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: non-small cell lung cancer, HER2 (ERBB2) mutation, pretreated)

of 16 May 2024

**Contents**


**1. Legal basis ... 2**

**2. Key points of the resolution ... 2**

**2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy ... 3**

2.1.1 Approved therapeutic indication of Trastuzumab deruxtecan (Enhertu) in accordance with the product information ... 3

2.1.2 Appropriate comparator therapy ... 3

2.1.3 Extent and probability of the additional benefit ... 9

2.1.4 Summary of the assessment ... 10

**2.2 Number of patients or demarcation of patient groups eligible for treatment ... 11**

**2.3 Requirements for a quality-assured application ... 12**

**2.4 Treatment costs ... 13**

**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 ... 20**

**3. Bureaucratic costs calculation ... 23**

**4. Process sequence ... 24**

## 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 on the internet and is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure of the active ingredient trastuzumab deruxtecan was on 1 December 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 VerfO on 15 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The GBA came to a resolution on whether an additional benefit of trastuzumab deruxtecan compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of trastuzumab deruxtecan.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

## 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 NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

**Therapeutic indication of the resolution (resolution of 16.05.2024):**

see the approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

- Docetaxel (only for patients with PD-L1 negative tumours)

*or*

- Pemetrexed (only for patients with PD-L1 negative tumours and except in cases of predominantly squamous histology)

*or*

- Nivolumab

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

*or*

– Pembrolizumab (only for patients with PD-L1 expressing tumours, Tumour Proportion Score (TPS) ≥ 1%)

*or*

– Atezolizumab

*or*

– Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology)

b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

Appropriate comparator therapy for trastuzumab deruxtecan as monotherapy:

– Docetaxel

*or*

– Docetaxel in combination with nintedanib (only for patients with adenocarcinoma histology)

*or*

– Docetaxel in combination with ramucirumab

*or*

– Pemetrexed (except for patients with predominantly squamous histology)

*or*

– Vinorelbine (only for patients who are unsuitable for docetaxel)

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

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.

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 it determines 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.

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.

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

on 1. In terms of authorisation status, the active ingredients cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine, afatinib, erlotinib, nintedanib, atezolizumab, nivolumab, pembrolizumab and ramucirumab are available for the treatment of advanced NSCLC.

Medicinal products with an explicit marketing authorisation for the treatment of treatable mutations or for molecularly stratified therapy (directed against ALK, BRAF, EGFR, Exon-20, METex14, RET or ROS1) are not listed.

Apart from trastuzumab deruxtecan, there are currently no other approved medicinal therapies that are explicitly used in adults with activating HER2 (ERBB2) mutation according to the marketing authorisation.

on 2. For the present therapeutic indication, it is assumed that the patients have no indication for definitive local therapy. Therefore, a non-medicinal treatment cannot be considered in the present therapeutic indication.

on 3. For pretreated advanced NSCLC, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on the

active ingredients afatinib, atezolizumab, nintedanib, nivolumab, pembrolizumab and ramucirumab are available.

Annex VI to Section K of the Pharmaceuticals Directive – Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use): carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) – combination therapy.

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 indication according to Section 35a, paragraph 7 SGB V. No written statements were available for the present determination of the appropriate comparator therapy.

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.

At the present time, it is assumed that no molecularly stratified therapy (targeting ALK, BRAF, EGFR, exon-20, METex14, RET or ROS1) will be considered for patients at the time of therapy with trastuzumab deruxtecan.

It should be noted that there are currently no approved medicinal therapies or other specific therapy options for the treatment of NSCLC with regard to the HER2 mutation for which higher-quality evidence is available. There is no evidence that patients with a HER2 mutation are currently treated fundamentally differently from patients without or with an unknown HER2 mutation. Therefore, those therapy options that are applied independently of a HER2 mutation are basically considered for the present treatment setting.

For the present therapeutic indication, it is also assumed that the patients are generally eligible for active antineoplastic therapy, which is why best supportive care is not considered as an appropriate comparator therapy in the present case.

In second-line treatment, depending on the first-line therapy, a distinction is made between a) adults with a cytotoxic chemotherapy pretreatment and b) adults with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD 1/PD-L1 antibody and a platinum-containing chemotherapy (regardless of which of the therapies was used first) as pretreatment.

