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: breast cancer, HER2+, after 1 prior therapy)

of 2 February 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. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. 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 online 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 11 July 2022, trastuzumab deruxtecan received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 27 July 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient trastuzumab deruxtecan with the new therapeutic indication (Enhertu as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one prior anti-HER2-based regimen).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2022 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, and the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. 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:

## 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

Trastuzumab deruxtecan (Enhertu) as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

**Therapeutic indication of the resolution (resolution of 02.02.2023):**

This is an extension of the therapeutic indication for trastuzumab deruxtecan as monotherapy indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one prior anti-HER2-based regimen.

The therapeutic indication as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have already received two or more prior anti-HER2-based regimens is the subject of the resolution on the benefit assessment of trastuzumab deruxtecan dated 02.02.2023.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with HER2-positive unresectable or metastatic breast cancer previously treated with one anti-HER2 based therapy

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

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

- Trastuzumab emtansine

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.

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

on 1. In the present therapeutic indication, the following active ingredients are generally available according to the authorisation status of the medicinal products: cytotoxic agents such as 5-fluorouracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, epirubicin, eribulin, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, nab-paclitaxel, vinblastine, vincristine and vinorelbine and HER2-targeted therapy lapatinib, trastuzumab and trastuzumab emtansine.

Medicinal products with explicit marketing authorisation for the treatment of hormone-receptor positive breast cancer or for endocrine therapy were not included.

on 2. For the present therapeutic indication, it is assumed that there is no indication for (secondary) resection or radiotherapy with a curative objective.

on 3. The following resolutions or guidelines of the G-BA for medical products and non-medicinal treatments are available:

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

- Eribulin: Resolution of 22 January 2015
- Trastuzumab emtansine: Resolution of 19 June 2014

Annex VI to Section K of the Pharmaceuticals Directive - Active ingredients that cannot be prescribed in applications beyond the scope of the approval (off-label use); last revised 17 October 2019:

- Gemcitabine in monotherapy for breast cancer in women

Methods Hospital Treatment Policy - Section 4 Excluded Methods, effective 19 December 2019: Proton therapy for breast cancer

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication and can be found in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V", which was sent to the pharmaceutical company.

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 indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

It is assumed that hormone receptor-positive patients are not eligible for endocrine therapy at the time of the treatment decision.

Among the approved active ingredients listed above, 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 health care.

The treatment regimen for unresectable, locally advanced or metastatic breast cancer is largely determined by the HER2 receptor status. In the presence of a HER2-positive tumour status, according to the guidelines, a therapy directed against HER2 is regularly recommended within the framework of adjuvant or first-line therapy. HER2 antibodies (trastuzumab, pertuzumab) and chemotherapeutic agents from the taxane group and, if necessary, anthracyclines are used in the therapy. For patients with positive hormone receptor status (in addition to HER2 positive receptor status), the above-mentioned targeted HER2 therapies are also recommended. According to the available evidence, the antibody-drug conjugate trastuzumab emtansine (T-DM1) is recommended for the subsequent line of treatment.

Trastuzumab emtansine is indicated for the treatment of adults with HER2-positive, unresectable locally advanced or metastatic breast cancer who have previously received trastuzumab and a taxane alone or in combination. With the resolution of the G-BA of 19 June 2014, it was determined for the sub-population of patients with metastatic breast cancer who were treated with anthracyclines, taxanes and trastuzumab in previous therapies that there is an indication of a major additional benefit for the active ingredient trastuzumab emtansine compared to lapatinib in combination with capecitabine. For the sub-population of patients with metastatic breast cancer treated with taxanes and trastuzumab in previous therapies (without anthracyclines), as well as for the sub-population of patients with unresectable locally advanced breast cancer, the pharmaceutical company did not provide the required evidence. The additional benefit compared to the appropriate comparator therapy is therefore not proven. The guidelines on which the appropriate comparator therapy is based do not refer to a necessary anthracycline pre-treatment in their therapy recommendation for trastuzumab emtansine. The approved therapeutic indication of trastuzumab emtansine also does not require prior therapy with anthracyclines.

