Gemeinsamer Bundesausschuss

Justification

to 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 scientific findings Section 14: gastric or gastroesophageal junction adenocarcinoma, HER2-positive, following trastuzumab-based therapy)

From 19 March 2026

Contents

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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) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have 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 decide 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

After the active ingredient trastuzumab deruxtecan (Enhertu) was first placed on the market on 1 February 2022, the G-BA conducted a benefit assessment of this active ingredient in accordance with Section 35a SGB V and passed a resolution on trastuzumab deruxtecan on 20 July 2023.

At their session on 3 July 2025, the G-BA decided to grant the pharmaceutical company, based on their request, a new benefit assessment according to Section 35a paragraph 5 SGB V.

The approval of the request was linked to the condition that the new benefit assessment is carried out pursuant to a data basis corresponding to the currently generally recognised state of medical-scientific knowledge, including the DESTINY-Gastric04 study for patient population a) (adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based first-line therapy).

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By resolution of 3 July 2025, the pharmaceutical company was requested to submit the evidence required for the benefit assessment pursuant to Section 35a, paragraph 1, sentence 3 SGB V within three months of the notification of the decision under point I.

Pursuant to Section 4, paragraph 3, No. 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 4 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 30 September 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2026 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 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, 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 have 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 have made 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 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 19.03.2026):

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 first-line therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

- For docetaxel, cf. Annex VI to Section K of the Pharmaceuticals Directive

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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or

- for irinotecan, cf. Annex VI to Section K of the Pharmaceuticals Directive

  or

- for paclitaxel, cf. Annex VI to Section K of the Pharmaceuticals Directive

  or

- ramucirumab in combination with paclitaxel

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

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

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

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

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

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

On 1. In 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 chemoradiotherapy 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 and oesophageal cancer (adenocarcinoma) with disease progression after platinum and fluoropyrimidine-containing 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.

According to the guidelines derived from the research and synopsis of the evidence, systemic therapy is recommended for the present treatment setting. In this regard, treatment with the active ingredient ramucirumab or the combination of active ingredients ramucirumab and paclitaxel, as well as treatment with the active ingredients irinotecan, docetaxel and paclitaxel, each as monotherapy, is recommended.

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).

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

In addition, the active ingredient pembrolizumab offers a further treatment option for a sub-population in the present therapeutic indication, namely for the treatment of adults with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) gastric cancer with disease progression on or after at least one therapy. Pembrolizumab was approved for the corresponding therapeutic indication on 25 April 2022. Given that this concerns only a presumably small sub-population in the present therapeutic indication, the size of which is defined by the coincidence of the relevant biomarkers from the approved therapeutic indications – HER2-positivity on the one hand and MSI-h/ dMMR on the other – pembrolizumab is not included in the appropriate comparator therapy for the present resolution.

In the overall assessment, docetaxel, irinotecan, paclitaxel or ramucirumab in combination with paclitaxel are therefore determined as appropriate comparator therapies for the present resolution.

The appropriate comparator therapy determined here includes several therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy. The relevant findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

2.1.3 Extent and probability of the additional benefit

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

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

Indication of a minor additional benefit

Justification:

The DESTINY-Gastric04 study

The pharmaceutical company presented results from the DESTINY-Gastric04 study to prove the additional benefit.

The still ongoing, open-label phase III RCT DESTINY-Gastric04 began in May 2021. Of the 494 patients, 246 were randomised to the intervention arm with trastuzumab deruxtecan and 248 to the control arm with ramucirumab in combination with paclitaxel. Adult patients with HER2-positive, unresectable, locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after trastuzumab-based first-line therapy were enrolled in the study. Trastuzumab-based neoadjuvant or adjuvant treatment could be counted as a line of therapy provided that disease progression occurred during treatment or within 6 months of the end of therapy.

