Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Datopotamab deruxtecan (breast cancer, HR-positive, HER2-negative, after at least 1 prior therapy)

of 20 November 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 pass a resolution 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 was the first placing on the (German) market of the active ingredient datopotamab deruxtecan on 1 June 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 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 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 23 May 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 September 2025 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 datopotamab 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 have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of datopotamab deruxtecan.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have 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 Datopotamab deruxtecan (Datroway) in accordance with the product information

Datroway as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

Therapeutic indication of the resolution (resolution of 20.11.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

Appropriate comparator therapy for datopotamab deruxtecan as monotherapy:

- Capecitabine
  or
- eribulin
  or
- vinorelbine
  or

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

- an anthracycline or taxane-containing therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment).

b) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

Appropriate comparator therapy for datopotamab deruxtecan as monotherapy:

- Trastuzumab deruxtecan

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

Appropriate comparator therapy for datopotamab deruxtecan as monotherapy:

- Sacituzumab govitecan

  or
- trastuzumab deruxtecan (only patients with HER2-low tumour status)

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication 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 they determine by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

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

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 addition to datopotamab deruxtecan, the cytostatic agents 5-fluorouracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, eribulin, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, nab-paclitaxel, vinblastine, vincristine, vinorelbine, the PARP inhibitors olaparib and talazoparib as well as the antibody-drug conjugates sacituzumab govitecan and trastuzumab deruxtecan are approved in the present therapeutic indication.

Medicinal products with explicit marketing authorisation for HER2-positive breast cancer and for endocrine-based therapy were not considered here.

Gemcitabine is approved in combination with paclitaxel for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer with recurrence following adjuvant/ neoadjuvant chemotherapy. Accordingly, gemcitabine monotherapy is not covered by the marketing authorisation for the present therapeutic indication.

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 and guidelines of the G-BA are available in the present therapeutic indication:

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

- Eribulin: resolution of 22 January 2015
- Olaparib: resolution of 16 January 2020
- Talazoparib: resolution of 20 November 2020
- Sacituzumab govitecan: resolution of 15 February 2024
- Trastuzumab deruxtecan: resolution of 20 July 2023

Annex VI to Section K of the Pharmaceuticals Directive - Active ingredients that cannot be prescribed for off-label use:

- Gemcitabine as monotherapy for breast cancer in women

Guideline on hospital examination and treatment methods (Directive on Inpatient Treatment Methods):

- Proton therapy for breast cancer
- Proton therapy for brain metastases

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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 (see “Information on Appropriate Comparator Therapy”). A written statement has been issued by the Working Group for Gynaecological Oncology (AGO) of the German Cancer Society (DKG) jointly with the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Senology (DGS).

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.

In the planned therapeutic indication, all patients are designated as HER2-negative, defined by a HER2 tumour status with IHC 0, IHC 1+ or IHC 2+/ISH-. In contrast, a HER2 tumour status with IHC 1+ or IHC 2+/ISH-, based on the marketing authorisation of trastuzumab deruxtecan, is referred to as "HER2-low breast cancer". For the determination of the appropriate comparator therapy, it was therefore assumed that the therapeutic indication includes patients with HER2-negative breast cancer (IHC 0, IHC 1+ or IHC 2+/ISH-) as well as with HER2-low breast cancer (IHC 1+ or IHC 2+/ISH-).

It was also assumed that the patients have usually received taxane and/or anthracycline-based chemotherapy as part of the prior therapies.

The evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women.

In the G-BA’s opinion, patient populations that differ in terms of HER2 tumour status and prior therapies are to be considered separately.

a) <u>Adults with unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting</u>

According to current guidelines, further cytotoxic chemotherapy is the current treatment standard for patients with HER2-negative, advanced / metastatic breast cancer who previously received chemotherapy in case of disease progression or relapse. According to the guidelines, primarily monotherapies should be used with regard to cytotoxic chemotherapies. According to guideline recommendations, combination therapy should only be considered for patients with a high burden of remission due to severe conditions or rapid tumour growth. Due to its high significance

in the treatment of breast cancer, treatment with anthracyclines and taxanes may be considered as a therapy option for patients who have not yet received anthracycline and/or taxane-containing therapy or also as re-therapy in the case of corresponding individual conditions. Of the active ingredients primarily mentioned in various guidelines, besides taxanes and anthracyclines, capecitabine, vinorelbine and eribulin are approved for use as monotherapy in the present therapeutic indication.

