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 (New Therapeutic Indication: Metastatic Gastric Carcinoma, Pretreated Patients)

of 2 April 2020

Contents

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient combination trifluridine/tipiracil (Lonsurf®) was listed for the first time on 15 August 2016 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 3 September 2019, trifluridine/tipiracil received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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, 12 December 2008, p. 7).

On 2 October 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 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 trifluridine/tipiracil with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication

“Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been

previously treated with at least two prior systemic treatment regimens for advanced disease (see section 5.1)."

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 January 2020, 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.

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 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 gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (see section 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with metastatic gastric cancer, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease

Appropriate comparator therapy:

Best supportive care

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] 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.

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 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 terms of authorisation status, the active ingredients 5-fluorouracil, carmustine, doxorubicin, epirubicin, mitomycin, and ramucirumab as well as the fixed combination tegafur/gimeracil/teracil are available for the treatment of advanced gastric cancer.

On 2. A non-medicinal treatment is not considered for the present therapeutic indication.

On 3. The following resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V are available:

- Ramucirumab: Resolution of 20 October 2016
- Tegafur/gimeracil/oteracil: Resolution of 20 December 2012

On 4. The general state of medical knowledge on which the findings of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

Within the scope of the benefit assessment according to Section 35a SGB V, the G-BA found a hint for a minor additional benefit for the combination therapy of ramucirumab and paclitaxel for the treatment of advanced adenocarcinoma of the stomach or gastroesophageal transition compared with paclitaxel monotherapy.

For patients who are not eligible for combination therapy with paclitaxel, an additional benefit of ramucirumab as monotherapy compared with best supportive care is not proven.

Ramucirumab in combination with paclitaxel as well as ramucirumab as monotherapy are used according to the marketing authorisation after previous platinum and/or fluoropyrimidine-containing chemotherapy. With regard to the therapeutic indication of ramucirumab, the necessary previous therapy corresponds to the first-line therapy of patients with advanced gastric carcinoma recommended in guidelines.

According to the marketing authorisation, the fixed combination tegafur/gimeracil/oteracil is to be used in combination with cisplatin (first line). For tegafur/gimeracil/oteracil, the required evidence for the benefit assessment according to Section 35a SGB V was not completely submitted by the pharmaceutical company, which is why the additional benefit is considered not proven.

Compared with the active ingredients tegafur/gimeracil/oteracil, ramucirumab in combination with paclitaxel and ramucirumab as monotherapy, the therapeutic indication of trifluridine/tipiracil under assessment is aimed at the treatment of patients who have already received at least two systemic therapy regimens for their advanced disease and thus explicitly addresses a later therapy situation.

The overall evidence for this therapy situation is very limited. For the treatment of patients with metastatic gastric carcinoma, including adenocarcinoma of the gastroesophageal junction, whose cancer progresses progressively after at least two systemic therapy regimens, no concrete therapy recommendation for a (further) antineoplastic therapy can be derived.

With regard to the therapeutic indication of trifluridine/tipiracil, an advanced stage of treatment in which the currently recommended and approved standard therapies for treatment in the metastatic stage have already been exhausted is assumed. Other antineoplastic therapies are not regularly considered. All the aforementioned therapeutic options can therefore not be considered as appropriate comparator therapies.

Taking into account the advanced disease and treatment stage, which is associated with a poor prognosis for the further course of the disease and life expectancy, best supportive care represents an appropriate comparator therapy.

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

With the determination of best supportive care as an appropriate comparator therapy, an exclusively palliative objective of the treatment is assumed.

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

2.1.3 Extent and probability of the additional benefit

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

For trifluridine/tipiracil as monotherapy for the treatment of adult patients with metastatic gastric cancer, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease, there is an indication of a minor additional benefit.

Justification:

The benefit assessment of the drug combination trifluridine/tipiracil is based on the pivotal, randomised, double-blind Phase III study TAS-102-302 (TAGS). This is a completed, international, multi-centre study that was conducted in 17 countries and 110 study centres.