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The study was conducted at 117 study sites in South America, Asia and Europe. HER2 status was determined using a tumour biopsy taken following disease progression and had to show a score of 3+ or 2+ by means of immunohistochemistry (IHC). In the case of IHC 2+, in situ hybridisation (ISH) had to be positive at the same time. Randomisation was stratified by HER2 status (IHC 3+ vs IHC 2+ / ISH+), region (Asia [excluding mainland China] vs Western Europe vs mainland China/ the rest of the world) and time to disease progression following first-line therapy (< 6 months vs ≥ 6 months). Patients.

The data from the 1st predefined data cut-off from 24 October 2024 form the basis.

Subsequent therapies:

In the DESTINY-Gastric04 study, only a small percentage of patients receiving at least one subsequent therapy in both study arms were treated with tipiracil/ trifluridine (approximately 4% in the third-line setting and approximately 10% across all subsequent lines of therapy). The assessment takes into account the probable assumption of a limited or declining number of patients, for whom subsequent therapy with tipiracil/ trifluridine could, in principle, be considered. With regard to all information on subsequent therapies and the resulting uncertainties, these are not estimated to be so serious overall in the present assessment as to result in reduced reliability of data.

Extent and probability of the additional benefit

Mortality

In the DESTINY-Gastric04 study, overall survival is defined as the time between randomisation and death from any cause.

For the endpoint of overall survival, there was a statistically significant difference in favour of trastuzumab deruxtecan compared to ramucirumab in combination with paclitaxel, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

Morbidity

Progression-free survival

Progression-free survival is operationalised in the study as the time between randomisation and the first objective radiological progression of the disease or death (irrespective of the underlying cause), depending on whichever event occurred earlier.

For the PFS endpoint, there was a statistically significant difference in favour of trastuzumab deruxtecan compared to ramucirumab in combination with paclitaxel.

The present PFS endpoint is a composite endpoint consisting of endpoints from the "mortality" and "morbidity" categories. The "mortality" endpoint component is already assessed via the "overall survival" endpoint as an independent endpoint. The "radiological progression of the disease" morbidity component is assessed according to RECIST criteria and thus not symptom-related, but only by means of imaging procedures.

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

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Symptomatology

In the DESTINY-Gastric04 study, disease symptomatology was assessed using the PGIS questionnaire. The pharmaceutical company submitted post hoc responder analyses for the time to 1st deterioration.

Health status

The health status was assessed using the PGIC and the visual analogue scale (VAS) of the EQ-5D questionnaire. The pharmaceutical company submitted post hoc responder analyses in each case for the time to 1st deterioration.

The data on symptomatology and health status submitted by the pharmaceutical company are not assessable due to the sharply declining and varying return rates. The respective return rates fall below 70% overall as early as the 2nd follow-up survey on day 43.

Quality of life

In the DESTINY-Gastric04 study, health-related quality of life was assessed using the FACT-Ga questionnaire, which comprises both the FACT-General (FACT-G) and the Gastric Cancer Subscale (GaCS). The pharmaceutical company submitted post hoc responder analyses for the time to 1st deterioration, along with pre-specified analyses of mean differences from a mixed model for repeated measures (MMRM) for the change compared with the start of the study.

The data on quality of life submitted by the pharmaceutical company are not assessable due to the sharply declining and varying return rates. As early as the 2nd follow-up survey on day 43, the return rates fell below 70% overall.

Side effects

Adverse events (AEs) in total

In the DESTINY-Gastric04 study, almost all patients in the control and intervention arms experienced AEs. The results are only presented additionally.

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

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs and discontinuation due to AEs.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, there was a statistically significant difference to the advantage of trastuzumab deruxtecan compared with ramucirumab in combination with paclitaxel.

There was also an effect modification by the age characteristic. In the process, the subgroup analyses showed a statistically significant advantage of trastuzumab deruxtecan only in patients < 65 years of age. In contrast, there was no statistically significant difference in patients ≥ 65 years of age. In the overall analysis of the available results from the DESTINY-Gastric04 study, this effect modification by the age characteristic is considered insufficient to derive corresponding separate statements on the additional benefit in the overall assessment.