For the treatment of patients who have experienced further progression after at least one course of chemotherapy for the treatment of advanced breast cancer, the G-BA identified a hint for a considerable additional benefit of eribulin compared to monotherapy with capecitabine or vinorelbine for patients who can no longer be treated with taxanes or anthracyclines (resolution of 22 January 2015). Taking into account the significance of eribulin in the current guideline recommendations in relation to other therapy options and in view of the restriction of the additional benefit to a part of the approved therapeutic indication, eribulin does not assume high significance in the appropriate comparator therapy and is considered as an equally appropriate comparator therapy alongside capecitabine and vinorelbine.

Overall, the G-BA determined capecitabine or eribulin or vinorelbine or an anthracycline or taxane-containing therapy as the appropriate comparator therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment).

b) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

and

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

Prior to the marketing authorisation of the medicinal products sacituzumab govitecan and trastuzumab deruxtecan, patients with HER2-low (ICH 1+ or IHC2+/ISH) breast cancer were treated according to guideline recommendations in the same way as patients with HER2-negative (ICH 0, IHC 1+ or IHC 2+/ISH) breast cancer, or no treatment options that were explicitly based on HER2-low status were available.

The current ASCO guideline[2,3,4] recommends sacituzumab govitecan for the treatment of HR-positive, HER2-negative breast cancer after at least two previous lines of

[2] Moy B et al. Chemotherapy and targeted therapy for human epidermal growth factor receptor 2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor-negative: ASCO guideline rapid recommendation update. J Clin Oncol 2022;40(26):3088-3090.

[3] Moy B et al. Chemotherapy and targeted therapy for endocrine-pretreated or hormone receptor-negative metastatic breast cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2023;41(6): 1318-1320.

[4] Moy B, Wolff AC, Rumble RB, Allison KH, Carey LA. Chemotherapy and targeted therapy for endocrine-pretreated or hormone receptor-negative metastatic breast cancer and human epidermal growth factor receptor 2 testing in breast cancer: ASCO guideline rapid recommendation update Q and A. JCO Oncol Pract 2023;19(8):547-550.

chemotherapy as well as trastuzumab deruxtecan for patients with HER2-low (IHC 1+ or IHC 2+ and ISH-) after at least one previous line of chemotherapy. In their written statement on the question of comparator therapy, the scientific-medical societies name these two therapy options in addition to the established chemotherapies.

In the benefit assessment procedure for trastuzumab deruxtecan, an indication of a considerable additional benefit thereof compared to a therapy according to doctor's instructions, which included capecitabine, eribulin, paclitaxel or nab-paclitaxel was identified for adults with unresectable or metastatic HER2-low breast cancer who have already received chemotherapy in the metastatic stage (resolution of 20 July 2023).

Likewise, in the benefit assessment procedure for sacituzumab govitecan, an indication of a considerable additional benefit thereof compared to capecitabine or eribulin or vinorelbine was identified for adults with unresectable or metastatic HR-positive, HER2-negative breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the advanced setting (resolution of 15 February 2024).

Based on the approved therapeutic indications of trastuzumab deruxtecan and sacituzumab govitecan, there are delimitations with regard to the patient populations eligible for treatment.

In the overall assessment, the G-BA determined trastuzumab deruxtecan and sacituzumab govitecan as the appropriate comparator therapy for the corresponding patient populations according to the approved therapeutic indication in each case.

For patient population b), trastuzumab deruxtecan is determined as the only appropriate comparator therapy.

For patient population c), trastuzumab deruxtecan (only for patients with HER2-low tumour status) or sacituzumab govitecan are determined as the appropriate comparator therapy.

The appropriate comparator therapy determined here for patient population c) includes several therapeutic alternatives. 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 datopotamab deruxtecan is assessed as follows:

a) Adults with unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

An additional benefit is not proven.

b) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

An additional benefit is not proven.

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

An additional benefit is not proven.

Justification:

To demonstrate an additional benefit, the pharmaceutical company presented the results from the ongoing, open-label, randomised, controlled phase III TROPION-Breast01 study comparing datopotamab deruxtecan with a therapy according to doctor's instructions with selection of capecitabine, eribulin, gemcitabine and vinorelbine. The study has been conducted in 166 study sites in Europe, North and South America, Asia and Africa since October 2021.

Adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer whose disease had progressed under endocrine therapy and who are not eligible for endocrine therapy were enrolled in the study. Patients should also have already received one or two lines of systemic chemotherapy in the advanced setting and be in a good general condition (Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) of 0 or 1).

A total of 732 patients were enrolled in the global cohort and randomly assigned in a 1:1 ratio either to treatment with datopotamab deruxtecan (N = 365) or to therapy according to doctor's instructions with selection of capecitabine, eribulin, gemcitabine and vinorelbine (N = 367). Which of the four available therapy options the patient would be treated with in the case of assignment to the control arm had to be decided prior to randomisation. Randomisation was stratified according to the number of previous lines of chemotherapy (1 vs 2), previous treatment with cyclin-dependent kinase (CDK)-4/6 inhibitors (yes vs no), and geographical region (USA, Canada and Europe vs rest of the world).