The TAGS study included adult patients with histologically confirmed, unresectable, metastatic adenocarcinoma of the stomach, including adenocarcinoma of the gastroesophageal junction (classification according to AJCC[2], version 7), who had been treated with at least two previous therapy regimens for the advanced disease. Prior therapies had to contain a fluoropyrimidine, platinum, and either a taxane and/or irinotecan containing therapy regimen. In addition, patients with HER2-positive tumours had to have received anti-HER2 therapy (if available) in advance.

The study participants (507 patients) were randomised at a ratio of 2:1 to treatment with trifluridine/tipiracil + best supportive care (BSC) (337 patients) or placebo + BSC (170 patients). The randomisation was stratified by region (Japan vs rest of the world), ECOG-Performance Status (PS) (0 vs 1), and previous treatment with ramucirumab (yes vs no).

The study participants had a median age of 63 years and an ECOG-PS of 0 (38%) or 1 (62%) at the time of study enrolment.

Treatment with trifluridine/tipiracil + BSC was continued until disease progression, unacceptable toxicity, decision of the investigator, withdrawal of informed consent, or pregnancy. A change of treatment after progression was not planned until the primary analysis.

[2] American Joint Committee on Cancer

Following the study treatment, 24.6% of the patients in the trifluridine/tipiracil + BSC arm and 26.5% of the patients in the placebo + BSC arm received systemic antineoplastic follow-up therapy.

The study assessed overall survival and endpoints of the morbidity (symptomatology, health status), health-related quality of life, and adverse events categories.

The present benefit assessment for the overall survival endpoint is based on the data cut-off of 27 March 2018. This is the event-driven primary analysis of the overall survival endpoint, which was performed after 384 deaths. For the other endpoints of the endpoint categories morbidity, health-related quality of life, and side effects, the data cut-off of 31 March 2018 is used.

Extent and probability of the additional benefit

Mortality

Overall survival

Treatment with trifluridine/tipiracil + BSC leads to a statistically significant prolongation of overall survival compared with placebo + BSC (hazard ratio (HR): 0.69 95% confidence interval (CI) [0.56; 0.86]; p value: < 0.001). The median survival time is prolonged by 2.1 months by therapy with trifluridine/tipiracil + BSC (5.7 months) compared with the control arm (3.6 months).

The prolongation of overall survival achieved by trifluridine/tipiracil + BSC compared with placebo + BSC is considered a relevant and more than a minor improvement.

Morbidity

Progression-free survival (PFS)

PFS was defined as the time from randomisation to the time of radiologically confirmed disease progression or to death by any cause. Proof of disease progression was based on RECIST[3]criteria (Version 1.1).

Trifluridine/tipiracil + BSC (2.0 months) prolongs median PFS by 0.2 months compared with the control arm (1.8 months); this is statistically significant (HR: 0.57; 95% CI [0.47; 0.70]; p < 0.0001). In the intervention arm, disease progression occurred in 85.2% of patients (287) and in the control arm in 91.8% of patients (156).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint using the endpoint overall survival.

The morbidity component was not surveyed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). 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.

In addition to the evaluation of disease progression using imaging techniques, the pharmaceutical company presented sensitivity analyses on PFS. In addition to the radiologically determined disease progression according to RECIST[3], events of symptomatic progression (“clinical progression”) and the initiation of antineoplastic follow-up therapies were considered in the evaluation. The deterioration of the symptomatology was assessed using the side effects as well as the EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires.

