Justification

Gemeinsamer Bundesausschuss

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 Emtansine (New Therapeutic Indication: Adjuvant Treatment of Early Breast Cancer)

of 2 July 2020

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient combination trastuzumab emtansine (Kadcyla®) was listed for the first time on 1 January 2014 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 18 December 2019, trastuzumab emtansine received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 10 January 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient trastuzumab emtansine with the new therapeutic indication (adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 April 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of trastuzumab emtansine 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. In order to determine the extent of the additional benefit, the G-BA has assessed 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 emtansine.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 emtansine (Kadycla®) in accordance with the product information

Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined by the G-BA as follows:

Adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

Continuation of anti-HER2 directed therapy with trastuzumab initiated preoperatively

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In the therapeutic indication at hand, the following aromatase inhibitors have been approved: anastrozole, exemestane and letrozole, the anti-oestrogen tamoxifen, the GnRH analogues goserelin and leuprorelin, the cytostatic drugs cyclophosphamide, docetaxel, doxorubicin, epirubicin, 5-fluorouracil, methotrexate, paclitaxel and vincristine, and the HER-2 antibodies pertuzumab and trastuzumab.

Medicinal products with explicit approval for metastatic breast carcinoma were not considered as a comparator therapy.

On 2. In the therapeutic indication under consideration, other than treatment with pharmaceutical agents, radiotherapy is generally considered to be a suitable therapeutic measure.

On 3. Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Pertuzumab: Resolution of 20 December 2018

Guidelines:
Annex VI to Section K of the Pharmaceuticals Directive – Prescribability of authorised medicinal products in non-approved therapeutic indications (off-label use):
- Gemcitabine in monotherapy for breast cancer in women (not prescribable)

Directive for methods of examination and treatment in hospital settings of the Federal Joint Committee (directive on hospital treatment methods):
- proton therapy for breast carcinoma

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in this indication.

In line with national and international guidelines, patients with resectable HER2-positive early breast cancer can be treated with both neoadjuvant and adjuvant approaches. Both approaches are regarded as equally appropriate, particularly with respect to overall survival. In the context of this assessment of the appropriate comparator therapy in the therapeutic indication under consideration, it is assumed that patients have already completed neoadjuvant chemotherapy before surgical treatment and have also started anti-HER2 therapy. If this is the case, the guidelines consistently recommend postoperative continuation of anti-HER2 directed therapy with trastuzumab. Trastuzumab should be administered for a period of one year.

Adjuvant radiotherapy is not part of the appropriate comparator therapy; this has no bearing on whether it should be employed as patient-individual therapeutic option. In alignment with the recommendations in the guidelines, it is also assumed that patients with hormone receptor-positive disease should receive additional endocrine therapy.

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

2.1.3 Extent and probability of the additional benefit

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

An indication of a minor additional benefit has been established for treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

Justification:

The pharmaceutical company has presented the KATHERINE study as evidence of an additional benefit for trastuzumab emtansine. The KATHERINE study is an ongoing, open, controlled, randomised parallel group study. The study compares trastuzumab emtansine and trastuzumab.

The study was initiated in April 2013 and includes a total of 1,486 patients.

According to its inclusion criteria, the study examines adult patients with HER2-positive breast cancer with a pathologically proven residual disease in the breast or axillary lymph nodes that was detected in the resectate after surgery. Patients are required to have received appropriate pre-treatment or surgery before entering the study. This means they must have received neoadjuvant taxane-based chemotherapy and trastuzumab-based HER2-targeted therapy.

The study is being conducted in 28 countries worldwide.

The first data cut-off on 25 July 2018 was performed after 256 iDFS (invasive disease-free survival) events occurred. This data cut-off is used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival

In the KATHERINE study, overall survival is defined as the time from randomisation to death from any cause.
For the endpoint overall survival, there was no statistically significant difference between the treatment groups (hazard ratio: 0.70 [95 % confidence interval (CI): 0.47; 1.05]; p = 0.085). At this data cut-off point, the total number of events is relatively small: 5.7 % vs 7.5 % deaths. Further planned interim analyses and the final analysis of overall survival data from the ongoing study have yet to be completed.

The validity of the DFS endpoint as a surrogate for overall survival

For the mortality endpoint category, the pharmaceutical company submits data based on the results of the DFS endpoint. In its evaluation, the IQWiG concludes that the submitted validation study for DFS is not well-suited for validating DFS as a surrogate endpoint for overall survival in the present indication. Therefore, DFS is not considered to be a valid surrogate for overall survival in the benefit assessment.