In addition to the primary endpoints of progression-free survival (PFS) according to a blinded independent central review (BICR) committee and overall survival, endpoints in the categories of morbidity, health-related quality of life and side effects were assessed.

For the TROPION-Breast01 study, three data cut-offs are available:

- 1st data cut-off from 17.07.2023: pre-specified final analysis of the PFS endpoint and 1st interim analysis for the endpoint of overall survival
- 2nd data cut-off from 29.04.2024; pre-specified 2nd interim analysis for the endpoint of overall survival
- 3rd data cut-off from 24.07.2024: pre-specified final analysis for the endpoint of overall survival

The present benefit assessment is based on the results of the current 3rd data cut-off from 24.07.2024. Only for the endpoint of progression-free survival are the results of the 1st data cut-off from 17.07.2023 (pre-specified final analysis) shown.

Relevant sub-population of the TROPION-Breast01 study

In the TROPION-Breast01 study, the active ingredients capecitabine, eribulin, vinorelbine and gemcitabine are available as part of the therapy according to doctor's instructions. Gemcitabine is however not part of the determined appropriate comparator therapy. In their dossier, the pharmaceutical company therefore presented evaluations of a sub-population of the TROPION-Breast01 study, whose intervention and control arms, respectively, only includes patients for whom capecitabine, eribulin or vinorelbine had been selected as a therapy option for possible treatment in the control arm prior to randomisation. Furthermore, the sub-population only includes patients with HER2-0 breast cancer who have received a line of chemotherapy in the advanced setting.

The sub-population constituted by the pharmaceutical company is used as the relevant population for the present benefit assessment. Overall, it comprises 118 patients, of which 63 were enrolled in the intervention arm and 55 in the control arm. This corresponds to 17.3% and 15.0% of patients in the total population.

On the implementation of the appropriate comparator therapy

The treatment with capecitabine and vinorelbine in the TROPION-Breast01 study deviated in part from the requirements in the product information.

A dosage range was provided for capecitabine, whereas only the higher dosage is stated in the product information for capecitabine[5] . However, the dosage range used by the pharmaceutical company can be found in the guidelines[6] and was assessed by the clinical experts in a previous procedure[7] as the therapeutic standard in clinical practice, leading to the assumption that there are no relevant effects on the present benefit assessment.

The dosage of vinorelbine administered in the study corresponds neither to the requirements in the product information[8] nor to the recommendations of the S3 guideline for the early detection, diagnosis, therapy and follow-up of breast cancer[9], but is consistent with the guideline recommendations of the National Comprehensive Cancer Network (NCCN)[6]. In the

[5] Medac. Capecitabine medac 150/500 mg film-coated tablets [online]. 02.2025 [accessed: 11.07.2025]. URL: https://www.fachinfo.de/

[6] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Breast Cancer; Version 4.2025 [online]. 2025 [accessed: 22.07.2025]. URL: https://www.nccn.org/guidelines/guidelines-detail?id=1419.

[7] Gemeinsamer Bundesausschuss (Federal Joint Committee). Justification to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Trastuzumab Deruxtecan (New Therapeutic Indication: Breast Cancer, HER2-low, Unresectable or Metastatic, Pretreated) [online]. 2023 [accessed: 11.07.2025]. URL: https://www.g-ba.de/downloads/40-268-9651/2023-07-20_AM-RL-XII_Trastuzumab_Deruxtecan_D-905_TrG.pdf.

[8] Onkovis. Vinorelbine onkovis 10 mg/ml for infusion solution concentrate [online]. 04.2025 [accessed: 11.07.2025]. URL: https://www.fachinfo.de/.

[9] Guideline programme in oncology. Interdisciplinary S3 guideline for the early detection, diagnosis, therapy and follow-up of breast cancer, long version 4.4 [online]. 2021 [accessed: 11.07.2025]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.4/LL_Mammakarzinom_Langversion_4.4.pdf.

control arm, around 9% of patients in the relevant sub-population received treatment with vinorelbine. Overall, it is assumed that this deviation has no relevant impact on the outcome of the benefit assessment.

Limitations of the TROPION-Breast01 study

Uncertainties exist for the TROPION-Breast01 study as a relevant percentage of patients in the sub-population considered did not receive prior therapy with anthracyclines or taxanes (17%). The percentage of patients for whom anthracyclines or taxanes are unsuitable is not known. The study did not include treatment with anthracyclines and/or taxanes. There is therefore uncertainty as to the extent to which treatment with an anthracycline or taxane would have been indicated for these patients. The European Public Assessment Report[10] (EPAR) states in this regard that the results for the comparator arm might have been better if treatment with anthracyclines and taxanes had been allowed in the study.

In addition, endocrine therapy or a CDK4/6 inhibitor was used as subsequent therapy in a relevant percentage of patients in both study arms of the study sub-population. This is viewed critically as only patients whose disease had progressed under endocrine therapy and who were not eligible for endocrine therapy were enrolled in the study.

a) Adults with unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

Extent and probability of the additional benefit

Mortality

Overall survival is a primary endpoint of the TROPION-Breast01 study and is operationalised as the time between randomisation and death from any cause.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

Morbidity

Progression-free survival

Progression-free survival (PFS) is a primary endpoint of the TROPION-Breast01 study. It is defined as the time from randomisation to the earliest date of first objective documentation of radiological tumour progression (defined using RECIST 1.1 criteria) or death of the patient regardless of the underlying cause, whichever occurred earlier.

For the PFS, there was a statistically significant difference to the advantage of datopotamab deruxtecan.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The mortality endpoint component is already assessed via the overall survival endpoint as an independent endpoint. The morbidity component is assessed according to RECIST criteria and thus predominantly by means of imaging procedures.

[10] European Medicines Agency. Datroway: EPAR - Public assessment report; Assessment report EMA/CHMP/785 22/2025 [online]. 2025 [accessed: 16.10.2025]. URL: https://www.ema.europa.eu/en/documents/assessment-report/datroway-epar-public-assessment-report_en.pdf

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 extent of the additional benefit remains unaffected.

Symptomatology (EORTC QLQ-C30 and PGI-S) and health status (EQ-5D VAS)

Symptomatology was assessed in the TROPION-Breast01 study using the EORTC QLQ-C30 and PGI-S questionnaires. The health status was assessed using the visual analogue scale of EQ-5D.

In the dossier, the pharmaceutical company presented responder analyses on the time to first deterioration as well as evaluations of mean differences from a mixed model for repeated measures (MMRM).

The return rates of the patient-reported endpoints presented by the pharmaceutical company in the dossier show that a relevant percentage of patients were not included in the analyses as early as the baseline survey. At baseline, the percentages of evaluated questionnaires included in the analyses for the EORTC QLQ-C30, EQ-5D VAS and PGI-S questionnaires was approx. between 54% and 71%. Returns also continue to decrease over the course of the study. Overall, the results of the patient-reported endpoints are unsuitable for use in the benefit assessment due to the high percentage of missing values.

Quality of life

EORTC QLQ-C30

Health-related quality of life was assessed in the TROPION-Breast01 study using the EORTC QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presented responder analyses on the time to first deterioration as well as evaluations of mean differences from a mixed model for repeated measures (MMRM).

However, the return rates presented by the pharmaceutical company in the dossier show – as previously described in the section on symptomatology and health status – that a relevant percentage of patients were not included in the analyses as early as the baseline survey and that returns continued to decline over the course of the study. The presented results on health-related quality of life are also unsuitable for use in the benefit assessment due to the high percentage of missing values.

Side effects

Adverse events (AEs) in total

In the TROPION-Breast01 study, adverse events occurred in the datopotamab deruxtecan arm in 96.8% of patients in the intervention arm and 96.4% of patients in the comparator arm. The results are only presented additionally.

Serious AEs (SAEs) and therapy discontinuation due to AEs

For the endpoints of SAEs and discontinuation due to AEs, there were no statistically significant differences between the treatment arms.

Severe AEs

For the endpoint of severe AEs, there was a statistically significant difference to the advantage of datopotamab deruxtecan compared to chemotherapy according to doctor's instructions.

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The information on PRO-CTCAE provided by the pharmaceutical company shows that a relevant percentage of patients are not included in the analyses. As early as the baseline survey, the percentage of completed questionnaires in the intervention and control arms was only a maximum of around 70% and 58% respectively. The evaluations presented are unsuitable for use in the assessment due to the insufficient number of returns to the questionnaire.

Specific adverse events

Interstitial lung disease and pneumonitis (AEs), hand-foot syndrome (AEs)

For the endpoints of interstitial lung disease and pneumonitis (AEs) as well as hand-foot syndrome (AEs), there was no statistically significant difference between the treatment arms.

Keratitis

In the dossier, the pharmaceutical company only presented results on PT punctate keratitis for the relevant sub-population. It is not clear from the data whether the PTs keratitis and ulcerative keratitis occurred, as only AEs with a frequency of at least 10% (serious and severe AEs: at least 5 %) were presented in at least one study arm. As part of the written statement procedure, the pharmaceutical company stated that no event was reported for PT ulcerative keratitis. There are still no results available for PT keratitis. In summary, no suitable data are available for the keratitis endpoint.

Nausea (AEs) and stomatitis (AEs)

For the endpoints of nausea (AEs) and stomatitis (AEs), there was a statistically significant difference to the disadvantage of datopotamab deruxtecan in each case.

Loss of appetite (AEs) and neutropenia (severe AEs)

For the endpoints of loss of appetite (AEs) and neutropenia (severe AEs), there was a statistically significant difference to the advantage of datopotamab deruxtecan in each case.

In summary, there was an advantage for severe adverse events as well as advantages or disadvantages for specific adverse events in the category of side effects.

<u>Overall assessment</u>

Results of the TROPION-Breast01 study on the endpoint categories of mortality and side effects are available for the benefit assessment of datopotamab deruxtecan compared with a therapy according to doctor's instructions with selection of capecitabine, eribulin or vinorelbine for the treatment of adults with unresectable or metastatic HR-positive and HER2-negative breast cancer who have received endocrine therapy and a line of chemotherapy in the advanced setting.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

There were no assessable data for the endpoints on symptomatology (assessed using EORTC QLQ-C30 and PGI-C) as well as for health status (assessed using EQ-5D VAS).

There were no assessable data on health-related quality of life (assessed using EORTC QLQ-C30).

In terms of side effects, there was a statistically significant advantage of datopotamab deruxtecan in severe AEs (CTCAE grade ≥ 3). In detail, there were advantages and disadvantages for the specific adverse events.

Assessment-relevant limitations of the TROPION-Breast01 study arise on the one hand from the fact that a relevant percentage of patients had not received any prior therapy with anthracyclines or taxanes. On the other, a relevant percentage of patients have received endocrine therapies and/or CDK4/6 inhibitors in the subsequent therapy. This is viewed critically as only patients whose disease had progressed under endocrine therapy and who were not eligible for endocrine therapy were enrolled in the study.

In the overall analysis of the available results on patient-relevant endpoints, the only advantage is in terms of side effects. For the endpoint of overall survival, there was neither an advantage nor a disadvantage. There were no assessable data on morbidity and health-related quality of life. Particularly in the present advanced, palliative treatment setting, data on health-related quality of life assumes high significance.

Taking into account the above-mentioned assessment-relevant limitations, the G-BA came to the conclusion in a weighted decision that the existing advantage in terms of side effects is considered inadequate to identify not only a minor improvement in the therapy-relevant benefit, but a relevant one overall. As a result, it was concluded that an additional benefit of datopotamab deruxtecan compared to a therapy according to doctor's instructions with selection of capecitabine, eribulin or vinorelbine was not proven.

b) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

Extent and probability of the additional benefit

No data are available to allow an assessment of the additional benefit. In their dossier, the pharmaceutical company only presented data on the sub-population of patients with HER2-0 breast cancer who have received a line of chemotherapy in the advanced setting (patient population a)).

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

Extent and probability of the additional benefit

No data are available to allow an assessment of the additional benefit. In their dossier, the pharmaceutical company only presented data on the sub-population of patients with HER2-0

breast cancer who have received a line of chemotherapy in the advanced setting (patient population a)).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Datroway with the active ingredient datopotamab deruxtecan.

Datopotamab deruxtecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

In the therapeutic indication under consideration, 3 patient groups were differentiated according to HER2 status and the number of lines of chemotherapy already received in the advanced setting.

a) Adults with **HER2-negative (IHC 0)** breast cancer; endocrine therapy and **one** line of chemotherapy in the advanced setting

b) Adults with **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer; endocrine therapy and **one** line of chemotherapy in the advanced setting

c) Adults with **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer; endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

On a)

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

There are no assessable data on the endpoints of symptomatology and health status.

There are also no assessable data on health-related quality of life.

In terms of side effects, there was a statistically significant advantage of datopotamab deruxtecan in severe AEs (CTCAE grade ≥ 3). In detail, there were advantages and disadvantages for the specific adverse events.

Assessment-relevant limitations of the TROPION-Breast01 study arise on the one hand from the fact that a relevant percentage of patients had not received any prior therapy with anthracyclines or taxanes. On the other, a relevant percentage of patients have received endocrine therapies and/or CDK4/6 inhibitors in the subsequent therapy. This is viewed critically as only patients whose disease had progressed under endocrine therapy and who were not eligible for endocrine therapy were enrolled in the study.