*a) After previous treatment with platinum-containing chemotherapy*

For patients with NSCLC for whom further antineoplastic therapy is indicated after first-line chemotherapy, several treatment options are available on the basis of the available evidence with the cytotoxic chemotherapeutic agents docetaxel and pemetrexed, in each case as monotherapy, docetaxel in combination with nintedanib and the immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, partly only under certain conditions.

With docetaxel and pemetrexed, both as monotherapy, two established chemotherapeutic agents are available for second-line chemotherapy, although pemetrexed is unsuitable for predominantly squamous histology. For the combination of docetaxel and nintedanib, which is indicated for adenocarcinoma histology, an indication of a minor additional benefit was identified in the benefit assessment compared to docetaxel monotherapy (resolution of 18 June 2015). In the guidelines, docetaxel in combination with nintedanib is recommended alongside the other chemotherapy options, but is not regularly preferred over them. Based on the available evidence and corresponding therapy recommendations in the guidelines, docetaxel and pemetrexed, each as monotherapy, as well as docetaxel in combination with nintedanib, are considered therapeutically comparable, subject to tumour histology and the different side effect profile.

For nivolumab for the treatment of adults after prior chemotherapy and squamous tumour histology, an indication of a considerable additional benefit was identified in the benefit assessment compared to docetaxel (resolution of 4 February 2016). For nivolumab for the treatment of adults after prior chemotherapy and non-squamous tumour histology, an indication of a considerable additional benefit was also identified in the benefit assessment compared to docetaxel (resolution of 20 October 2016).

For pembrolizumab and atezolizumab, used after prior chemotherapy, the benefit assessment also found an indication of a considerable additional benefit compared to docetaxel (pembrolizumab: resolution of 2 February 2017, atezolizumab: resolution of 16 March 2018). According to the marketing authorisation for the present therapeutic indication, pembrolizumab is only indicated for patients with PD-L1 expressing tumours (TPS ≥ 1%).

Nivolumab, pembrolizumab and atezolizumab each lead to a significant prolongation in overall survival compared with docetaxel and also to a significant reduction in side effects. Accordingly, the guidelines regularly prefer immune checkpoint inhibitors over cytotoxic chemotherapeutic agents. However, PD-L1 negative tumours are a fundamental exception. In these cases, the guidelines predominantly do not recommend a regular preference of immune checkpoint inhibitors over cytotoxic chemotherapy. Therefore, in PD-L1 negative tumours, alternative cytotoxic chemotherapeutic agents are also determined as an appropriate comparator therapy for the immune checkpoint inhibitors.

For ramucirumab in combination with docetaxel, no additional benefit was shown in the benefit assessment compared to docetaxel (resolution of 1 September 2016). Likewise, no additional benefit was identified in the benefit assessment of afatinib compared to docetaxel (resolution of 20 October 2016). Taking into account that benefit-assessed medicinal treatments with an additional benefit are available in the present indication, the treatment options ramucirumab in combination with docetaxel as well as afatinib, for which no additional benefit could be determined in each case, are not considered as an appropriate comparator therapy.

In the overall assessment, the G-BA determined docetaxel, pemetrexed, nivolumab, pembrolizumab, atezolizumab and docetaxel in combination with nintedanib as equally appropriate comparator therapies for this patient group. The additional benefit can be demonstrated compared to one of the treatment options mentioned.

The appropriate comparator therapy determined here includes several therapy options. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics

specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

b) *Following prior therapy with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy*

The treatment setting addressed in the present case may include patients who have either already received a platinum-containing chemotherapy in combination with an anti-PD-1/PD-L1 therapy as part of first-line therapy or have received a platinum-containing chemotherapy and an anti-PD-1/PD-L1 therapy sequentially in the first and second line of therapy (regardless of which of the therapies was administered first).

For both the treatment setting after platinum-containing chemotherapy in combination with an anti-PD-1/PD-L1 therapy and for further treatment after sequential therapy with a platinum-containing chemotherapy and an anti-PD-1/PD-L1 therapy in the first and second line of therapy, there is no higher-quality evidence based on clinical studies.

For patients in this therapeutic indication, antineoplastic subsequent therapy is considered in accordance with the guidelines, in particular taking into account the prior therapy and tumour histology. Docetaxel, docetaxel in combination with ramucirumab or nintedanib and pemetrexed are mentioned as therapy options in this regard. However, taking into account the recommendations of the guidelines for docetaxel-containing therapy, vinorelbine is only considered to be indicated for patients who are unsuitable for docetaxel. Based on the respective marketing authorisations, pemetrexed is again not indicated for predominantly squamous histology and docetaxel in combination with nintedanib is only indicated for adenocarcinoma histology.

