for trifluridine/tipiracil + bevacizumab for the treatment of adults with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens, whereby these therapies include fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents, a hint for a considerable additional benefit over trifluridine/tipiracil was identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of a study. In this study, trifluridine/tipiracil + bevacizumab was compared with the appropriate comparator therapy trifluridine/tipiracil in an open-label, randomised controlled comparison.

The risk of bias at study level is rated as low.

With the exception of the endpoint of overall survival, the endpoint-specific risk of bias for the other endpoints is estimated to be high due to the open-label study design.

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

In addition, there are uncertainties for the endpoints of nausea and vomiting, pain and health status due to the existing effect modification by the sex characteristic.

In the overall assessment of the described limitations, the reliability of data for the additional benefit determined is classified in the hint category.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient trifluridine/tipiracil.

Trifluridine/tipiracil in combination with bevacizumab is approved for the treatment of adult patients with metastatic colorectal carcinoma who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

The G-BA determined trifluridine/tipiracil as an appropriate comparator therapy.

For the assessment of the additional benefit, results are available from the open-label, randomised, controlled SUNLIGHT study in comparison with trifluridine/tipiracil on mortality, morbidity, quality of life and side effects.

For overall survival, there is an advantage of trifluridine/tipiracil + bevacizumab which is assessed as a significant improvement.

In the morbidity endpoint category, there is an advantage of trifluridine/tipiracil + bevacizumab for the health status.

Overall, no relevant difference for the benefit assessment is derived for the endpoint category of quality of life.

With regard to the evaluations submitted on side effects, the G-BA takes into account that it is particularly difficult to separate drug-related adverse events from disease-related events in the present indication. Based on the available evaluations, there is an advantage of trifluridine/tipiracil + bevacizumab compared to trifluridine/tipiracil in terms of serious adverse events.

Overall, the G-BA identifies a considerable additional benefit of trifluridine/tipiracil + bevacizumab, in particular due to the advantages in overall survival associated with the advantages in health status and the avoidance of serious adverse events.

Uncertainties remain in particular due to the open-label study design and with regard to the transferability of the study results to the reality of care. The reliability of data of the additional benefit identified is therefore classified in the hint category.

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 specified in the pharmaceutical company's dossier, which are, however, underestimated due to the lack of consideration of patients in later lines of therapy and patients who have received exactly two prior therapies. There are also uncertainties with regard to the sources used.

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 Lonsurf (active ingredient: trifluridine/tipiracil) at the following publicly accessible link (last access: 18 October 2023):

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.

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 January 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.

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:				
Trifluridine/tipiracil	2 x daily on day 1-5 and day 8-12 of a 28-day cycle	13.0	10	130.0
Bevacizumab	1 x every 14 days	26.1	1	26.1
Appropriate comparator therapy:				
Trifluridine/tipiracil	2 x daily on day 1-5 and day 8-12 of a 28-day cycle	13.0	10	130.0

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 comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[3].

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					
Trifluridine/ tipiracil	35 mg/m² = 66.9 mg	133.8 mg	6 x 15 mg/6.14 mg + 2 x 20 mg/8.19 mg	130.0	780 x 15 mg/6.14 mg + 260 x 20 mg/8.19 mg
Bevacizumab	5 mg/kg = 388.5 mg	388.5 mg	1 x 400 mg	26.1	26.1 x 400 mg
Appropriate comparator therapy					
Trifluridine/ tipiracil	35 mg/m² = 66.9 mg	133.8 mg	6 x 15 mg/6.14 mg + 2 x 20 mg/8.19 mg	130.0	780 x 15 mg/6.14 mg + 260 x 20 mg/8.19 mg

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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 Section 130 and Section 130a 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 fixed reimbursement rates 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					
Trifluridine/tipiracil 15 mg/ 6.14 mg	60 FCT	€ 2,348.76	€ 2.00	€ 0.00	€ 2,346.76
Trifluridine/tipiracil 20 mg/8.19 mg	60 FCT	€ 3,112.46	€ 2.00	€ 0.00	€ 3,110.46
Bevacizumab 400 mg	1 CIS	€ 1,553.33	€ 2.00	€ 85.42	€ 1,465.91
Appropriate comparator therapy					
Trifluridine/tipiracil 15 mg/ 6.14 mg	60 FCT	€ 2,348.76	€ 2.00	€ 0.00	€ 2,346.76
Trifluridine/tipiracil 20 mg/8.19 mg	60 FCT	€ 3,112.46	€ 2.00	€ 0.00	€ 3,110.46
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 January 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.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory

services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

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 information 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 (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 and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for trifluridine/tipiracil (Lonsurf); Lonsurf; last revised: July 2023

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 7 March 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 02 August 2023.

On 14 August 2023, the pharmaceutical company submitted a dossier for the benefit assessment of trifluridine/tipiracil to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 15 August 2023 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 trifluridine/tipiracil.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 November 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 November 2023. The deadline for submitting statements was 6 December 2023.

The oral hearing was held on 8 January 2024.

By letter dated 9 January 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 January 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 6 February 2024, and the proposed resolution was approved.

At its session on 15 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 March 2023	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	2 August 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	20 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 January 2024	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 January 2024 31 January 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 February 2024	Concluding discussion of the draft resolution
Plenum	15 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 February 2024

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

Prof. Hecken