[3] Response Evaluation Criteria in Solid Tumours

However, of the total 463 events included in the PFS sensitivity analyses, only 76 events can be attributed to symptomatic progression and 4 events to the initiation of follow-up therapy. The majority of events included in the sensitivity analysis are thus also based on radiological, non-symptom-related findings. Moreover, on the basis of the information available, the operationalisation of symptomatic deterioration is unclear. In addition, a significant proportion of patients are not included in the evaluation because of significantly lower return rates of the EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires used to record the deterioration of symptomatology (see also: comments on EORTC QLQ-C30 and EORTC QLQ-STO22 in the "Symptomatology" section). Overall, the sensitivity analyses of the PFS are therefore not taken into account for the assessment.

Symptomatology

The disease symptomology was assessed using the symptom scales of the cancer-specific EORTC QLQ-C30 questionnaire and the gastric cancer-specific EORTC QLQ-STO22 questionnaire.

For both questionnaires, the pharmaceutical company considered both the time to deterioration by at least 5 and 10 points or improvement by at least 10 points as well as analyses of the change in values since the start of study.

Evaluations of symptomatology are available only for the baseline of ≥ 70% of patients for both treatment arms. In the course of the study there are decreasing return rates and, from the second survey onwards, significantly lower return rates with < 70% of the randomised patients, which also increasingly differ and cannot be explained mainly by deaths.

This means that a significant proportion of the patients are not included in the evaluation. The corresponding results are therefore not considered useful for the symptomatology as a whole.

Quality of life

Health-related quality of life was assessed using the functional scales and the global health status scale of the cancer-specific EORTC QLQ-C30 questionnaire.

As with the survey of disease symptomatology, both the time to deterioration by at least 5 and 10 points or improvement by at least 10 points as well as analyses of the change in values since the start of study were presented.

The limitations of the data mentioned in connection with the survey of disease symptomatology because of the low and increasingly different return rates of randomised patients in the course of the study apply equally to the survey of health-related quality of life.

For this reason, the results on health-related quality of life, as described in the "Symptomatology" section, are not considered useful.

Side effects

The results of the endpoint category side effects on which the present benefit assessment is based also include events that can be attributed to the progression and symptomatology of the underlying disease.

The pharmaceutical company presented sensitivity analyses in which events based on the progression of the underlying disease or on laboratory parameters were excluded. However, the exclusion of the progression events or events based on laboratory parameters for the sensitivity analysis carried out by the pharmaceutical company cannot be reconstructed on the basis of the information available. Furthermore, there are neither separate analyses without progression events for the individual events at the SOC[4] and PT[5] level nor sub-group

[4] SOC: system organ class
[5] PT: preferred term

analyses. An assessment of the extent to which the respective effects of the individual endpoints are based on events of progression/symptomatology is therefore not possible using the data available. Overall, the sensitivity analyses are therefore not used for the assessment of the endpoint category side effects.

Adverse events (AE) in total

Almost all study participants experienced adverse events. The results are presented only as a supplement because the operationalisation of side effects also includes events that are not patient-relevant.

Serious adverse events (SAE), severe AE (CTCAE grade ≥ 3)

For the endpoint SAE, there is no statistically significant difference between treatment arms.

Regarding the severe AE (CTCAE grade ≥ 3), there is a statistically significant difference between the treatment arms to the disadvantage of trifluridine/tipiracil + BSC. According to this, adverse events with CTCAE grade ≥ 3 occur 0.3 months (median) earlier under treatment with trifluridine/tipiracil + BSC (1.5 months) than in the control arm (1.8 months).

Effect modifications for the endpoints SAE and severe AE (CTCAE grade ≥ 3)

As part of the approval process, the European Medicines Agency (EMA) required the pharmaceutical company to conduct additional subgroup analyses for patients enrolled in centres in member states of the European Union (EU) (EU member states versus rest of the world).

For the endpoint SAE, this results in an effect modification by the characteristic “region”. In detail, there is a statistically significant difference between the treatment arms in favour of treatment with trifluridine/tipiracil + BSC for patients in the sub-group “EU member states”. The median time to first occurrence of SAE is prolonged by 2.1 months under trifluridine/tipiracil + BSC (4.6 months) compared with the control arm (2.5 months). For the sub-group “Rest of the world”, on the other hand, there was no statistically significant difference between the intervention arm and the control arm.

