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) Trastuzumab deruxtecan (new therapeutic indication: gastric or gastroesophageal junction adenocarcinoma, HER2+, after trastuzumab-based therapy)

of 20 July 2023

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 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 active ingredient trastuzumab deruxtecan (Enhertu) was listed for the first time on 1 February 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 16.09.2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for trastuzumab deruxtecan in the therapeutic indication in question here "advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma" in accordance with Section 35a paragraph 5b SGB V.

In its session on 3 November 2022, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first

relevant date. The marketing authorisation for the additional therapeutic indication "adults with unresectable or metastatic HER2-low breast cancer who have already received chemotherapy in the metastatic situation or who have had a recurrence during or within 6 months after the end of adjuvant chemotherapy", which is covered by the application according to Section 35a paragraph 5b SGB V, was granted within the 6-month period.

For the therapeutic indication in question here "advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma", trastuzumab deruxtecan received the marketing authorisation as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) number 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, 12.12.2008, sentence 7) on 12 December 2022. By resolution of 3 November 2022, the benefit assessment of the active ingredient trastuzumab deruxtecan in this therapeutic indication thus began at the latest within four weeks of the marketing authorisation granted on 23 January 2023 for trastuzumab deruxtecan in the therapeutic indication for the treatment of adults with "unresectable or metastatic HER2-low breast cancer who have already received chemotherapy in the metastatic situation or who have had a recurrence during or within 6 months after completion of adjuvant chemotherapy" as well as 6 months after the first relevant date, i.e. no later than 9 July 2023.

The pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 of the 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 trastuzumab deruxtecan with the new therapeutic indication "advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma following prior trastuzumab-based therapy" in due time on 31 January 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 May 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 trastuzumab deruxtecan compared to 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 trastuzumab deruxtecan.

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:

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

2.1.1 Approved therapeutic indication of trastuzumab deruxtecan (Enhertu) in accordance with the product information

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Therapeutic indication of the resolution (resolution of 20.07.2023):

"see approved therapeutic indication"

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

- Docetaxel cf. Annex VI to Section K of the Pharmaceuticals Directive

or

- Irinotecan cf. Annex VI to Section K of the Pharmaceuticals Directive

or

- Paclitaxel cf. Annex VI to Section K of the Pharmaceuticals Directive

or

- Ramucirumab in combination with paclitaxel

b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

- Trifluridine/ tipiracil

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 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.

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

on 1. In addition to trastuzumab deruxtecan, the active ingredients 5-fluorouracil, doxorubicin, epirubicin, mitomycin, carmustine, pembrolizumab and ramucirumab as well as the combinations of active ingredients ramucirumab in combination with paclitaxel and trifluridine/ tipiracil are approved in the present therapeutic indication.

on 2. It is assumed that curative treatment with definitive radiotherapy is not indicated for patients with unresectable cancer. In the present therapeutic indication, a 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
- Trifluridine/ tipiracil: Resolution of 2 April 2020
- Ramucirumab: Resolution of 20 October 2016

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use): Paclitaxel, docetaxel or irinotecan as monotherapy for both gastric cancer or gastroesophageal junction carcinoma (adenocarcinoma) with disease progression after prior platinum or fluoropyrimidine chemotherapy.

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

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

Overall, the evidence is limited for patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma after pretreatment with a trastuzumab-

based therapy regimen. At this stage, there are no specific HER2-targeted therapy recommendations for the second or subsequent lines of therapy.

The available evidence does not show any indications of HER2-positive gastric or gastroesophageal junction adenocarcinoma being characterised by certain factors that clearly argue against treatment with the previous or current standard therapies. Thus, those therapy options that are independent of the HER2-status and thus, eligible for the unselected patient population in this respect are considered for the appropriate comparator therapy.

The present therapeutic indication addresses several lines of therapy. For patients who have already received a previous trastuzumab-based first-line therapy and for patients who have already received at least two prior therapy regimens including trastuzumab, different treatment options can be considered according to the available evidence. Therefore, in the present therapeutic indication, a distinction is made between a) adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; following prior trastuzumab-based first-line therapy and b) adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; following at least two prior treatment regimens, including trastuzumab.

a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy

According to the guidelines, systemic therapy is recommended for the present treatment setting.

According to the authorisation status and guideline recommendation, the active ingredient ramucirumab or the combination of active ingredients ramucirumab with paclitaxel can be considered for this.