The recommendation of further therapy with a (different) anti-PD-1/PD-L1 does not emerge from the available evidence.

For the combination of docetaxel and nintedanib, an indication of a minor additional benefit was identified in the benefit assessment compared to docetaxel monotherapy (resolution of 18 June 2015).

For ramucirumab in combination with docetaxel, no additional benefit was shown in the benefit assessment compared to docetaxel (resolution of 1 September 2016).

Overall, the G-BA determined docetaxel, docetaxel in combination with nintedanib, docetaxel in combination with ramucirumab, pemetrexed and vinorelbine as appropriate comparator therapies. The additional benefit can be demonstrated compared to one of the treatment options mentioned.

The appropriate comparator therapy determined here includes several therapy options. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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

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

### 2.1.3 Extent and probability of the additional benefit

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

a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy

   An additional benefit is not proven.

b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

   An additional benefit is not proven.

Justification:

a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy

   and

b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

In the absence of direct comparator studies of trastuzumab deruxtecan versus the appropriate comparator therapy, the pharmaceutical company used the randomised, uncontrolled dose-finding DESTINY-Lung02 study to demonstrate an additional benefit.

Description of the DESTINY-Lung02 study

The DESTINY-Lung02 study is an ongoing, randomised, two-arm, double-blind, multicentre phase II study investigating the efficacy and safety of two different doses of trastuzumab deruxtecan (6.4 mg/kg vs 5.4 mg/kg, once every three weeks) in adults with metastatic HER2-mutated NSCLC. The study is being conducted at 47 study sites in North America, Europe and the Asia-Pacific region. The start of study was 19 March 2021.

Adults with pathologically documented metastatic NSCLC with a known activating HER2 mutation were enrolled. Patients should have already received previous platinum-containing

therapy in the metastatic stage and must not be candidates for curative surgery or radiotherapy.

In the Destiny-Lung02 study, 152 patients were enrolled and randomised to treatment with trastuzumab deruxtecan at a dose of 6.4 mg/kg (N = 50) or 5.4 mg/kg (N = 102)

Among others, response, overall survival, safety endpoints and patient-reported endpoints were collected in the study.

From this study, the pharmaceutical company uses the study arm for the dosage according to the product information (5.4 mg/kg body weight) for the statement on additional benefit. A comparison with the appropriate comparator therapy is not presented by the pharmaceutical company.

Due to the single-arm study design, the Destiny-Lung02 study presented by the pharmaceutical company does not allow a comparison with the appropriate comparator therapy and is therefore unsuitable for the assessment of an additional benefit of trastuzumab deruxtecan compared with the appropriate comparator therapy.

An additional benefit of trastuzumab deruxtecan as monotherapy for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy after platinum-based chemotherapy with or without immunotherapy is therefore not proven.

Conclusion:

The results of the single-arm Destiny-Lung02 study are available for the assessment of the additional benefit of trastuzumab deruxtecan. The results of the single-arm study presented are unsuitable for assessment of the additional benefit as they do not allow a comparison with the appropriate comparator therapy. Therefore, an additional benefit of trastuzumab deruxtecan as monotherapy for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy after platinum-based chemotherapy with or without immunotherapy is not proven.

### 2.1.4 Summary of the assessment

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

The therapeutic indication assessed here is as follows:

Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

In the therapeutic indication under consideration, two patient groups were distinguished and the appropriate comparator therapy was determined as follows (abbreviated version):

a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy

The appropriate comparator therapy includes various immune checkpoint inhibitors, both as monotherapy and various chemotherapies.

b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

The appropriate comparator therapy comprises various chemotherapies.

Patient group a) and patient group b)

For the benefit assessment, the pharmaceutical company submitted the results of the single-arm DESTINY-Lung02 study. The data presented are unsuitable for comparison with the appropriate comparator therapy.

An additional benefit of trastuzumab deruxtecan as monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC), whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy after platinum-based chemotherapy with or without immunotherapy is therefore not proven.

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

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

For the number of German patients with lung cancer, the projected incidence for 2022 (59,700 patients)[2] is used as the basis for the calculations.

The following calculation steps are used to narrow down this patient group to the target population:

1. The percentage of lung cancer patients with NSCLC is between 73.6% and 83.6%[3] (43,939 to 49,909 patients).
2. Of these, 46.63% of patients are in stage IV at initial diagnosis[4]. Of the remaining 53.37% of patients who are in stage I-IIIB, 37.7% will progress to stage IV in 2022[5]. The percentage of patients in stage IIIB/IIIC is 4.5% to 6.1%[6]. The total number of patients is 31,230 to 36,272.
3. First-line therapy is given in 76.9% to 96.1%[3] of cases (24,016 - 34,856 patients).