Specific AEs

Thrombocytopenia (severe AEs) and ILD / pneumonitis (SAEs)

For the endpoints "thrombocytopenia" (severe AEs) and "interstitial lung disease" (ILD) / pneumonitis (SAEs), there was no statistically significant difference between the treatment groups in either case.

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Stomatitis (AEs), epistaxis (AEs), musculoskeletal and connective tissue disorders (AEs), renal and urinary disorders (AEs), hypertension (severe AEs) and nervous system disorders (severe AEs)

For the endpoints of stomatitis (AEs), epistaxis (AEs), musculoskeletal and connective tissue disorders (AEs), renal and urinary disorders (AEs), hypertension (severe AEs) and nervous system disorders (severe AEs), there was a statistically significant difference to the advantage of trastuzumab deruxtecan compared with ramucirumab in combination with paclitaxel in each case.

Vomiting (AEs), nausea (severe AEs)

For the endpoints of vomiting (AEs) and nausea (severe AEs), there was a statistically significant difference to the disadvantage of trastuzumab deruxtecan compared with ramucirumab + paclitaxel.

Detailed analysis of some specific AEs in the endpoint category of side effects showed advantages and disadvantages of trastuzumab deruxtecan; however, these are not reflected in the overall rates of SAEs and severe AEs. For the endpoint of discontinuation due to AEs, there was a statistically significant difference to the advantage of trastuzumab deruxtecan. For the endpoint of discontinuation due to AEs in the side effects category, a moderate advantage of trastuzumab deruxtecan over ramucirumab in combination with paclitaxel can be identified overall.

According to the product information, premedication must be administered prior to the use of paclitaxel to prevent hypersensitivity reactions. The product information for ramucirumab recommends premedication to prevent infusion-related reactions. However, the study protocol did not explicitly specify premedication in the control arm to prevent hypersensitivity reactions. Based on the data on concomitant treatments, from which the use of premedication can be roughly inferred, it can be assumed that only around 50% of patients in the control arm received premedication for paclitaxel in accordance with the product information. Similarly, it must be assumed that not all patients receiving ramucirumab were given premedication to prevent infusion-related reactions. This gives rise to a risk of bias for the respective endpoints.

Overall assessment

Results from the randomised, multicentre, controlled DESTINY-Gastric04 study regarding mortality, morbidity, health-related quality of life and side effects are available for the assessment of the additional benefit of trastuzumab deruxtecan in the treatment of adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based first-line therapy.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of trastuzumab deruxtecan compared to ramucirumab in combination with paclitaxel, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

In the morbidity endpoint category, disease symptomatology (PGIS) and health status (EQ-5D VAS and PGIC) were assessed. However, the data submitted are not assessable due to the sharply declining and varying return rates.

Health-related quality of life was assessed using the FACT-Ga. However, the data submitted are not assessable due to the sharply declining and varying return rates.

Detailed analysis of some specific AEs in the endpoint category of side effects showed advantages and disadvantages of trastuzumab deruxtecan; however, these are not reflected

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in the overall rates of SAEs and severe AEs. For the endpoint of discontinuation due to AEs, there was a statistically significant difference to the advantage of trastuzumab deruxtecan. For the endpoint of discontinuation due to AEs in the side effects category, a moderate advantage of trastuzumab deruxtecan over ramucirumab in combination with paclitaxel can be identified overall.

In the overall analysis, the advantage in terms of overall survival is not offset by any disadvantages. Overall, the G-BA concluded the presence of a minor additional benefit of trastuzumab deruxtecan for the treatment of adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based first-line therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, phase III RCT DESTINY-Gastric04.

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

The risk of bias in the results regarding overall survival and side effects is considered low, based on the data submitted by the pharmaceutical company in the written statement procedure. For the endpoint of discontinuation due to AEs, the risk of bias is assessed as high, as premature therapy discontinuation may also occur for reasons other than AEs, and these reasons constitute a competing event for the assessed endpoint of discontinuation due to AEs.

Due to the high significance of the results regarding overall survival, from which the identified additional benefit is largely derived, an indication of an additional benefit can be derived overall, despite the uncertainties described.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient trastuzumab deruxtecan based on an application due to new scientific knowledge according to Section 14 VerfO.

The therapeutic indication assessed here is the treatment of adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based first-line therapy.

The G-BA determined treatment with docetaxel, irinotecan or paclitaxel, each as monotherapy, or with ramucirumab in combination with paclitaxel as the appropriate comparator therapy.

The pharmaceutical company submitted results from the ongoing, open-label phase III RCT DESTINY-Gastric04 to demonstrate the additional benefit.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of trastuzumab deruxtecan compared to ramucirumab in combination with paclitaxel, the extent of which was assessed as a relevant improvement, but no more than a minor improvement.

In the morbidity endpoint category, disease symptomatology (PGIS) and health status (EQ-5D VAS and PGIC) were assessed. However, the data submitted are not assessable due to the sharply declining and varying return rates.

Health-related quality of life was assessed using the FACT-Ga. However, the data submitted are not assessable due to the sharply declining and varying return rates.

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Detailed analysis of some specific AEs in the endpoint category of side effects showed advantages and disadvantages of trastuzumab deruxtecan; however, these are not reflected in the overall rates of SAEs and severe AEs. For the endpoint of discontinuation due to AEs, there was a statistically significant difference to the advantage of trastuzumab deruxtecan. For the endpoint of discontinuation due to AEs in the side effects category, a moderate advantage of trastuzumab deruxtecan over ramucirumab in combination with paclitaxel can be identified overall.

In the overall analysis, the advantage in terms of overall survival is not offset by any disadvantages. Overall, the G-BA concluded the presence of a minor additional benefit of trastuzumab deruxtecan for the treatment of adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based first-line therapy.

The reliability of data for the additional benefit identified is classified in the "indication" category in the present assessment.

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).

530 – 1,560 patients

The G-BA base their resolution on the patient numbers indicated by the pharmaceutical company in the written statement procedure.

Compared with the patient numbers from the initial resolution on the benefit assessment of trastuzumab deruxtecan dated 20 July 2023 for the therapeutic indication "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", there is therefore an increase in the number of patients for the patient group assessed here within the therapeutic indication. In light of the derivation steps justifying the increase, it is not to be assumed that the ratio of the number of patients in the two patient groups as set forth in the initial resolution of 20 July 2023 will relatively change.

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: 5 January 2026):

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, who are experienced in the treatment of patients with gastric cancer, as well as specialists in internal medicine and gastroenterology and other doctors from other specialist groups participating in the Oncology Agreement.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European

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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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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 is different 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/m², every 3 weeks; irinotecan: 150 mg/m², every 2 weeks; and paclitaxel: 80 mg/m², weekly.

Treatment period:

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

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				
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
For 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

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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: 77.7 kg). This results in a body surface area of 1.91 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 dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dosage strengths as well as the scalability of the respective dosage form.

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

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 = 497.3 mg	497.3 mg	5 x 100 mg	17.4	87 x 100 mg
Appropriate comparator therapy					
Ramucirumab + paclitaxel					
Ramucirumab	8 mg/kg = 621.6 mg	621.6 mg	1 x 500 mg + 2 x 100 mg	26.0	26 x 500 mg + 52 x 100 mg
Paclitaxel	80 mg/m² = 152.8 mg	152.8 mg	1 x 100 mg + 2 x 30	39.0	39 x 100 mg + 78 x 30 mg
For monotherapies, cf. Annex VI to Section K of the Pharmaceuticals Directive					
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	17.4	17.4 x 160 mg
Irinotecan	150 mg/m² = 286.5 mg	286.5 mg	1 x 300 mg	26.1	26.1 x 300 mg
Paclitaxel	80 mg/m² = 152.8 mg	152.8 mg	1 x 100 mg + 2 x 30 mg	52.1	52.1 x 100 mg + 104.2 x 30 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

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

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in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based first-line 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
Medicinal product to be assessed					
Trastuzumab deruxtecan	1 PCI	€ 1,516.86	€ 1.77	€ 83.36	€ 1,431.73
Appropriate comparator therapy					
Ramucirumab + paclitaxel					
Paclitaxel 30 mg	1 CIS	€ 94.15	€ 1.77	€ 3.93	€ 88.45
Paclitaxel 100 mg	1 CIS	€ 289.36	€ 1.77	€ 13.19	€ 274.40
Ramucirumab 100 mg	1 CIS	€ 441.18	€ 1.77	€ 23.80	€ 415.61
Ramucirumab 500 mg	1 CIS	€ 2,141.35	€ 1.77	€ 119.00	€ 2,020.58
For monotherapies, cf. Annex VI to Section K of the Pharmaceuticals Directive					
Docetaxel 160 mg	1 CIS	€ 515.78	€ 1.77	€ 23.94	€ 490.07
Irinotecan 300 mg	1 CIS	€ 568.26	€ 1.77	€ 66.44	€ 500.05
Paclitaxel 30 mg	1 CIS	€ 94.15	€ 1.77	€ 3.93	€ 88.45
Paclitaxel 100 mg	1 CIS	€ 289.36	€ 1.77	€ 13.19	€ 274.40

Abbreviations:
CIS = concentrate for the preparation of an infusion solution, PCI = powder for a concentrate for the preparation of an infusion solution

LAUER-TAXE® last revised: 15 January 2026

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.

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The calculation of the additionally required SHI services is based on packs in distribution with the LAUER-TAXE® last revised on 15 September 2025 and fee structure items (FSI) - last revised in the 3rd quarter of 2025 of the uniform value scale (UVS 2025/Q3).

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	Costs/ patient/ year
Appropriate comparator therapy							
Paclitaxel							
Dexamethasone[3] 2 x 20 mg	20 TAB x 40 mg	€ 81.59	€ 1.77	€ 0.00	€ 79.82	17.4	€ 69.44
Dimetindene IV 1 mg/10 kg = 7.7 mg	5 SFI x 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	17.4	€ 122.15
Cimetidine IV 300 mg	10 AMP x 200 mg	€ 22.56	€ 1.77	€ 1.42	€ 19.37	17.4	€ 67.41
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

LAUER-TAXE® last revised: 15 September 2025

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 1 October 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 agents 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-apply unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the 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 Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

[3] Fixed reimbursement rate

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authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

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

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

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

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

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

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

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

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can

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be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

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

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

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

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

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a

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

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

Legal effects of the designation

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

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

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

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient approved in monotherapy.

Product information for trastuzumab deruxtecan (Enhertu); Enhertu 100 mg powder for a concentrate for the preparation of an infusion solution; last revised: November 2025

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.

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4. Process sequence

By letter dated 30 April 2025, the pharmaceutical company submitted an application for a new benefit assessment according to Section 35a SGB V, which the G-BA approved by resolution of 3 July 2025.

On 30 September 2025, 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 1, number 4 VerfO.

By letter dated 30 September 2025 in conjunction with the G-BA resolution 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 29 December 2025, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2026. The deadline for submitting statements was 23 January 2026.

The oral hearing took place on 9 February 2026.

By letter dated 10 February 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by the IQWiG were submitted to the G-BA on 26 February 2026 and 27 February 2026.

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 Subcommittee's session on 10 March 2026, and the draft resolution was conclusively discussed.

At their session on 19 March 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal products	11 May 2021	Determination of the appropriate comparator therapy
Subcommittee on Medicinal products	21 February 2023	New determination of the appropriate comparator therapy
Working group Section 35a	4 February 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal products	9 February 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents

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Working group Section 35a	18 February 2026 4 March 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal products	10 March 2026	Concluding discussion of the draft resolution
Plenum	19 March 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 March 2026

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

Prof. Hecken

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