Morbidity

Relapses / disease-free survival (DFS)

Patients who, after neoadjuvant taxane-based and HER2-targeted therapy, have invasive residual disease in the breast and/or lymph nodes detected in the resectate after surgery are treated curatively in the present therapeutic indication as part of adjuvant treatment. Tumour cells can remain and result in a relapse in the future. A relapse means that the attempt to cure the disease with the curative therapy approach was not successful. The occurrence of a relapse is patient-relevant.

The combined relapses endpoint comprises the following individual components:

- Invasive ipsilateral local recurrence in the breast
- Invasive ipsilateral regional recurrence in the breast
- Contralateral invasive breast cancer
- Secondary primary carcinoma
- Ductal carcinoma in situ (ipsilateral or contralateral)
- Distant recurrence

- Death from any cause

The relapses endpoint operationalised as relapse rate describes the proportion of patients with a relapse event or death at the corresponding data cut-off (event rate). In the DFS endpoint, the time to event (relapse or death) is also considered (time-to-event analysis).

Relapses (event rate)

For the relapse rate, a statistically significant difference to the benefit of trastuzumab emtansine exists compared with trastuzumab (relative risk [RR]: 0.59 [95 % CI: 0.47; 0.74]; $p < 0.001$). The extent of this effect is assessed as a significant improvement in therapy-relevant benefit. At the time of the data cut-off, 13.2 % of patients in the trastuzumab emtansine arm and 22.5 % of patients in the trastuzumab arm had experienced a relapse. The relapse rate endpoint comprises the same individual components and thus the same relapse events and deaths before relapse as other components, such as the DFS endpoint.

Disease-free survival (DFS)

Time-to-event analysis shows a clear and statistically significant positive effect for trastuzumab emtansine compared to trastuzumab (hazard ratio: 0.53 [95 % CI: 0.41; 0.68]; $p < 0.001$).

Regarding the results on relapses, trastuzumab emtansine is found to be associated with a marked positive effect compared to trastuzumab.

Symptomatology

In the KATHERINE study, the symptomatology was measured using the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23.

For the benefit assessment, the pharmaceutical company has presented responder analyses with a deterioration of ≥ 10 points for two different points in time: end of therapy and at 12-month follow-up. The IQWiG's evaluation of the dossier did not draw on the responder analyses at the 12-month follow-up, as a high percentage of patients (> 30 %) were not included in the analysis. Therefore, evaluations of the mean difference compared with baseline, based on an analysis with mixed models for repeated measurements (MMRM) were drawn on for the 12-month follow-up.

The group treated with trastuzumab emtansine showed statistically significant disadvantages in the endpoints "loss of appetite", "constipation" and "side effects of systemic therapy" at the end of therapy and at the time of the 12-month follow-up.

The endpoints "fatigue", "nausea and vomiting", "pain" and "symptoms in the area of the arm" also show statistically significant detrimental effects in the group treated with trastuzumab emtansine at the end of therapy. For the 12-month follow-up, no statistically significant differences were found for the endpoints "fatigue", "nausea and vomiting" and "pain".

The results for the 12-month follow-up showed significant differences: a detrimental effect for the endpoint "symptoms of the chest" and a beneficial effect for trastuzumab emtansine for the endpoint "diarrhoea".

However, for all statistically significant 12-month follow-up analyses, the Hedges´ g values calculated by the IQWiG are not completely outside the irrelevance range. Therefore, it cannot be concluded that the observed effects at the 12-month follow-up are relevant.

In overall consideration of the symptomatology endpoints, statistically significant disadvantages of treatment with trastuzumab emtansine exist at the end of therapy for the specified endpoints. These detrimental effects are only partially present at the 12-month follow-up. Although the findings from the 12-month follow-up cannot be drawn on to infer that the detrimental effects at this point in time are relevant, it can nevertheless be assumed that there are significant detrimental effects regarding symptomatology over the entire treatment

period. Overall, therefore, trastuzumab emtansine treatment is associated with a clear detriment regarding symptomatology compared to trastuzumab.

Health status (EQ-5D VAS)

In the KATHERINE study, health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The pharmaceutical company submits both consistent evaluations (difference in mean values from the start of the study) and responder analyses recording a deterioration of ≥ 10 points. For the latter, the pharmaceutical company employs a minimal important difference (MID) of ≥ 10 points.

The IQWIG's evaluation of the dossier draws on assessments of the mean difference. The responder analyses were not drawn on, as the study used to derive the MID (Pickard *et al.* 2007) was classified by the IQWIG as unsuitable to validate the MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID.

Due to the fact that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and due to the fact that the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status. For the 12-month follow-up, evaluations of the mean difference are presented, since a high percentage of patients (> 30 %) were not included in the responder analyses for the 12-month follow-up.