In the overall analysis of the available results on patient-relevant endpoints, the only advantage is in terms of side effects. For the endpoint of overall survival, there was neither an advantage nor a disadvantage. There were no assessable data on morbidity and health-related quality of life. Particularly in the present advanced, palliative treatment setting, data on health-related quality of life assumes high significance.

Taking into account the above-mentioned assessment-relevant limitations, the G-BA came to the conclusion in a weighted decision that the existing advantage in terms of side effects is considered inadequate to identify not only a minor improvement in the therapy-relevant

benefit, but a relevant one overall. As a result, it was concluded that an additional benefit of datopotamab deruxtecan compared to a therapy according to doctor's instructions with selection of capecitabine, eribulin or vinorelbine was not proven.

On b)
In their dossier, the pharmaceutical company did not present any data for this patient population. No suitable data are therefore available to allow an assessment of the additional benefit. As a result, the G-BA stated that an additional benefit is not proven.

On c)
In their dossier, the pharmaceutical company did not present any data for this patient population. No suitable data are therefore available to allow an assessment of the additional benefit. As a result, the G-BA stated that an additional benefit is not proven.

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

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

With the exception of the upper limit for patient population c), the G-BA base their resolution on the patient numbers stated by the pharmaceutical company in the dossier. For the upper limit for patient population c), the upper limit from the procedure for sacituzumab govitecan by resolution of 15 February 2024[11] is used.

An underestimation can be assumed overall for information provided by the pharmaceutical company for patient groups a), b) and c). The decisive factor here is that, on the one hand, only patients diagnosed with metastases for the first time in the analysis year were taken into account. On the other, patients with unresectable breast cancer as well as patients who were already eligible for treatment with datopotamab deruxtecan prior to fourth-line (patient populations a) and b)) or fifth-line therapy (patient population c)) were not considered. For the upper limit for patient population c), the uncertainties addressed in the resolution on sacituzumab govitecan must be taken into account.

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 Datroway (active ingredient: datopotamab deruxtecan) at the following publicly accessible link (last access: 24 September 2025):

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

[11] Gemeinsamer Bundesausschuss (Federal Joint Committee). 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; sacituzumab govitecan (new therapeutic indication: breast cancer, HR-positive, HER2-negative, at least 3 prior therapies) [online]. 2024 [accessed: 14.08.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/.

Treatment with datopotamab 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 from other specialist groups participating in the Oncology Agreement.

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 September 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For doxorubicin and epirubicin, the total cumulative dose was considered (450 – 550 mg/m^2 BSA for doxorubicin or 900 – 1,000 mg/m^2 BSA for epirubicin). Product information with different dosage recommendations is available for doxorubicin and epirubicin (doxorubicin: 50 – 80 mg/m² BSA and 60 – 75 mg/m² BSA; epirubicin: 75 – 90 mg/m² BSA and 60 – 90 mg/m² BSA). The dosage recommendations with the largest range were used for the cost calculation: Doxorubicin 50 – 80 mg/m² BSA and epirubicin: 60 – 90 mg/m² BSA. In the table "Consumption", only the dosage regimens that result in the range of annual treatment costs when calculated are shown.

Treatment period:

a) Adults with unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Datopotamab deruxtecan	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Capecitabine as monotherapy				
Capecitabine	2 x on day 1-14 of a 21-day cycle	17.4	14	243.6
Eribulin as monotherapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Eribulin	2 x per 21-day cycle (Day 1 and 8)	17.4	2	34.8
Vinorelbine as monotherapy				
Vinorelbine	1 x every 7 days	52.1	1	52.1
An anthracycline or taxane-containing therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment)				
Taxanes				
Docetaxel	1 x per 21-day cycle	17.4	1	17.4
Paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Nab-paclitaxel	1 x per 21-day cycle	17.4	1	17.4
Anthracyclines				
Doxorubicin	1 x per 21-day cycle	5 - 11[12]	1	5.0 – 11.0
Doxorubicin PEG-liposomal	1 x per 28-day cycle	13.0	1	13.0
Epirubicin	1 x per 21-day cycle	10 - 16[13]	1	10.0 – 16.0

b) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Datopotamab deruxtecan	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				

[12] The maximum total doxorubicin dose of 450 – 550 mg/m² body surface area should not be exceeded to avoid cardiotoxicity.