2 Robert Koch Institute, Society of Epidemiological Cancer Registries in Germany. Cancer in Germany for 2017/2018. 2021

3 Benefit assessment according to Section 35a SGB V, A21-27, selpercatinib, 11.06.2021

4 Benefit assessment according to Section 35a SGB V, A23-29 | A23-31, durvalumab and tremelimumab, 29.06.2023

5 Tumour Registry Munich ICD-10 C34: Non-small cell. BC Survival [online]. 2022. URL: https://www.tumorregister-muenchen.de/facts/surv/sC34N_G-ICD-10-C34-Nicht-kleinzell.-BC-Survival.pdf; 37.7% (for the longest possible observation period of 15 years)

6 Benefit assessment according to Section 35a SGB V, A23-37, cemiplimab, 28.04.2023

4. The percentage of patients of an activating HER2 (ERBB2) mutation is 1.0-1.7%[7,8] (241 to 593 patients).
5. Of these, as first-line treatment

   5a 10.7 % (25 to 62 patients) received a platinum-based chemotherapy,

   5b 75% (181 to 445 patients) received a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy and

   5c 14.3% (35 to 85 patients) received monotherapy with a PD-1/PD-L1 antibody.
6. Of these, 38.7% to 45.9% of patients received second-line therapy.

   6a 10 to 29 patients with platinum-based chemotherapy in the first line,

   6b 70 to 204 patients with anti-PD-1/PD-L1 in combination with a platinum-containing chemotherapy in the first-line and

   6c 14 to 39 patients with monotherapy with a PD-1/PD-L1 antibody in the first line; of these, 30.0% to 40.0% of patients received third-line therapy (4 to 16 patients with monotherapy with a PD-1/PD-L1 antibody in the first line and received second-line therapy)
7.

   7a Patients after prior treatment with platinum-containing chemotherapy without immunotherapy (step 6a): 10 to 29 patients (patient population a)

   7b Patients after prior treatment with a PD-1/PD-L1 antibody in combination with a platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and a platinum-containing chemotherapy (sum of steps 6a and 6c): 74 to 220 patients (patient population b)
8. Taking into account a percentage of patients insured by the SHI of 88.3%, this results in:

   8a 9 to 25 patients after prior treatment with platinum-containing chemotherapy without immunotherapy (patient population a)

   8b 66 to 194 patients after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

Due to uncertainties regarding the data basis in the target population in Germany, both an overestimation and an underestimation of patient numbers are possible.

### 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: 3 April 2024):

7 Frost, N., Griesinger, F., Hoffmann, H., Länger, F., Nestle, U. et al. Lung Cancer in Germany. J. Thorac. Oncol. 2022; 17(6): 742-750

8 Mazieres, J., Peters, S., Lepage, B., Cortot, A. B., Barlesi, F. et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013; 31(16): 1997-2003

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 non-small cell lung cancer, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from 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 Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

In particular, the training material contains information and warnings on important risks of interstitial lung disease and pneumonitis associated with the use of trastuzumab deruxtecan.

## 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 April 2024).

Treatment period:

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 the maximum treatment duration, if specified in the product information.

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Trastuzumab deruxtecan | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Appropriate comparator therapy | | | | |
| a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy | | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Docetaxel (only for patients with PD-L1 negative tumours) | | | | |
| Docetaxel | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Pemetrexed (only for patients with PD-L1 negative tumours and except in cases of predominantly squamous histology) | | | | |
| Pemetrexed | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Nivolumab | | | | |
| Nivolumab | 1 x per 14-day cycle | 26.1 | 1 | 26.1 |
| Pembrolizumab (only for patients with PD-L1 expressing tumours, Tumour Proportion Score (TPS) ≥ 1%) | | | | |
| Pembrolizumab | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| | or | | | |
| | 1 x per 42-day cycle | 8.7 | 1 | 8.7 |
| Atezolizumab | | | | |
| Atezolizumab | 1 x per 14-day cycle | 26.1 | 1 | 26.1 |
| | or | | | |
| | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| | or | | | |
| | 1 x per 28-day cycle | 13.0 | 1 | 13.0 |
| Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology) | | | | |
| Docetaxel | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Nintedanib | 2 x on day 2-21 of a 21-day cycle | 17.4 | 20 | 348.0 |
| b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy | | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Docetaxel | | | | |
| Docetaxel | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology) | | | | |
| Docetaxel | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Nintedanib | 2 x on day 2-21 of a 21-day cycle | 17.4 | 20 | 348.0 |
| Docetaxel in combination with ramucirumab | | | | |
| Docetaxel | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Ramucirumab | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Pemetrexed (except for patients with predominantly squamous histology) | | | | |
| Pemetrexed | 1 x per 21-day cycle | 17.4 | 1 | 17.4 |
| Vinorelbine (only for patients who are unsuitable for docetaxel) | | | | |
| Vinorelbine | 1 x every 7 days | 52.1 | 1 | 52.1 |