For the endpoint severe AE (CTCAE grade ≥ 3), an effect modification by the characteristic “region” is also shown. For patients of the sub-group “EU member states”, there is no statistically significant difference between the treatment arms. In contrast, treatment with trifluridine/tipiracil + BSC in the subgroup “Rest of the world” leads to a statistically significant disadvantage in the median time to the first occurrence of a severe AE (CTCAE grade ≥ 3). This was shortened by 2.0 months under trifluridine/tipiracil + BSC (1.6 months) compared with the control arm (3.6 months).

In addition, further effect modifications are available for the endpoints SAE and severe AE (CTCAE grade ≥ 3):

For the endpoint SAE, an effect modification is shown by the characteristic “number of previous therapies (2/3/≥ 4)”. Accordingly, there is a statistically significant difference in favour of trifluridine/tipiracil + BSC only for the sub-group of patients with ≥ 4 previous therapies. For patients with 2 or 3 previous therapies, there is no statistically significant difference between the treatment arms.

For severe AE (CTCAE grade ≥ 3), there is an effect modification by the characteristic “number of organs/tissues affected by metastases (1-2/≥ 3)”. For the sub-group of patients with 1–2 organs/tissues affected by metastases, there was a statistically significant difference to the disadvantage of trifluridine/tipiracil + BSC. For patients with ≥ 3 organs/tissues affected by metastases, there is no statistically significant difference between treatment arms.

With regard to the characteristics “number of previous therapies (2/3/≥ 4)” and “number of organs/tissues affected by metastases (1-2/≥ 3)”, the overall view of the effect modifications

observed shows that these effect modifications do not occur in any other endpoints. Against this background, these effect modifications are not taken into account for further assessment.

With regard to the effect modifications using the characteristic “region” (EU member states versus rest of the world), it should be noted that these effect modifications are not reflected in other relevant endpoint categories (e.g. mortality).

Taking into account the aforementioned aspects, in the present case, the total population is used for the derivation of the additional benefit. The effect modifications by the characteristic “region” are nevertheless considered a relevant result of the present benefit assessment.

Therapy discontinuation because of AE

With regard to therapy discontinuations because of AE, there is a statistically significant difference in favour of trifluridine/tipiracil + BSC. In both the intervention and the control arm, the median time to the event was not yet achieved.

Specific adverse events

For the specific adverse events, advantages and disadvantages for trifluridine/tipiracil + BSC compared with placebo + BSC can be identified.

In detail, for the endpoints gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3]) and general disorders and administration site conditions (SOC, severe AE [CTCAE grade ≥ 3]), there are statistically significant differences to the advantage of trifluridine/tipiracil + BSC.

For the other specific adverse events anaemia (PT, severe AE [CTCAE grade ≥ 3]), neutropenia (PT, severe AE [CTCAE grade ≥ 3]), leukopenia (PT, severe AE [CTCAE grade ≥ 3]) and skin and subcutaneous tissue disorders (SOC, AE), statistically significant differences to the detriment of trifluridine/tipiracil + BSC are shown.

In the overall assessment of the results on side effects, trifluridine/tipiracil + BSC showed an advantage over placebo + BSC in terms of therapy discontinuation because of adverse events; this contrasted by a disadvantage in terms of severe adverse events (CTCAE grade ≥ 3). Regarding the specific adverse events, there are both advantages and disadvantages for trifluridine/tipiracil + BSC compared with placebo + BSC.

<u>Overall assessment</u>

For the assessment of the additional benefit of trifluridine/tipiracil for the treatment of adult patients with metastatic gastric cancer, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease, results are available for the endpoint categories mortality, morbidity, quality of life, and side effects.

The assessment is based on the TAS-102-302 study in which trifluridine/tipiracil + best supportive care (BSC) was compared with placebo + BSC.