Based on the available evidence, trastuzumab emtansine is determined to be an appropriate comparator therapy.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

### 2.1.3 Extent and probability of the additional benefit

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

For the treatment of adults with HER2-positive unresectable or metastatic breast cancer previously treated with anti-HER2-based therapy, an indication of non-quantifiable additional benefit is identified.

Justification:

For the proof of additional benefit of trastuzumab deruxtecan for the treatment of adults with HER2-positive unresectable or metastatic breast cancer previously treated with anti-HER2 based therapy, the pharmaceutical company has submitted the results of the DESTINY-Breast03 study.

DESTINY-Breast03 is a randomised, multicentre, open-label, controlled phase III study comparing trastuzumab deruxtecan with trastuzumab emtansine. The study has been conducted in 172 study sites and 14 countries (North America, Europe, Australia and Asia) since August 2018.

The study, which is still ongoing, included adults with unresectable or metastatic HER2-positive breast cancer who had previously been treated with trastuzumab and an advanced/metastatic stage taxane or who had progressed within 6 months of neoadjuvant or adjuvant treatment with a trastuzumab and taxane-containing regimen.

The 524 patients included are stratified according to hormone receptor status (positive vs negative), previous treatment with pertuzumab (yes vs no) and history of visceral disease (yes vs no) and randomised in a 1:1 ratio to the two study arms.

The primary study endpoint was progression-free survival (PFS). In addition, data on mortality, morbidity (symptomatology (EORTC QLQ-C30 and QLQ-BR23) and health status (EQ-5D-5L VAS)), quality of life (EORTC QLQ-C30 and QLQ-BR23) and side effects are collected.

The pharmaceutical company shall submit the results for all patient-relevant endpoints in the dossier with the data cut-off from 21 May 2021. In the context of the written comments, they also present results of the data cut-off from 25 July 2022, which is used for the present benefit assessment.

<u>Limitations of the DESTINY-Breast02 study</u>

Regarding prior therapies in the DESTINY-Breast03 study, 60% of patients have already received ≥ 2 systemic therapies in the metastatic stage, most of which are not anti-HER2 therapies. With regard to the therapy recommendations in guidelines for HER2-positive breast cancer, the previous therapies in the DESTINY-Breast03 study thus partly deviate from the guideline recommendations. These include dual anti-HER2 therapy with trastuzumab and pertuzumab in combination with a taxane as the option of choice in the 1st line of treatment. In the DESTINY-Breast03 study, only about 60% of the patients were pretreated with pertuzumab. Furthermore, in the DESTINY-Breast03 study, almost 20% of patients had already been treated twice or more with anti-HER2 therapy in the metastatic stage. This corresponds to a later stage of treatment in the sequence of anti-HER2 therapies than that on which the present research question is based.

Extent and probability of the additional benefit

Mortality

Overall survival was operationalised in the DESTINY-Breast02 study as the time from randomisation to death, regardless of the underlying cause.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of trastuzumab deruxtecan.

There is an effect modification due to the characteristic "age". For subjects < 65 years, the subgroup analysis shows a statistically significant difference to the benefit of trastuzumab deruxtecan. However, for subjects ≥ 65 years, there was no statistically significant difference. These subgroup results are considered a relevant outcome of the present benefit assessment. However, these are not considered sufficient to differentiate by age in the overall assessment and to derive corresponding separate statements on the additional benefit. However, in combination with the additional limitations of the DESTINY-Breast03 study with regard to previous therapies, a relevant uncertainty remains with regard to the quantification of the extent of additional benefit for the entire study population.

Morbidity

*Progression-free survival*

Progression-free survival (PFS) is the primary endpoint of the DESTINY-Breast03 study. PFS was defined as the time from randomisation to the first documentation of radiological tumour progression or patient death, regardless of the cause of death. The occurrence of disease progression was assessed using RECIST criteria (version 1.1).

There is a statistically significant difference between the treatment arms.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component assessment is not done in a symptom-related manner but by means of imaging (disease progression assessed by radiology according to the RECIST criteria, version 1.1).

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

*Symptomatology*

Symptomatology was assessed in the DESTINY-Breast02 study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

The pharmaceutical company submits responder analyses for the proportion of patients with a change of ≥ 10 points and ≥ 15 points each for the time to first deterioration and for the time to confirmed deterioration. For the EORTC questionnaires, only evaluations for the response criterion 10 points are to be presented in the dossier.

With regard to confirmed deterioration, confirmation was operationalised in the DESTINY-Breast03 study such that deterioration was considered confirmed if it was observed on two or more consecutive visits or occurred at the last assessment.

In the study, no data is available on the actual duration of observation for the endpoint symptomatology. The different observation periods regarding symptomatology can be estimated from the large differences in the treatment durations, which are more than twice

as long in the intervention arm than in the control arm. Furthermore, in the DESTINY-Breast03 study, the responses to the questionnaire in the comparator arm dropped sharply after only a few observation points. In addition, it is problematic that the study counted a single deterioration that occurred at the last assessment as a confirmed deterioration and that there is no information on how many patients were found to have deteriorated at the last data collection time point or how these cases are distributed between the treatment arms. In this situation, potentially a confirmed deterioration in the intervention arm is contrasted with a single deterioration in the comparator arm.

Although both operationalisations ("time to first deterioration" and "time to confirmed deterioration") are considered patient-relevant, the time-to-event analysis for the first deterioration is used against the background of the uncertainties described for the confirmed deterioration, since the evaluations for the confirmed deterioration cannot be interpreted meaningfully.

For the endpoints nausea and vomiting, appetite loss and diarrhoea, there were statistically significant differences to the disadvantage of trastuzumab deruxtecan.

Regarding the endpoint symptoms in the arm, there is a statistically significant difference to the advantage of trastuzumab deruxtecan.

No usable data are available for the endpoint hair loss burden, as significantly fewer patients were included in the analyses and the proportion of patients with missing values at the start of the study and during the course of the study is unclear. For all other presented endpoints no statistically significant difference was detected between the treatment groups.

*Health status (EQ-5D VAS)*

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

The pharmaceutical company shall submit responder analyses for the endpoint of health status operationalised as time to first deterioration or to confirmed deterioration by ≥ 15 points.

The results for time to confirmed deterioration are classified as potentially highly biased due to the uncertainties described under the comments on symptomatology. For the present assessment, the analyses for time to first deterioration are therefore also used for the endpoint health status.

There is no statistically significant difference in the health status (EQ-5D VAS).

In the overall consideration of the results, there is both an advantage and disadvantage of trastuzumab deruxtecan compared to trastuzumab emtansine with regard to morbidity. Overall, there is no relevant difference.

Quality of life

Health-related quality of life was assessed in the DESTINY-Breast02 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.

The pharmaceutical company shall submit evaluations for the time to first deterioration and for the time to multiple confirmed deterioration by ≥ 10 points or ≥ 15 points. For the EORTC questionnaires, only evaluations for the response criterion 10 points are to be presented in the dossier.

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

For the endpoints role functioning and cognitive functioning, there are statistically significant differences to the advantage of trastuzumab deruxtecan.

For the endpoint body image, there is a statistically significant difference to the disadvantage of trastuzumab deruxtecan.

There were no statistically significant differences for the remaining endpoints. No usable data are available for the sex pleasure scale.

In the overall consideration of the results for all scales, no clear advantage or disadvantage of trastuzumab deruxtecan compared to trastuzumab emtansine can be determined with regard to quality of life.

Side effects

*Adverse events (AEs) in total*

In the DESTINY-Breast02 study, AEs occurred in both study arms in almost all patients enrolled. The results were only presented additionally.

*Serious adverse events (SAEs) and severe adverse events (CTCAE grade ≥ 3)*

For the endpoints SAEs and severe AEs, there are statistically significant differences to the advantage of trastuzumab deruxtecan.

*Discontinuation due to AEs*

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

*Specific adverse events*

For the specific endpoints thrombocytopenia (severe AEs), alanine aminotransferase increased (severe AEs), aspartate aminotransferase increased (severe AEs), nosebleeds (AEs) and pyrexia (AEs), there is a statistically significant difference to the advantage of trastuzumab deruxtecan in each case.

With regard to the specific AEs general disorders and administration site conditions (serious AEs), neutropenia (serious AEs), leukopenia (serious AEs), fatigue (serious AEs), nausea (serious AEs), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) and malaise (AEs), there is a statistically significant difference to the disadvantage of trastuzumab deruxtecan in each case.

For the endpoint cardiac disorders (severe AE), no events occurred in either treatment group.

In the overall view of the results on side effects, an advantage can be determined for trastuzumab deruxtecan compared to trastuzumab emtansine.

Overall assessment

For the benefit assessment of trastuzumab deruxtecan for the treatment of adults with HER2-positive unresectable or metastatic breast cancer previously treated with one anti-HER2 based therapy, results from the DESTINY-Breast03 study on mortality, morbidity (symptomatology and health status), health-related quality of life and side effects are available.

The results for the endpoint overall survival show that treatment with trastuzumab deruxtecan prolongs overall survival compared to trastuzumab emtansine. For this endpoint, there is an effect modification due to the age characteristic. For subjects < 65 years of age, there is a statistically significant difference to the advantage of trastuzumab deruxtecan. However, for subjects ≥ 65 years, there was no statistically significant difference. In

combination with the additional limitations of the DESTINY-Breast03 study with regard to previous therapies, this results in a relevant uncertainty with regard to the quantification of the extent of additional benefit for the entire study population.

In the morbidity category, there are both advantages and disadvantages for trastuzumab deruxtecan regarding symptomatology. An additional benefit is not proven for the endpoint health status (EQ-5D VAS). In the overall analysis of the results, there is no clear advantage or disadvantage of trastuzumab deruxtecan compared to trastuzumab emtansine for the endpoint category morbidity.

Overall, there is no clear advantage or disadvantage of trastuzumab deruxtecan compared to trastuzumab emtansine in terms of quality of life.

For side effects, an advantage for trastuzumab deruxtecan is observed for the endpoints serious adverse events and severe AEs. There is no significant difference in the endpoint discontinuation due to AEs. With regard to specific adverse events, there are both advantages and disadvantages. In summary, the side effects endpoints show predominantly advantages for trastuzumab deruxtecan compared to trastuzumab emtansine.

Overall, there are advantages in terms of overall survival and side effects. There were no relevant differences between the treatments in terms of symptomatology, health status and health-related quality of life. With regard to the advantage in overall survival, there is relevant uncertainty regarding the quantification of the extent of the additional benefit for the entire study population due to the effect modification by the characteristic age. Furthermore, there are uncertainties regarding the previous therapies of the patients included in the DESTINY-Breast03 study. For these reasons, the extent of the additional benefit cannot be quantified with certainty in the overall assessment.

As a result, the G-BA identified a non-quantifiable additional benefit for trastuzumab deruxtecan compared to trastuzumab emtansine in the treatment of adults with HER2-positive unresectable or metastatic breast cancer who were previously treated with anti-HER2-based therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of a study. In this study, trastuzumab deruxtecan was compared with the appropriate comparator therapy trastuzumab emtansine in an open-label, randomised controlled comparison.

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

With the exception of the endpoints overall survival, SAE and severe AE, the endpoint-specific risk of bias for the other endpoints is estimated to be high.