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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – 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)[9].

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

| 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 = 419.6 mg | 419.6 mg | 5 x 100 mg | 17.4 | 87 x 100 mg |
| Appropriate comparator therapy | | | | | |
| a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy | | | | | |
| Docetaxel (only for patients with PD-L1 negative tumours) | | | | | |
| Docetaxel | 75 mg/m² = 143.3 mg | 143.3 mg | 1 x 160 mg | 17.4 | 17.4 x 160 mg |
| Pemetrexed (only for patients with PD-L1 negative tumours and except in cases of predominantly squamous histology) | | | | | |
| Pemetrexed | 500 mg/m² = 955 mg | 955 mg | 2 x 500 mg | 17.4 | 34.8 x 500 mg |
| Nivolumab | | | | | |
| Nivolumab | 240 mg | 240 mg | 2 x 120 mg | 26.1 | 52.2 x 120 mg |
| Pembrolizumab (only for patients with PD-L1 expressing tumours, Tumour Proportion Score (TPS) ≥ 1%) | | | | | |
| Pembrolizumab | 200 mg | 200 mg | 2 x 100 mg | 17.4 | 34.8 x 100 mg |
| | or | | | | |
| | 400 mg | 400 mg | 4 x 100 mg | 8.7 | 34.8 x 100 mg |
| Atezolizumab | | | | | |
| Atezolizumab | 840 mg | 840 mg | 1 x 840 mg | 26.1 | 26.1 x 840 mg |
| | or | | | | |
| | 1,200 mg | 1,200 mg | 1 x 1,200 mg | 17.4 | 17.4 x 1,200 mg |
| | or | | | | |
| | 1,680 mg | 1,680 mg | 2 x 840 mg | 13.0 | 26 x 840 mg |
| Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology) | | | | | |

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Docetaxel | 75 mg/m² = 143.3 mg | 143.3 mg | 1 x 160 mg | 17.4 | 17.4 x 160 mg |
| Nintedanib | 200 mg | 400 mg | 4 x 100 mg | 348.0 | 1,392 x 100 mg |
| b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy | | | | | |
| Docetaxel | | | | | |
| Docetaxel | 75 mg/m² = 143.3 mg | 143.3 mg | 1 x 160 mg | 17.4 | 17.4 x 160 mg |
| Docetaxel in combination with nintedanib (only for patients with PD-L1 negative tumours and adenocarcinoma histology) | | | | | |
| Docetaxel | 75 mg/m² = 143.3 mg | 143.3 mg | 1 x 160 mg | 17.4 | 17.4 x 160 mg |
| Nintedanib | 200 mg | 400 mg | 4 x 100 mg | 348.0 | 1,392 x 100 mg |
| Docetaxel in combination with ramucirumab | | | | | |
| Docetaxel | 75 mg/m² = 143.3 mg | 143.3 mg | 1 x 160 mg | 17.4 | 17.4 x 160 mg |
| Ramucirumab | 10 mg/kg = 777 mg | 777 mg | 1 x 500 mg + 3 x 100 mg | 17.4 | 17.4 x 500 mg + 52.2 x 100 mg |
| Pemetrexed (except for patients with predominantly squamous histology) | | | | | |
| Pemetrexed | 500 mg/m² = 955 mg | 955 mg | 2 x 500 mg | 17.4 | 34.8 x 500 mg |
| Vinorelbine (only for patients who are unsuitable for docetaxel) | | | | | |
| Vinorelbine | 25 mg/m² = 47.8 mg - 30 mg/m² = 57.3 mg | 47.8 mg - 57.3 mg | 1 x 50 mg - 1 x 50 mg + 1 x 10 mg | 52.1 | 52.1 x 50 mg - 52.1 x 50 mg + 52.1 x 10 mg |