Trifluridine/tipiracil + BSC leads to a statistically significant prolongation of median overall survival of 2.1 months (5.7 months vs 3.6 months) compared with placebo + BSC, thus achieving a relevant prolongation of overall survival.

For both the endpoint categories morbidity and health-related quality of life, no usable data from the EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires are available because the proportion of patients for whom no data are available is already very high at early evaluation points. It is therefore not possible to assess how trifluridine/tipiracil affects the disease-specific symptomatology and the health-related quality of life of patients. Statements on quality of life and morbidity are given high priority, especially in the present palliative therapy situation.

In the side effects endpoint category, both positive and negative effects of trifluridine/tipiracil + BSC compared with placebo + BSC are observed. The advantage for therapy discontinuation because of adverse events is offset by a disadvantage with regard to the occurrence of severe adverse events (CTCAE grade ≥ 3). For the specific adverse events, both advantages and disadvantages for trifluridine/tipiracil + BSC can be identified.

In the overall assessment of the results available for all patient-relevant outcomes, the G-BA concludes that for trifluridine/tipiracil + BSC compared with placebo + BSC, the advantages in overall survival and therapy discontinuation because of adverse events are not entirely called into question by the disadvantage in severe adverse events (CTCAE grade ≥ 3). There is a moderate and not only minor improvement in the therapy-relevant benefit that has not yet been achieved.

The G-BA concluded that trifluridine/tipiracil has a minor additional benefit for the treatment of adult patients with metastatic gastric cancer, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.

Reliability of data (probability of additional benefit)

Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

In the randomised, double-blind Phase III study TAS-102-302 (TAGS), trifluridine/tipiracil was compared with the appropriate comparator therapy best supportive care (BSC). The risk of bias at the study level is classified as low.

The results on side effects also include events that can be attributed to the progression and symptomatology of the underlying disease, which is why these are considered to be potentially highly biased and thus of limited significance.

Uncertainties also arise from the lack of usable data on the endpoint categories morbidity and health-related quality of life. These were not usable because the proportion of patients for whom no data are available is already very high at early evaluation points. It is therefore not possible to assess how trifluridine/tipiracil affects the disease-specific symptomatology and the health-related quality of life of patients. Meaningful data on morbidity and health-related quality of life are of great importance, especially in the palliative therapy situation presented here.

The data basis is thus subject to uncertainties. However, these are not considered to be so high overall that a downgrading of the reliability of data would be justified for the overall assessment. In particular, the risk of bias of the endpoint overall survival is considered low. The reliability of data supporting the finding of an additional benefit is therefore classified as “indication”.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient combination trifluridine/tipiracil (Lonsurf®).

The therapeutic indication assessed here is as follows: Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (see section 5.1).

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA. For the assessment, the pharmaceutical company presents the randomised, controlled, double-blind TAS-102-302 (TAGS) Phase III study in which trifluridine/tipiracil + BSC was compared with placebo + BSC.

The endpoint overall survival shows a relevant prolongation of overall survival for trifluridine/tipiracil + BSC compared with the appropriate comparator therapy.

There are no usable data for the endpoint categories morbidity and health-related quality of life. It is therefore not possible to assess how trifluridine/tipiracil + BSC affects the disease-specific symptomatology and the health-related quality of life of patients.

In the endpoint category side effects, the advantage for therapy discontinuation because of adverse events is offset by a disadvantage for the occurrence of severe adverse events (CTCAE grade ≥ 3). For the specific adverse events, trifluridine/tipiracil + BSC has both advantages and disadvantages compared with placebo + BSC.

In the overall view, there is an indication of a minor additional benefit of trifluridine/tipiracil + BSC compared with placebo + BSC.

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 resolution will be based on the information from the dossier of the pharmaceutical company.