In the benefit assessment, a hint for a minor additional benefit was identified for ramucirumab in combination with paclitaxel by resolution of 20 October 2016 compared to therapy according to doctor's instructions. In contrast, by resolution of 20 October 2016, no additional benefit was identified for ramucirumab as a monotherapy compared to best supportive care, against the background that no suitable data were submitted for the benefit assessment. Ramucirumab as monotherapy is therefore not determined to be an appropriate comparator therapy.

The still fairly new treatment option pembrolizumab is available for adults with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) gastric cancer with disease progression during or after at least one therapy. The active ingredient was approved on 25 April 2022. According to the guideline, therapy with immune checkpoint inhibitors can be considered in patients with proven microsatellite instability after other approved therapies have been exhausted; however, according to the guideline, the significance is unclear in unselected adults. In the benefit assessment, a hint for a non-quantifiable additional benefit was identified in patients with MSI-H or dMMR gastric cancer with disease progression during or after prior therapy (resolution of 19 January 2023). For the present resolution, pembrolizumab is not determined to be an appropriate comparator therapy.

According to current guidelines, monotherapies with the active ingredients irinotecan, docetaxel and paclitaxel are also recommended for the present treatment setting.

A discrepancy can be found between medicinal products approved in the indication and those used in healthcare/ recommended in guidelines.

Paclitaxel, docetaxel and irinotecan (as monotherapy) are not approved for the treatment of advanced gastric or oesophageal adenocarcinoma with progression after platinum and fluoropyrimidine-containing chemotherapy, but may be prescribed as "off-label use" (cf. Annex VI to Section K of the Pharmaceuticals Directive).

In the overall assessment, the G-BA therefore determined docetaxel, irinotecan, paclitaxel or ramucirumab in combination with paclitaxel as the appropriate comparator therapy.

The appropriate comparator therapy determined here includes several therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy.

b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab

According to current guidelines and statements of the scientific-medical societies, a treatment with the combination of active ingredients trifluridine/ tipiracil is recommended for the present treatment setting after two or more previous systemic therapies, including trastuzumab.

Trifluridine/ tipiracil is approved in patients who have already been treated with at least two systemic treatment regimens for advanced disease. In the benefit assessment, the G-BA determined an indication of a minor additional benefit for trifluridine/ tipiracil compared to best supportive care by resolution of 2 April 2020.

Patients with MSI-H or dMMR gastric cancer after at least two prior treatment regimens, including trastuzumab, can also be considered for the new treatment option pembrolizumab according to the marketing authorisation. In the benefit assessment of pembrolizumab, no additional benefit was identified over trifluridine/ tipiracil in patients with MSI-H or dMMR gastric cancer with disease progression during or after at least two previous therapies, as no suitable data were submitted (resolution of 19 January 2023). For the present resolution, pembrolizumab is not determined to be an appropriate comparator therapy.

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

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.

Change of the appropriate comparator therapy

Originally, the following were considered as suitable comparators for patient group a) in the context of a therapy according to doctor's instructions:

- Irinotecan
- Docetaxel
- Paclitaxel
- Ramucirumab in combination with paclitaxel

The active ingredients irinotecan, docetaxel and paclitaxel (as monotherapy) are not approved for the present indication, but can be prescribed as "off-label use" for patients with progression after a platinum and fluoropyrimidine-containing therapy (see Annex VI to Section K of the Pharmaceuticals Directive). By the present resolution, the G-BA takes into account its resolution of 13 April 2023 on Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in unapproved therapeutic indications (off-label use): Paclitaxel, docetaxel or irinotecan as monotherapy for both gastric cancer or gastroesophageal junction carcinoma (adenocarcinoma) with disease progression after prior platinum or fluoropyrimidine chemotherapy.

The change in the appropriate comparator therapy has no impact on the benefit assessment of trastuzumab deruxtecan for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy

An additional benefit is not proven.

b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab

An additional benefit is not proven.

Justification:

a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy

and

b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab

For the demonstration of the additional benefit of trastuzumab deruxtecan for the total population, adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have already received prior trastuzumab-based therapy regimen, the pharmaceutical company presented the results of the DESTINY-Gastric01 and DESTINY-Gastric02 studies in the dossier.

DESTINY-Gastric01

The open-label, randomised, controlled phase II DESTINY-Gastric01 study enrolled adults (20 years and older) with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma with progression during or after at least 2 prior treatment regimens including a fluoropyrimidine, platinum and trastuzumab. In the two relevant study arms, trastuzumab deruxtecan was compared with therapy according to doctor's instructions selecting irinotecan or paclitaxel. The study has been conducted in 66 study sites in Japan and South Korea since 2017.

A total of 188 patients were randomised in the ratio 2:1 into the two relevant study arms. 126 patients were allocated to the intervention arm with trastuzumab deruxtecan and 62 patients to the control arm. Stratification was by geographic region (Japan or South Korea), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0 or 1) and HER2 status.

Treatment was carried out according to the requirements in the product information with 6.4 mg/kg trastuzumab deruxtecan every 3 weeks in the intervention arm. For treatment with the chemotherapies in the control arm, irinotecan was administered at a dose of 150 mg/m^2 body surface area (BSA) (every 2 weeks) and paclitaxel at 80 mg/m^2 BSA (weekly); dose reduction was allowed.

Treatment of the study population in both study arms was until disease progression, unacceptable toxicity, medical decision, withdrawal of consent, onset of pregnancy, end of study or loss to follow-up, or death. The patients were able to start subsequent therapy after discontinuation of the study medication. No information on subsequent therapies was given in the dossier.

The primary endpoint of the study was the overall response rate (ORR) after independent central review. Patient-relevant secondary endpoints were collected in the categories of mortality, morbidity, health-related quality of life, and adverse events (AEs).

Data cut-offs from 8 November 2019 and 3 June 2020 are available for the DESTINY-Gastric01 study.

DESTINY-Gastric02

DESTINY-Gastric02 is an uncontrolled, open-label phase II study that enrolled patients with unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma with progression during or after trastuzumab-based first-line therapy. The single-arm study has been conducted in 24 study sites in Belgium, Italy, Spain, the UK and the US since 2019. A total of 79 patients were enrolled in the study.

Treatment was carried out according to the requirements in the product information with 6.4 mg/kg trastuzumab deruxtecan every 3 weeks.

The study population was treated until disease progression, unacceptable toxicity, medical decision, withdrawal of consent, onset of pregnancy or death.

The primary endpoint of the study was the overall response rate (ORR) after independent central review. Patient-relevant secondary endpoints were collected in the categories of mortality, morbidity, health-related quality of life, and adverse events (AEs).

For the DESTINY-Gastric02 study, data cut-offs from 9 April 2021 and 8 November 2021 are available. The second data cut-off of 8 November 2021 was only evaluated by the pharmaceutical company for the efficacy and safety endpoints, not for patient-reported endpoints. According to the pharmaceutical company, the DESTINY-Gastric02 study was conducted to collect efficacy and safety data in North America and the European Union in accordance with the EMA recommendations.

Assessment

The pharmaceutical company considered a pooled patient group in the dossier and submitted the DESTINY-Gastric01 and DESTINY-Gastric02 studies for the proof of additional benefit in this patient group. In this respect, as a comparison, the pharmaceutical company used a therapy according to doctor's instructions, which includes the active ingredients irinotecan, docetaxel, paclitaxel as well as ramucirumab in combination with paclitaxel and additionally trifluridine/ tipiracil for patients from the third line of therapy onwards. The pharmaceutical company justifies this procedure with the fact that after 2 or more previous therapies, the respective unused treatment options assume significance in the following line of therapy. It cannot be deduced from the information provided by the pharmaceutical company that in addition to trifluridine/ tipiracil, irinotecan, docetaxel, paclitaxel as well as ramucirumab in combination with paclitaxel are also eligible as appropriate comparator therapy in the third line of therapy. For the studies on irinotecan mentioned by the pharmaceutical company, the criteria according to which the sources used were selected is furthermore unclear. Overall, the arguments of the pharmaceutical company are unsuitable to justify a deviation from the appropriate comparator therapy determined by the G-BA. Reference is made to the justification of the appropriate comparator therapy determined by the G-BA in section 2.1.2. Thus, the approach of the pharmaceutical company is inappropriate.

The present assessment was carried out for patients in the second line of therapy (patient group a)) and in the third line of therapy (patient group b)) compared to the respective appropriate comparator therapy determined by the G-BA.

a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy

For adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, following prior trastuzumab-based first-line therapy, the pharmaceutical company does not present suitable data for the assessment of additional benefit in second-line therapy. The DESTINY-Gastric01 study enrolls patients with progression during or after at least two previous therapy regimens including trastuzumab (in third-line therapy) and does not include a patient population relevant for the benefit assessment of second-line therapy. The DESTINY-Gastric02 study is a single-arm study and does not allow comparison with the appropriate comparator therapy defined by the G-BA. Both studies are unsuitable for demonstrating an additional benefit of trastuzumab deruxtecan in second-line therapy. Thus, an additional benefit compared to the appropriate comparator therapy is not proven.

b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab

For the benefit assessment of adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, following at least two previous treatment regimens, including trastuzumab, the pharmaceutical company does not present suitable data for the assessment of additional benefit in third-line therapy. The data of the DESTINY-Gastric01 study are unsuitable for the assessment of the additional benefit because the appropriate comparator therapy trifluridine/ tipiracil named by the G-BA has not been implemented, as the patients in the comparator arm received a therapy according to doctor's instructions selecting irinotecan or paclitaxel. The DESTINY-Gastric02 study is a single-arm study and does not allow comparison with the appropriate comparator therapy defined by the G-BA. Both studies are unsuitable to demonstrate an additional benefit of trastuzumab deruxtecan after at least two previous treatment regimens, including trastuzumab. Thus, an additional benefit compared to the appropriate comparator therapy is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient trastuzumab deruxtecan.

Enhertu was approved under special conditions.

Trastuzumab deruxtecan as monotherapy is approved for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

The therapeutic indication assessed here is as follows:

"Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen."

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy

   and

b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab

The pharmaceutical company performed a summary analysis of the two patient groups using the DESTINY-Gastric01 study, which compared trastuzumab deruxtecan with a therapy according to doctor's instructions selecting irinotecan and paclitaxel, and the single-arm DESTINY-Gastric02 study. The approach adopted by the pharmaceutical company was considered inappropriate and the present assessment was conducted separately for patient groups a) and b) against the respective appropriate comparator therapies determined by the G-BA.

Patient group a)

Docetaxel or irinotecan or paclitaxel or ramucirumab in combination with paclitaxel were determined as the appropriate comparator therapy.

The DESTINY-Gastric01 study enrolls patients with progression during or after at least two previous therapy regimens, including trastuzumab (in third-line therapy). The DESTINY-

Gastric02 study is a single-arm study and does not allow comparison with the appropriate comparator therapy defined by the G-BA. Both studies are unsuitable for demonstrating an additional benefit of trastuzumab deruxtecan after a previous trastuzumab-based first-line therapy. Thus, an additional benefit compared to the appropriate comparator therapy is not proven.

Patient group b)

Trifluridine/ tipiracil was determined to be the appropriate comparator therapy.

The data from the DESTINY-Gastric01 study are unsuitable for the assessment of additional benefit, as the appropriate comparator therapy trifluridine/ tipiracil named by the G-BA for third-line therapy has not been implemented. The DESTINY-Gastric02 study is a single-arm study and does not allow comparison with the appropriate comparator therapy defined by the G-BA. Both studies are unsuitable to demonstrate an additional benefit of trastuzumab deruxtecan after at least two previous treatment regimens, including trastuzumab. Thus, an additional benefit compared to the appropriate comparator therapy is not proven.

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 bases its resolution on the information from the dossier of the pharmaceutical company. An underestimate can be assumed here. The reasons for this are the lack of consideration of periods longer than 5 years in the cumulative incidence of disease progression to UICC stage IV and the non-consideration of patients with unresectable locally advanced cancer. Furthermore, only patients who actually received second or third-line therapy were recorded and not all patients with a progression after previous therapy. Patients with more than 3 lines of therapy were also not taken into account when deriving the patient numbers.

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 Enhertu (active ingredient: trastuzumab deruxtecan) at the following publicly accessible link (last access: 17 May 2023).

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

Treatment with trastuzumab deruxtecan 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 gastric cancer.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at least once a year and update the product information where necessary.

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 July 2023).

The annual treatment costs shown refer to the first year of treatment.

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.

For the use of docetaxel, irinotecan and paclitaxel as monotherapies, the following is specified as dosage in the off-label indication of gastric cancer with progression after platinum and fluoropyrimidine-containing chemotherapy in Annex VI to the Pharmaceuticals Directive: Docetaxel: 75 mg/m^2, every 3 weeks; irinotecan: 150 mg/m^2, every 2 weeks; and paclitaxel: 80 mg/m^2, weekly.

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				
Trastuzumab deruxtecan	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Patient population a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy				
Docetaxel or irinotecan or paclitaxel or ramucirumab + paclitaxel				
Ramucirumab + paclitaxel				
Ramucirumab	Day 1 and 15 per 28-day cycle	13.0	2	26.0
Paclitaxel	Day 1, 8 and 15 per 28-day cycle	13.0	3	39.0
Monotherapies cf. Annex VI to Section K of the Pharmaceuticals Directive				
Paclitaxel	1 x weekly	52.1	1	52.1
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Irinotecan	1 x per 14-day cycle	26.1	1	26.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Patient population b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab				
Trifluridine/ tipiracil	20 x per 28-day cycle (twice daily on day 1-5 and day 8-12)	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.

The (daily) doses recommended in the product information were used as the calculation basis.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2].

As it is not always possible to achieve the exact target dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Trastuzumab deruxtecan	6.4 mg/kg = 492.8 mg	492.8 mg	5 x 100 mg	17.4	87 x 100 mg
Appropriate comparator therapy					
Patient population a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy					
Docetaxel or irinotecan or paclitaxel or ramucirumab + paclitaxel					
Ramucirumab + paclitaxel					

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Ramucirumab	8 mg/kg = 616 mg	616 mg	1 x 500 mg	26.0	26 x 500 mg
			2 x 100 mg	26.0	52 x 100 mg
Paclitaxel	80 mg/m² = 152 mg	152 mg	1 x 100 mg	39.0	39 x 100 mg
			2 x 30 mg	39.0	78 x 30 mg
Monotherapies cf. Annex VI to Section K of the Pharmaceuticals Directive					
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	2 x 80 mg	17.4	34.8 x 80 mg
Irinotecan	150 mg/m² = 285 mg	285 mg	8 x 40 mg	26.1	208.8 x 40 mg
Paclitaxel	80 mg/m² = 152 mg	152 mg	1 x 100 mg	52.1	52.1 x 100 mg
			2 x 30 mg	52.1	104.2 x 30 mg
Patient population b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab					
Trifluridine/ tipiracil	65 mg	130 mg	6 x 15 mg	130.0	780 x 15 mg
			2 x 20 mg	130.0	260 x 20 mg

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.

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					
Trastuzumab deruxtecan	1 PCI	€ 2,405.72	€ 2.00	€ 229.89	€ 2,173.83
Appropriate comparator therapy					

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
Patient population a) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after prior trastuzumab-based first-line therapy					
Docetaxel or irinotecan or paclitaxel or ramucirumab + paclitaxel					
Ramucirumab + paclitaxel					
Ramucirumab 500 mg	1 CIS	€ 2,141.31	€ 2.00	€ 204.00	€ 1,935.31
Ramucirumab 100 mg	1 CIS	€ 441.14	€ 2.00	€ 40.80	€ 398.34
Paclitaxel 100 mg	1 CIS	€ 289.43	€ 2.00	€ 13.20	€ 274.23
Paclitaxel 30 mg	1 CIS	€ 94.12	€ 2.00	€ 3.93	€ 88.19
Monotherapies cf. Annex VI to Section K of the Pharmaceuticals Directive					
Docetaxel 80 mg	1 CIS	€ 415.86	€ 2.00	€ 19.20	€ 394.66
Irinotecan 40 mg	1 CIS	€ 85.56	€ 2.00	€ 9.41	€ 74.15
Paclitaxel 100 mg	1 CIS	€ 289.43	€ 2.00	€ 13.20	€ 274.23
Paclitaxel 30 mg	1 CIS	€ 94.12	€ 2.00	€ 3.93	€ 88.19
Patient population b) Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma; after at least two prior treatment regimens, including trastuzumab					
Trifluridine/ tipiracil 15 mg	60 FCT	€ 2,348.73	€ 2.00	€ 93.46	€ 2,253.27
Trifluridine/ tipiracil 60 mg	60 FCT	€ 3,112.42	€ 2.00	€ 124.62	€ 2,985.80
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PCI = powder for concentrate for solution for infusion					

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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.

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	Treatment days/ year	Cost/ patient/ year
Appropriate comparator therapy							
Paclitaxel							
Dexamethasone[3] 2 x 20 mg	20 TAB x 40 mg	€ 81.55	€ 2.00	€ 0.00	€ 79.55	17.4	€ 69.21
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 SFI x 4 mg	€ 23.67	€ 2.00	€ 5.53	€ 16.14	17.4	€ 112.33
Cimetidine IV 300 mg	10 AMP x 200 mg	€ 19.77	€ 2.00	€ 0.40	€ 17.37	17.4	€ 60.45
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

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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 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 Trastuzumab deruxtecan

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

3 Fixed reimbursement rate

medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 11 May 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 21 February 2023.

On 31 January 2023, the pharmaceutical company submitted a dossier for the benefit assessment of trastuzumab deruxtecan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 2, VerfO.

By letter dated 3 February 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 trastuzumab deruxtecan.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2023. The deadline for submitting statements was 23 May 2023.

The oral hearing was held on 5 June 2023.

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 11 July 2023, and the proposed resolution was approved.

At its session on 20 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 May 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	21 February 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	30 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 June 2023	Conduct of the oral hearing
Working group Section 35a	13 June 2023 5 July 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 July 2023	Concluding discussion of the draft resolution
Plenum	20 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 July 2023

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

Prof. Hecken