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

**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 PIS | € 2,405.75 | € 2.00 | € 134.10 | € 2,269.65 |
| Appropriate comparator therapy | | | | | |
| Docetaxel 160 mg | 1 CIS | € 515.78 | € 2.00 | € 23.94 | € 489.84 |
| Pemetrexed 500 mg | 1 CIS | € 567.62 | € 2.00 | € 26.40 | € 539.22 |
| Nivolumab 120 mg | 1 CIS | € 1,546.96 | € 2.00 | € 85.05 | € 1,459.91 |
| Pembrolizumab 100 mg | 1 CIS | € 2,974.82 | € 2.00 | € 166.60 | € 2,806.22 |
| Atezolizumab 1,200 mg | 1 CIS | € 4,129.23 | € 2.00 | € 232.53 | € 3,894.70 |
| Atezolizumab 840 mg | 1 CIS | € 2,907.75 | € 2.00 | € 162.77 | € 2,742.98 |
| Nintedanib 100 mg | 120 SC | € 2,761.30 | € 2.00 | € 0.00 | € 2,759.30 |
| Ramucirumab 100 mg | 1 CIS | € 441.18 | € 2.00 | € 23.80 | € 415.38 |
| Ramucirumab 500 mg | 1 CIS | € 2,141.35 | € 2.00 | € 119.00 | € 2,020.35 |
| Vinorelbine 10 mg | 10 CIS | € 1,424.56 | € 2.00 | € 67.07 | € 1,355.49 |
| Vinorelbine 50 mg | 10 CIS | € 294.01 | € 2.00 | € 13.42 | € 278.59 |
| Abbreviations: CIS = concentrate for the preparation of an infusion solution, SC = soft capsules, PIS = powder for the preparation of an infusion suspension | | | | | |

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Costs for additionally required SHI services:

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

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

Non-prescription medicinal products that are reimbursable at the expense of the statutory

health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

| 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 |
|---|---|---|---|---|---|---|---|
| Medicinal product to be assessed: Trastuzumab deruxtecan | | | | | | | |
| Not applicable | | | | | | | |
| Appropriate comparator therapy: | | | | | | | |
| *Pemetrexed* | | | | | | | |
| Dexamethasone [10,11] (2 x 4 mg P.O.) | 100 TAB 4 mg each | € 79.54 | € 2.00 | € 5.40 | € 72.14 | 52.2 | € 75.31 |
| Folic acid[12] (350 – 1,000 µg/day, P.O.) | 100 TAB 400 µg each | € 17.29 | € 0.86 | € 2.32 | € 14.11 | 365.0 | € 51.50 - € 103.00 |
| Vitamin B12[11] (1,000 µg/day, every 3 cycles, IM) | 10 AMP 1000 µg each | € 8.19 | € 0.41 | € 0.37 | € 7.41 | 5.8 | € 4.30 |
| Abbreviations: TAB = tablets; AMP = ampoules | | | | | | | |

Other SHI benefits:

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 agents a maximum amount of € 100 per ready-to-use preparation, and

[10] To reduce the frequency and severity of skin reactions, a corticosteroid must be given the day before and on the day of pemetrexed administration as well as the day after.

[11] Fixed reimbursement rate

[12] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1000 µg is given in the product information.

for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

### 2.5 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 designates 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.

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 has 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 has 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 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 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 information 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 has 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 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 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:

a) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation, following platinum-based chemotherapy without immunotherapy

– 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 authorised in monotherapy.

b) Adults with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation after prior treatment with a PD-1/PD-L1 antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy

– 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.

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

## 3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

## 4. Process sequence

At its session on 11 July 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 28 November 2023.

On 15 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of trastuzumab deruxtecan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 20 November 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient trastuzumab deruxtecan.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

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 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 11 July 2023 | Implementation of the appropriate comparator therapy |
| Subcommittee Medicinal products | 28 November 2023 | New implementation of the appropriate comparator therapy |
| Working group Section 35a | 4 April 2024 | Information on written statements received, preparation of the oral hearing |
| Subcommittee Medicinal products | 8 April 2024 | Conduct of the oral hearing |
| Working group Section 35a | 17 April 2024<br>30 April 2024 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee Medicinal products | 7 May 2024 | Concluding discussion of the draft resolution |
| Plenum | 16 May 2024 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 16 May 2024

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

Prof. Hecken