However, the number of patients derived by the pharmaceutical company in the dossier is subject to uncertainties:

With regard to the Oncology Dynamics study used, it remains unclear why only patients newly documented in Oncology Dynamics in Germany in 2017 are included in the calculation. Furthermore, a higher proportion of patients in advanced stages can be expected than the 5.6 % determined in the Oncology Dynamics study because most patients (approx. 70%) are not diagnosed until the inoperable locally advanced or metastasised stage[6,7]. Furthermore, the systematics for determining the various lines of therapy as well as metastasis are not presented. Moreover, the extrapolation to the total population of treated patients in Germany is not comprehensible in detail. It is also unclear how many doctors from which speciality were questioned with which content in the questionnaires. Taken together, the Oncology Dynamics study and the lower limit of the number of patients in the SHI system derived from it are subject to very high uncertainties, particularly because of a lack of information on the methodological procedure.

With regard to the InGef research database, uncertainties arise on one hand because of the low percentage of patients with metastatic gastric cancer. According to the InGef research database, this amounts to only about 36.8%; other sources report a significantly higher proportion of about 70%[6,7]. On the other hand, it is unclear whether all relevant patients have been included based on the ICD-10 diagnoses C77, C78, C79, and C80 used for the metastatic stage. Based on the data of the InGef research database, the pharmaceutical company uses the number of patients in the SHI system with beginning third line in the year under consideration as the upper limit. However, patients who have received 2 therapies are already eligible for trifluridine/tipiracil. The 2nd therapy can also be a repetition of the first therapy. In addition, a possible third line treatment may begin before the year under consideration.

Overall, the patient numbers are subject to significant uncertainties and are to be considered an underestimation, in particular because of the procedure of considering only those patients for whom second-line therapy is not a repeat of first-line therapy.

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[6] Robert Koch Institute. Cancer in Germany 2013/2014 [on-line]. 2017 [Last accessed: 31 October 2018]. URL: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2017/krebs_in_deutschland_2017.pdf?__blob=publicationFile.

[7] Wöll E. Aktueller Stand der Therapie des Magenkarzinoms [Current status of the therapy of gastric carcinoma]. ONKOLOGIE heute 2017; November/2017: 39–42.

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 combination: trifluridine/tipiracil) at the following publicly accessible link (last access: 18 March 2020):

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

Treatment with trifluridine/tipiracil should only 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 gastric 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: 15 March 2020).

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

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 patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time intervals between individual treatments, and for 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	20 x per 28-day cycle (twice daily on Days 1–5 and Day 8–12)	13 cycles	10	130
Best supportive care	different for each individual patient			

(Continuation)

Appropriate comparator therapy	
Best supportive care	different for each individual patient

Usage and consumption:

Because trifluridine/tipiracil is dosed as a function of body surface area (BSA), the BSA is calculated using the DuBois formula with an average body weight of 77.00 kg and an average height of 1.72 m according to the 2017 microcensus = 1.90 m²[8]. Differences between women and men were not to be considered because of the therapeutic indication.

Designation of the therapy	Dose/ use	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Trifluridine/tipiracil	65 mg	130 mg	6 × 15 mg	130	780 tablets with 15 mg
			2 × 20 mg	130	260 tablets with 20 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				

Costs:

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

[8] German Federal Office For Statistics, Wiesbaden 2018: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179005.html

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	60 FCT, 15 mg	€ 2,348.49	€ 1.77	-	€ 2,346.72
	60 FCT, 20 mg	€ 3,112.18	€ 1.77	-	€ 3,110.41
Best supportive care	different for each individual patient				
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 March 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 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 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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 July 2019.

On 2 October 2019, 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 VerfO.

By letter dated 2 October 2019 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 13 January 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 January 2020. The deadline for submitting written statements was 5 February 2020.

The oral hearing was held on 24 February 2020.

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 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	23 July 2019	Determination of the appropriate comparator therapy
Working group Section 35a	19 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 February 2020	Conduct of the oral hearing
Working group Section 35a	4 March 2020 18 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken