Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Trifluridine/Tipiracil (Reassessment after the Deadline: Metastatic Colorectal Cancer)

of 1 October 2020

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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 proof 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 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 proof 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company first submitted a dossier for the early benefit assessment of the active ingredient combination trifluridine/tipiracil (Lonsurf®) on 2 August 2016. The resolution of 2 February 2017 passed by the G-BA in these proceedings was limited until 31 January 2019. At the request of the pharmaceutical company, this limitation was prolonged to 1 April 2020 by a resolution of the G-BA of 5 July 2018.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO, the benefit assessment procedure for the medicinal product Lonsurf® shall start again on the day the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 31 March 2020

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2020 on the website of the G-BA (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

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pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed 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 arrived at 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 as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents was determined as follows:

Best supportive care

Best supportive care is the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life.

The present therapeutic indication is based on an advanced stage of treatment in which the currently recommended and approved standard therapies for treatment in the metastatic stage have already been exhausted and for which further anti-neoplastic therapies are not regularly considered. With the determination of best supportive care as an appropriate comparator therapy, an exclusively palliative objective of the treatment is assumed.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In addition to trifluridine/tipiracil, medicinal products with the following active ingredients are approved for the present therapeutic indication: 5-fluorouracil, aflibercept, bevacizumab, calcium-folinate, capecitabin, cetuximab, irinotecan, mitomycin, oxaliplatin, panitumumab, ramucirumab and regorafenib, encorafenib.

On 2. Non-medicinal treatment is not considered.

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

Ramucirumab: Resolution of 1 September 2016

Regorafenib: Resolution of 17 March 2016

Aflibercept: Resolution of 15 August 2013

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

Various therapy lines are available for the treatment of metastasised colorectal carcinoma with palliative objectives. In accordance with the national and international guidelines, the active ingredients 5-fluoropyrimidine (or another fluoropyrimidine), irinotecan, oxaliplatin, and anti-VEGF as well as anti-EGFR agents are used as part of various combinations or partly as monotherapy. The MAP kinase inhibitor encorafenib can also be used for patients with BRAF mutation. A benefit assessment procedure is currently being carried out for this active ingredient.

For the initial treatment, a fluoropyrimidine-based therapy regime should always be selected. In the case of sequential therapy with the recommended therapy regimens, all aforementioned active ingredients are generally used provided that they are suitable for the individual patient. However, the superiority of a particular sequence has not yet been proven.

The therapeutic indication for trifluridine/tipiracil describes a treatment stage of metastatic colorectal cancer in which patients have been previously treated with fluoro-pyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies as well as anti-VEGF and anti-EGFR therapies or are unsuitable for these. It is therefore assumed that the treatment is at an advanced stage in which the recommended treatment regimes have already been followed.

Thus, in view of the advanced palliative therapy situation, best supportive care can be considered as a comparator therapy.

The active ingredient regorafenib is not on the market in Germany and cannot therefore be considered an appropriate comparator therapy.

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

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2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of trifluridine/tipiracil is assessed as follows:

For adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, there is a hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company presents the results of the randomised RECOURSE and TERRA studies as well as the non-randomised TALLISUR study. The results of the RECOURSE and TERRA randomised studies are used for the present benefit assessment.

RECOURSE study

The RECOURSE study is an international, randomised, double-blind Phase III study comparing trifluridine/tipiracil directly versus placebo; BSC was part of therapy in both treatment groups. The study included 800 patients with histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum with tumour progression after at least two previous standard regimens, which should have contained fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF, and anti-EGFR substances according to the marketing authorisation. The Kirsten rat sarcoma viral oncogene homologous (KRAS) gene status should have been determined in the patients included, and the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) should not have exceeded 1 at the start of study. Randomisation was performed at a ratio of 2:1 in the trifluridine/tipiracil arm (534 patients) and comparator arm (266 patients) and stratified by KRAS mutation status, time since diagnosis of the first metastasis, and geographical region (Asia [Japan] versus Western countries [Europe, Australia, US])

The primary endpoint of the RECOURSE study is overall survival with the final data cut-off on 8 October 2014. The study was unblinded in May 2014; after this, two patients switched from the comparator arm to the verum arm before the second data cut-off on overall survival. The data cut-off for the side effects that formed the secondary endpoint of the study was made at the end of the observation period up to 30 days after study treatment or the start of a new cancer therapy (31 January 2014). After completion of study treatment, 41.6% and 42.5% of patients in the trifluridine/tipiracil or comparator arm, respectively, received one or more medicinal cancer therapies in the follow-up phase.

TERRA study

The TERRA study is a double-blind RCT conducted in Asia to compare trifluridine/tipiracil + BSC with placebo + BSC. Included were patients with a pre-treated mKRK with adenocarcinoma and an ECOG-PS from ≤ 1. For the metastatic stage, patients should have received at least 2 standard therapy regimens containing fluoropyrimidine, oxaliplatin, and irinotecan as well as an anti-VEGF monoclonal antibody. Pre-treatment with an anti-EGFR monoclonal antibody in the presence of a KRAS wild type was neither an inclusion nor an exclusion criterion. 406 patients were randomised at a ratio of 2:1. Stratification factors were KRAS mutation status and country (China, Korea, and Thailand). Only data from patients who were pretreated in accordance with the marketing authorisation were presented (94 patients (n = 61 for trifluridine/tipiracil vs 33 in the treatment arm). The formation of this sub-population is not fully comprehensible because of the lack of data on patients not included. In the TERRA study, palliative radiotherapy was allowed as part of the BSC for pain relief of bone metastases. A list of subsequent medicinal therapies was submitted by the pharmaceutical company with the written statement.

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The primary endpoint was the overall survival. The 1st data cut-off was planned for the time of the 288th death, which occurred on 22 December 2015. After this date, the collection of data on side effects was discontinued; however, data collection for overall survival ended on 16 February 2016 (2nd data cut-off), although the reasons for the 2nd data cut-off remain unclear. The results of the 1st data cut-off are used for the endpoints of side effects and the results of the 2nd data cut-off for the results of overall survival.

The RECOURSE and TERRA studies are suitable for a meta-analytical summary. The results of the meta-analysis are the basis for the present assessment.

On the transferability to the context of the German healthcare system:

In terms of Best Supportive Care (BSC), in both arms of the RECOURSE and TERRA studies, palliative radiotherapy was completely excluded in the RECOURSE study as well as in the TERRA study except for pain relief from bone metastases.

This does not correspond to the reality of care and the recommendations for the use of radiotherapy for symptom relief in metastatic colorectal cancer. Thus, it cannot be assumed that the patients are optimally cared for within the framework of the BSC. There may therefore also be an insufficient care of patients, especially in the RECOURSE study.

The median age of the study population (63 years in the RECOURSE study and 56 years in the TERRA study) is significantly below the median age of onset of the disease for pretreated metastatic colorectal cancer in Germany. The patients in the therapeutic indication are thus, on average, older than the patients investigated in the study. Moreover, patients with an ECOG-PS of > 1 were excluded in both studies.

Only patients with adenocarcinoma were included in the RECOURSE and TERRA studies; this histological type accounts for the majority of this disease (over 95%).

Because of the aspects mentioned, relevant uncertainties result in the assessment of the additional benefit of trifluridine/tipiracil compared with BSC with regard to transferability to the German healthcare context.

On the implementation of conditions for a time limit:

<u>Data on all patient-relevant endpoints</u>

Since no results are available from the RECOURSE and TERRA studies for the endpoints morbidity and health-related quality of life, the TALLISUR study was submitted to fulfil the conditions for a time limit from the initial assessment.

TALISSUR study

The TALISSUR trial is a non-randomised trial conducted in Germany to compare trifluridine/tipiracil + BSC with BSC in the endpoint categories morbidity and health-related quality of life. The non-randomised allocation led to a large imbalance in patient numbers and patient characteristics between study arms. Although 185 patients were included in the trifluridine/tipiracil + BSC arm, only 9 patients were included in the comparator arm. The most relevant differences in patient characteristics were found in average age (67 vs 78 years), median duration of the disease (34 vs 50 months), and ECOG status (40 vs 0% with ECOG-PS of 0). The return rates of the instruments used to record morbidity/symptomatology and health-related quality of life were also too low to allow interpretation of the data.

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The results of the TALISSUR study can therefore not be used to derive any reliable overall conclusions for an assessment of the health-related quality of life and symptomatology of trifluridine/tipiracil + BSC compared with BSC.

The written statements in the present benefit assessment procedure emphasised the difficulty of a randomised comparison or the questionable feasibility of such a study in the period after the marketing authorisation of trifluridine/tipiracil. This is also fundamentally comprehensible from the perspective of the G-BA, and the G-BA did not necessarily base its initial assessment on a randomised comparison in the time limit requirement but rather stated that if randomisation is not considered, the best possible comparability or similarity of patient characteristics in the treatment groups should be aimed for.

Further data on side effects

The conditions for a time limit regarding the submission of data on side effects, taking into account the survey of adverse events without symptoms of progression, the breakdown of adverse events by all degrees of severity (CTCAE grades) and the presentation of specific adverse events, have been fulfilled. However, the evaluations of adverse events without symptoms of progression from the TERRA study cannot be used because the pharmaceutical company used a procedure that differs from the study protocol (for which results-driven reporting cannot be ruled out here).

Study population corresponding to the German healthcare reality

In accordance with the conditions for a time limit, the study population should sufficiently correspond to the German healthcare reality; patients with an ECOG performance status of 2 or higher should therefore also be considered. The TALLISUR study also included patients with ECOG > 1. However, the data are not usable for the reasons already mentioned.

Extent and probability of the additional benefit

Mortality

Overall survival

The meta-analysis from the RECOURSE and TERRA studies shows a statistically significant prolongation in overall survival through treatment with trifluridine/tipiracil + BSC compared with BSC. Taking into account the advanced stage of the disease and treatment, the prolongation in survival time is assessed as a relevant but no more than a minor improvement.

For the subgroup characteristic “Number of previous therapy regimens (2 vs ≥ 3)”, the sub-group analysis used by IQWiG for this characteristic in the RECOURSE study shows an effect modification for the overall survival endpoint. Corresponding analyses for the TERRA study were not available from the dossier of the pharmaceutical company. These were presented by the pharmaceutical company in the written statement for the TERRA study as well as a corresponding meta-analysis of this sub-group analysis. The present assessment is based on these analyses, which do not show any effect modification according to the number of previous treatment regimes.

Morbidity

Symptomatology

In the RECOURSE and TERRA studies, the symptomatology was not surveyed.

Progression-free survival (PFS)

The PFS was surveyed as a secondary endpoint in the RECOURSE and TERRA studies and was defined as the time between randomisation and radiologically confirmed disease progression (according to the RECIST criteria in version 1.1) or death by any cause.

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The meta-analysis shows a statistically significant prolongation of PFS for treatment with trifluridine/tipiracil + BSC compared with BSC.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present RECOURSE AND TERRA studies, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint “overall survival”. In the present studies, the morbidity component "tumour progression" was assessed solely by means of imaging procedures (radiologically determined disease progression according to the RECIST criteria). Morbidity is thus not assessed primarily on the basis of disease symptoms but rather solely on the basis of asymptomatic, not directly patient-relevant findings.

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Quality of life

The health-related quality of life was not investigated in the RECOURSE and TERRA studies.

The data on health-related quality of life from the TALLISUR study are very limited in their interpretability and cannot be used for the benefit assessment.

Side effects

For endpoints on the overall rates of side effects from the RECOURSE study, the pharmaceutical company submits evaluations on adverse events (AE) – both with and without events attributable to disease progression – in the dossier. For the TERRA study, the classification of whether or not a AE can be attributed to the progression of the underlying disease was based on a list, the criteria of which are not comprehensible. The evaluations without AEs attributable to progression of the underlying disease can therefore not be considered.

However, because in the present case, there are particularly large methodological and content-related uncertainties in the separation of AE with and without events attributable to disease progression or symptoms, the AE with progression of the underlying disease are used decisively for the benefit assessment and interpreted as a mixture of progression/symptomatology as well as side effects. Because no data are available for the symptomatology, there is therefore no multiple assessment. For the assessment of side effects, a descriptive assessment is made at endpoint level as to the extent to which these effects can be interpreted as pure side effects without progression of the underlying disease.

Adverse events (total)

Adverse events (with and without progression of the underlying disease) occurred at least once in almost all patients in the RECOURSE and TERRA studies. Thus, no conclusions can be drawn for the assessment of the additional benefit by comparing the two study arms.

Serious AE (SAE)

The meta-analysis shows a statistically significant advantage for trifluridine/tipiracil compared with BSC.

However, in the evaluation of the SAEs without events attributable to progression of the underlying disease, the RECOURSE study showed no statistically significant difference between the treatment arms. This suggests that this benefit is largely because of the delay of progression events rather than therapy-related AEs.

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Severe AE (CTCAE grade ≥ 3)

The meta-analysis shows a statistically significant difference to the disadvantage of trifluridine/tipiracil compared with BSC.

For the RECOURSE study, the evaluation of severe AEs (CTCAE grade ≥ 3) without events attributable to a deterioration of the underlying disease also shows a significant disadvantage for the intervention arm with trifluridine/tipiracil. This suggests that this disadvantage results from therapy-related AEs rather than from the prevention of progression events.

Discontinuation because of AE

For the endpoint discontinuation because of AE, the meta-analysis shows a statistically significant advantage for treatment with trifluridine/tipiracil compared with BSC.

In the evaluation of the endpoint without events attributable to deterioration of the underlying disease, the RECOURSE study shows no statistically significant difference between the treatment arms. This suggests that the benefit in the endpoint discontinuation because of AE is mainly due to the delay of progression events rather than to therapy-related AEs.

Specific AEs

In detail, there is a statistically significant disadvantage for trifluridine/tipiracil in the specific AEs for the endpoint “myelosuppression (CTCAE grade ≥ 3)” with the frequent manifestations of anaemia, febrile neutropoenia, leukopoenia, and neutropoenia as well as a statistically significant disadvantage for trifluridine/tipiracil for the endpoint “gastrointestinal toxicity (SOC gastrointestinal disorders)” with frequent manifestations of diarrhoea, nausea, and vomiting. There are significant differences compared with BSC.

For the endpoints “psychiatric disorders (SOC, AEs)” and “hypertension (PT, severe AEs [CTCAE grade ≥ 3])”, the frequency criterion was exceeded only in the RECOURSE and not in the TERRA study. For this reason, only results of the RECOURSE study are used. For the two endpoints, there was a statistically significant advantage for trifluridine/tipiracil compared with BSC.

<u>Overall assessment</u>

For the assessment of the additional benefit of trifluridine/tipiracil compared with best supportive care, there are results on mortality (overall survival) and side effects from the RECOURSE and TERRA studies.

For overall survival, a prolongation in survival time is shown by treatment with trifluridine/tipiracil compared with best supportive care. This is assessed as a relevant yet minor improvement.

The RECOURSE and TERRA studies did not assess the symptomatology or health-related quality of life. Statements on quality of life are particularly important in the present advanced palliative therapy situation. The pharmaceutical company provided data on quality of life from the TALLISUR study. However, the interpretability of this data is very limited and therefore cannot be used for the assessment.

In endpoints on the side effects, adverse events attributable to disease progression or symptomatology are also included to a relevant extent. In this respect, there are additional evaluations that allow an assessment of the extent to which the effects can be interpreted as side effects without progression of the underlying disease. In the present case, however, the evaluations without separation of events are decisive for the assessment. These are interpreted as a mixture of disease progression or symptomatology and side effects.

Overall, there are mixed results in the side effects category: a positive effect because of the prolonged time to onset of SAE as well as a negative effect in severe AE (CTCAE grade ≥ 3),

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which occurred earlier in the trifluridine/tipiracil arm. There is an advantage in therapy discontinuation because of AE; however, this is mainly due to the delay of progression events and not to therapy-related AE. In the results for the specific AE, the disadvantages outweigh the disadvantages. In the overall view of the results of the side effects, neither an advantage nor a disadvantage can be derived.

The overall assessment shows a moderate and not only slight improvement in the therapy-relevant benefit and thus a minor additional benefit of trifluridine/tipiracil compared with best supportive care.

Reliability of data (probability of additional benefit)

The present assessment is based on the meta-analytically evaluated results of the randomised, double-blind RECOURSE and TERRA Phase III studies. The risk of bias at the study level is rated as low for both studies.

Because of the high risk of bias, the certainty of results for all endpoints is classified as limited – except for the endpoints overall survival in the RECOURSE study and discontinuation because of AE.

In the endpoints on the side effects, adverse events attributable to disease progression or symptomatology are also included to a relevant extent. The evaluations presented on adverse events without events attributable to disease progression are subject to uncertainties in terms of content and methodology. Therefore, the degree of certainty for the results on side effects is considered limited.

No robust data on morbidity or health-related quality of life are available for the overall assessment of the additional benefit. In this respect, great importance is attached to meaningful data, particularly in view of the advanced stage of the disease and treatment available.

With regard to the transferability of the study results to the German healthcare context, there are relevant uncertainties that result in particular from the implementation of best supportive care in the studies (no or limited use of palliative radiotherapy) as well as the significantly lower age of the patients in the studies compared with the healthcare reality.

A further uncertainty factor for the TERRA study is that the formation of the sub-population considered by the pharmaceutical company is not sufficiently described.

In addition, a relevant proportion of patients treated with trifluridine/tipiracil and receiving best supportive care were treated with medicinal cancer therapies after the studies. Thus, there are uncertainties about whether only one BSC was suitable as a therapy for the patients in the study population and to what extent they had already been treated with all available therapies (at the time) according to the marketing authorisation text.

Although a meta-analysis of 2 studies is available, for these reasons the reliability of data (probability of additional benefit) of the overall statement on the additional benefit is regarded as a hint.

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2.1.4 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient trifluridine/tipiracil because of the expiry of the limitation of the resolution of 2 February 2017.

The assessment refers to the following patient populations: Adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. Best supportive care was determined as an appropriate comparator therapy by the G-BA.

For this patient group, the pharmaceutical company presents the RECOURSE and TERRA RCTs in which trifluridine/tipiracil + best supportive care was compared with placebo + best supportive care. In addition, the non-randomised study TALLISUR, which also examined health-related quality of life, was presented. However, the interpretability of the data from the TALLISUR study is very limited and can therefore not be used for the assessment. For the TERRA study, only the patient population that has been pretreated in accordance with the marketing authorisation is used (mITT). In the RECOURSE study, the results of the total population from the final data cut-off are relevant for the assessment. All studies have been completed.

In the overall survival endpoint, trifluridine/tipiracil showed a relevant but not more than a minor improvement compared with the appropriate comparator therapy.

There are no data on symptomatology and quality of life suitable for the benefit assessment.

In the endpoints on the side effects, adverse events attributable to disease progression or symptomatology are also included to a relevant extent and are interpreted here as a mixture of disease progression or symptomatology and side effects. In the overall view of the results of the side effects, neither an advantage nor a disadvantage can be derived.

There are still considerable uncertainties because of the high risk of bias at the endpoint level as well as the uncertainties regarding the transferability of the study results to the healthcare reality and the potentially insufficient care of patients in the studies.

Overall, there is a hint for a minor additional benefit for trifluridine/tipiracil compared with best supportive care.

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 number of 6454 patients in the SHI target population reported by the pharmaceutical company in the reassessment is an underestimate overall. Because patients with less than three previous therapies were not included, the derivation is not fully comprehensible, and an upper range is no longer specified. Because the calculation of the patient numbers of the initial assessment is plausible and comprehensible, they were used again.

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: 7 May 2020):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 2020).

Costs of the appropriate comparator therapy:

The treatment costs for best supportive care are different for each individual 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 duration:

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 is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

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 × daily on Days 1–5 and Days 8–12 of a 28-day cycle	13 cycles	10	130
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Best supportive care	different for each individual patient			

Usage and consumption:

As trifluridine/tipiracil is dosed as a function of body surface area (BSA), the average body measurements are used for the calculation (average height: 1.72 m, average body weight: 77

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kg)[2]. From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916). Because it is not always possible to achieve the exact calculated dose per day with the commercially available potencies, in these cases, the dose is rounded up or down to the next higher or lower available dose that can be achieved with the commercially available dosage strengths and the scalability of the pharmaceutical form concerned as specified in the product information.

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 = 66.5 mg	133mg	6 × 15 mg +	130	780 × 15 mg +
			2 × 20 mg		260 × 20 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Costs:

To calculate the costs of the medicinal products, the required number of packs of a particular potency was first determined on the basis of consumption. Based on the determined number of packages required, the medicinal product costs were then calculated based on the costs per package after deduction of the statutory rebates. 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 130a SGB V (paragraph 1, 1a, 3a) and Section 130, paragraph 1 SGB V.

Costs of the medicinal product:

Designation of the therapy	Package 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	60 FCT	€ 2,289.28	€ 1.77	€ 0.00	€ 2,287.51
Trifluridine/tipiracil 20 mg	60 FCT	€ 3,033.72	€ 1.77	€ 0.00	€ 3,031.95

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

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Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

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 24 November 2015, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 March 2020, 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 5 VerfO.

By letter dated 31 March 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 29 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2020. The deadline for submitting written statements was 22 July 2020.

The oral hearing was held on 10 August 2020.

By letter dated 10 August 2020 and 11 August 2020, the IQWiG was commissioned with supplementary assessments of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 11 September 2020.

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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 were discussed at the session of the subcommittee on 22 September 2020, and the proposed resolution was approved.

At its session on 1 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	24 November 2015	Determination of the appropriate comparator therapy
Working group Section 35a	4 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 August 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 August 2020 1 September 2020 15 September 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	22 September 2020	Concluding discussion of the draft resolution
Plenum	1 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

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Berlin, 1 October 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

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