[13] The total cumulative epirubicin dose of 900 – 1,000 mg/m² should not be exceeded to avoid cardiotoxicity.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Trastuzumab deruxtecan	1 x per 21-day cycle	17.4	1	17.4

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Datopotamab deruxtecan	1 x per 21-day cycle	17.4	1	17.4
Appropriate comparator therapy				
Sacituzumab govitecan				
Sacituzumab govitecan	2 x per 21-day cycle (Day 1 and 8)	17.4	2	34.8
Trastuzumab deruxtecan (only patients with HER2-low tumour status)				
Trastuzumab deruxtecan	1 x per 21-day cycle	17.4	1	17.4

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

The information on dosages refers to applications in women, as breast cancer is relatively rare in men. The average body measurements of adult females were applied for dosages, depending on body weight (BW) or body surface area (BSA) (average body height: 1.66 m; average body weight: 69.2 kg). This results in a body surface area of 1.77 m² (calculated according to Du Bois 1916).[14]

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

a) Adults with unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

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					
Datopotamab deruxtecan	6 mg/kg = 415.2 mg	415.2 mg	5 x 100 mg	17.4	87 x 100 mg
Appropriate comparator therapy					
Capecitabine as monotherapy					
Capecitabine	1,250 mg/m^2 = 2,150 mg[15]	4,300 mg	8 x 500 mg + 2 x 150 mg	243.6	1,948.8 x 500 mg + 487.2 x 150 mg
Eribulin as monotherapy					
Eribulin	1.23 mg/m^2 = 2.18 mg	2.18 mg	3 x 0.88 mg	34.8	104.4 x 0.88 mg
Vinorelbine as monotherapy					
Vinorelbine	25 mg/m^2 – 30 mg/m^2 = 44.3 mg - 53.1 mg	44.3 mg – 53.1 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
An anthracycline or taxane-containing therapy (only for patients who have not yet received anthracycline and/or taxane-containing therapy or who are eligible for renewed anthracycline or taxane-containing treatment)					
Taxanes					
Docetaxel	100 mg/m^2 = 177 mg	177 mg	1 x 160 mg + 1 x 20 mg	17.4	17.4 x 160 mg + 17.4 x 20 mg
Paclitaxel	175 mg/m^2 = 309.8 mg	309.8 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Nab-paclitaxel	260 mg/m^2 = 460.2 mg	460.2 mg	5 x 100 mg	17.4	87 x 100 mg
Anthracyclines					
Doxorubicin	50 mg/m^2 – 80 mg/m^2 =	88.5 mg – 141.6 mg	2 x 50 mg – 3 x 50 mg	5 – 11[12]	15 x 50 mg – 22 x 50 mg

[15] Product information for capecitabine: Standard dosage for a BSA of 1.67 m^2 – 1.78 m^2: 2,150 mg.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	88.5 mg – 141.6 mg				
Doxorubicin PEG-liposomal	50 mg/m^2 = 88.5 mg	88.5 mg	1 x 50 mg + 2 x 20 mg	13.0	13 x 50 mg + 26 x 20 mg
Epirubicin	90 mg/m^2 = 159.3 mg	159.3 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	10 – 11[13]	10 x 100 mg + 10 x 50 mg + 10 x 10 mg – 11 x 100 mg + 11 x 50 mg + 11 x 10 mg

b) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and one line of chemotherapy in the advanced setting

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					
Datopotamab deruxtecan	6 mg/kg = 415.2 mg	415.2 mg	5 x 100 mg	17.4	87 x 100 mg
Appropriate comparator therapy					
Trastuzumab deruxtecan	5.4 mg/kg = 373.7 mg	373.7 mg	4 x 100 mg	17.4	69.6 x 100 mg

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

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					
Datopotamab deruxtecan	6 mg/kg = 415.2 mg	415.2 mg	5 x 100 mg	17.4	87 x 100 mg
Appropriate comparator therapy					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Sacituzumab govitecan					
Sacituzumab govitecan	10 mg/kg = 692.0 mg	692.0 mg	4 x 200 mg	34.8	139.2 x 200 mg
Trastuzumab deruxtecan (only patients with HER2-low tumour status)					
Trastuzumab deruxtecan	5.4 mg/kg = 373.7 mg	373.7 mg	4 x 100 mg	17.4	69.6 x 100 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 reference prices 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					
Datopotamab deruxtecan 100 mg	1 PCI	€ 2,040.84	€ 1.77	€ 113.26	€ 1,925.81
Appropriate comparator therapy					
Capecitabine 500 mg[16]	120 FCT	€ 151.84	€ 1.77	€ 11.11	€ 138.96
Capecitabine 150 mg[16]	120 FCT	€ 54.15	€ 1.77	€ 3.39	€ 48.99
Docetaxel 160 mg	1 CIS	€ 820.48	€ 1.77	€ 38.40	€ 780.31
Docetaxel 20 mg	1 CIS	€ 112.47	€ 1.77	€ 4.80	€ 105.90
Doxorubicin 50 mg[16]	6 SFI	€ 812.52	€ 1.77	€ 63.37	€ 747.38
Doxorubicin, PEG-liposomal 20 mg	1 CIS	€ 721.49	€ 1.77	€ 89.87	€ 629.85
Doxorubicin, PEG-liposomal 50 mg	1 CIS	€ 1,778.90	€ 1.77	€ 224.69	€ 1,552.44
Epirubicin 100 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Epirubicin 50 mg	1 CIS	€ 155.45	€ 1.77	€ 6.84	€ 146.84
Epirubicin 10 mg	1 CIS	€ 39.51	€ 1.77	€ 1.34	€ 36.40
Eribulin 0.88 mg	6 SFI	€ 1,112.48	€ 1.77	€ 52.26	€ 1,058.45
Paclitaxel 300 mg	1 CIS	€ 845.77	€ 1.77	€ 39.60	€ 804.40

[16] Fixed reimbursement rate

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
Paclitaxel 30 mg	1 CIS	€ 94.76	€ 1.77	€ 3.96	€ 89.03
Nab-paclitaxel	1 PIS	€ 429.36	€ 1.77	€ 19.84	€ 407.75
Sacituzumab govitecan 200 mg	1 PCI	€ 1,115.07	€ 1.77	€ 61.11	€ 1,052.19
Trastuzumab deruxtecan 100 mg	1 PCI	€ 1,516.86	€ 1.77	€ 83.36	€ 1,431.73
Vinorelbine 50 mg	1 CIS	€ 152.64	€ 1.77	€ 6.71	€ 144.16
Vinorelbine 10 mg	1 CIS	€ 38.90	€ 1.77	€ 1.31	€ 35.82
Abbreviations: CIS = concentrate for the preparation of an infusion solution, SFI = solution for injection; PIS = powder for the preparation of an infusion suspension, PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 September 2025

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.

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

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Appropriate comparator therapy:							
Paclitaxel							
Dexamethasone[16] 2 x 20 mg	50 TAB 20 mg each	€ 118.88	€ 1.77	€ 0.00	€ 117.11	17.4	€ 81.51
Dimetindene IV 1 mg/10 kg = 6.9 mg	5 SFI 4 mg each	€ 26.24	€ 1.77	€ 6.92	€ 17.55	17.4	€ 122.15
Cimetidine IV 300 mg	10 AMP 200 mg each	€ 22.56	€ 1.77	€ 1.42	€ 19.37	17.4	€ 67.41

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-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 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

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

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

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with

regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

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

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic

indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a 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 unresectable or metastatic HR-positive and **HER2-negative (IHC 0)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

   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 unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **one** line of chemotherapy in the advanced setting

   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.

c) Adults with unresectable or metastatic HR-positive and **HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-)** breast cancer who have received endocrine therapy and **at least two** lines of chemotherapy in the advanced setting

   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.

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Datroway is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5 per cent (0.9%) of the total number of study participants according to the information provided by the pharmaceutical company.

The pharmaceutical company provide information on the four studies (TROPION-Breast01, TROPION-PanTumor01, TROPION-Lung01, TROPION-Lung05) and state the percentage of study participants at study sites within the scope of SGB V as 0.85% for across all relevant studies. This information is basically comprehensible. However, it is questionable whether the stated sample sizes (295 across all study sites, of which 0 at German study sites) in the TROPION-PanTumor01 study represent the status post recruitment. The pharmaceutical company stated the date for the "last patient in" as 14.09.2021 and for the "last patient first visit" as 07.10.2021. However, the registry entry[17] shows that the estimate of the number of subjects to be included was raised from 770 to 890 on 15.06.2023. In the event that recruitment for this study has not yet been completed and it is to be excluded accordingly, the percentage of study participants at study sites within the scope of SGB V is still less than 5%.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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 their session on 26 March 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 23 May 2025, the pharmaceutical company submitted a dossier for the benefit assessment of datopotamab 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 26 May 2025 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

[17] Daiichi Sankyo Germany. First-in-human Study of DS-1062a for Advanced Solid Tumours (TROPION-PanTumor01) [online]. 2025 [accessed: 18.08.2025]. URL: https://clinicaltrials.gov/study/NCT03401385.

new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient datopotamab deruxtecan.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 August 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 September 2025. The deadline for submitting statements was 22 September 2025.

The oral hearing was held on 6 October 2025.

By letter dated 7 October 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 31 October 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the Subcommittee on 11 November 2025, and the proposed draft resolution was approved.

At their session on 20 November 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 March 2025	Determination of the appropriate comparator therapy
Working group Section 35a	1 October 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 October 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 October 2025 5 November 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 November 2025	Concluding discussion of the draft resolution
Plenum	20 November 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 November 2025

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

Prof. Hecken