Overall, an indication is derived for the reliability of data.

### 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 is approved as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

In this case, the therapeutic indication was evaluated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have already received pre-treatment directed against HER2.

The G-BA determined trastuzumab emtansine as the appropriate comparator therapy.

For the assessment of the additional benefit, results are available from the open-label, randomised, controlled DESTINY-Breast03 study in comparison with trastuzumab emtansine on mortality, morbidity, quality of life and side effects.

There is no statistically significant advantage for overall survival. Due to an effect modification by the characteristic age, which is shown in subgroup analyses (≥ 65 years; < 65 years), in combination with additional limitations of the study with regard to previous therapies, uncertainty remains with regard to the quantification of the extent of the additional benefit for the entire study population.

With regard to morbidity and quality of life, there is no clear advantage or disadvantage of trastuzumab deruxtecan compared to trastuzumab emtansine.

An advantage is observed for the endpoints SAEs and severe AEs. There is no difference in the endpoint discontinuation due to AEs. With regard to specific adverse events, there are both advantages and disadvantages. Overall, the side effects endpoints show predominantly advantages for trastuzumab deruxtecan.

Due to the effect modification by the characteristic age, there is uncertainty with regard to the quantification of the extent of the additional benefit for the entire study population. Furthermore, there are uncertainties regarding the previous therapies of the patients included in the DESTINY-Breast03 study. For these reasons, the extent of the additional benefit cannot be quantified with certainty in the overall assessment.

With regard to the reliability of data, an overall indication of an additional benefit is derived. In the overall assessment, an indication of a non-quantifiable additional benefit for trastuzumab deruxtecan compared to trastuzumab emtansine is identified.

## 2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties with regard to the percentages for stage distribution, the percentages for unresectable breast cancer, the uncertainty of the transferability of an incomprehensible HER2 positivity rate without stage restriction to metastatic or unresectable breast cancer and the proportion values for the receipt of second-line therapy.

## 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 November 2022):

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 breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

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 a minimum once per 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: 15 January 2023).

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.

The information on dosages refers to applications in women, as breast cancer is relatively rare in men. For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight of adult women: 68.7 kg)[2].

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 | | | | |
| Trastuzumab emtansine | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |

[2] 4 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Consumption:

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Trastuzumab deruxtecan | 5.4 mg/kg = 370.98 mg | 370.98 mg | 4 x 100 mg | 17.4 | 69.6 x 100 mg |
| Appropriate comparator therapy | | | | | |
| Trastuzumab emtansine | 3.6 mg/kg = 247.32 mg | 247.32 mg | 1 x 100 mg + 1 x 160 mg | 17.4 | 17.4 x 100 mg + 17.4 x 160 mg |

Costs:

**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 | € 2,405.72 | € 1.77 | € 229.89 | € 2,174.06 |
| Appropriate comparator therapy | | | | | |
| Trastuzumab emtansine 100 mg | 1 | € 1,939.44 | € 1.77 | € 184.24 | € 1,753.43 |
| Trastuzumab emtansine 160 mg | 1 | € 3,068.55 | € 1.77 | € 294.78 | € 2,772.00 |

LAUER-TAXE® last revised: 15 January 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs 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 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 Federal Joint Committee shall 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 authorisation under Medicinal Products Act.

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 29 May 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 July 2022, 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 1, sentence 2 VerfO.

By letter dated 28 July 2022 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 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 19 December 2022.

By letters dated 6 December 2022 and 19 December 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 11 January 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 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 29 May 2020 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 29 November 2022 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 6 December 2022 | Commissioning of the IQWiG with the supplementary assessment of documents |
| Subcommittee Medicinal products | 19 December 2022 | Conduct of the oral hearing and commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 3 January 2023<br>17 January 2023 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee Medicinal products | 24 January 2023 | Concluding discussion of the draft resolution |
| Plenum | 2 February 2023 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 2 February 2023

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

Prof. Hecken