At the end of therapy, no statistically significant differences between the two treatment arms were found for the responder analyses. A statistically significant difference in mean values at the 12-month follow-up to the detriment of trastuzumab emtansine has been identified. Based on the Hedges' g values, it cannot be concluded that the observed effects at the 12-month follow-up are relevant.

Quality of life

Health-related quality of life was evaluated in the study using the functional scales and the scale recording global health-related quality of life employed by the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23.

At the end of therapy, the percentage of patients with a deterioration of ≥ 10 points is assessed. For the 12-month follow-up, evaluations of the mean difference were drawn on by means of an MMRM.

For the endpoints "physical functioning" and "social functioning", there were statistically significant disadvantages associated with the trastuzumab emtansine arm at the end of therapy and at the 12-month follow-up.

For the endpoints "role functioning" and "body image", the evaluation of the 12-month follow-up revealed statistically significant differences. For the "role functioning" endpoint, the difference is to the detriment of trastuzumab emtansine and for the "body image" endpoint it is to the benefit.

For the "global health status" endpoint no statistically significant difference between the treatment arms has been identified for the entire population.

However, for all statistically significant 12-month follow-up analyses, the Hedges´ g values are not completely outside the irrelevance range. Therefore, it cannot be concluded that the observed effects at the 12-month follow-up are relevant.

Although neither a benefit nor a detriment for trastuzumab emtansine can be established for the 12-month follow-up on the basis of the available results, detrimental effects on quality of life are nevertheless assumed for the treatment period.

Side effects

Total adverse events (AEs)

By the time of the first data cut-off, 98.8 % of patients in the trastuzumab emtansine arm and 93.3 % of patients in the trastuzumab arm had experienced an adverse event. The results are only presented as a supplement.

Serious adverse events (SAEs)

With regards to serious adverse events, there is a statistically significant difference to the detriment of trastuzumab emtansine compared with trastuzumab.

Severe adverse events (CTCAE grade ≥ 3)

Adverse events with a CTCAE grade ≥ 3 occurred statistically significantly more frequently in patients treated with trastuzumab emtansine.

Therapy discontinuations due to AEs

With regards to therapy discontinuations due to AEs, there is a statistically significant difference to the detriment of trastuzumab emtansine.

Specific AEs

Specific AEs were selected by the IQWiG based on frequency and differences between the treatment arms and taking into account patient relevance.

In detail, statistically significant differences to the detriment of trastuzumab emtansine have been established for platelet count decrease (PT, CTCAE grade ≥ 3), gastrointestinal disorders (SOC, CTCAE grade ≥ 3), peripheral sensory neuropathy (PT, CTCAE grade ≥ 3), infections and infestations (SOC, SAE), fatigue (PT), fever (PT), nausea (PT), constipation (PT), dry mouth (PT), stomatitis (PT), headache (PT), respiratory, thoracic and mediastinal disorders (SOC) and eye disorders (SOC).

In overall consideration of the results on side effects, a clear detriment for trastuzumab emtansine is established compared to trastuzumab. This detriment is apparent in the increase in the number of serious adverse events, severe adverse events with CTCAE grade of ≥ 3 and in the number of discontinuations of therapy due to adverse events, as well as in the detail of specific adverse events.

Overall assessment

To evaluate the additional benefit of trastuzumab emtansine, results on mortality (overall survival), morbidity, quality of life and side effects compared to the appropriate comparative therapy (trastuzumab) were presented from the open, controlled, randomised parallel group study KATHERINE.

Regarding mortality, the data on the overall survival endpoint are preliminary, and therefore no assessment of effectiveness can as yet be drawn for the overall survival endpoint category. Based on the available data, there is no statistically significant difference in overall survival between the study arms. Final analyses on the overall survival endpoint are pending. An additional benefit for trastuzumab emtansine is not proven for overall survival.

Regarding disease relapses, which are reported as relapse rate and DFS, trastuzumab emtansine is associated with statistically significantly fewer relapses than trastuzumab. The extent of this effect is assessed as a significant improvement in therapy-relevant benefit. The prevention of relapses is an essential therapeutic goal in the present curative therapy situation.

At the end of therapy and at the 12-month follow-up, treatment with trastuzumab emtansine has been shown to be associated with a detriment in symptomatology. Findings from the 12-month follow-up do not demonstrate that the established negative effects are relevant.

Nevertheless, significant adverse effects in symptomology can be assumed over the entire treatment period. For the general health status endpoint (measured by EQ-5D VAS), there are no adverse effects associated with trastuzumab emtansine.

With regards to patient quality of life, it can be assumed that trastuzumab emtansine is associated with adverse effects over the treatment period.

With regards to side effects, treatment with trastuzumab emtansine is associated with significant detriments, due to an increase in serious adverse events, severe adverse events (CTCAE-grade ≥ 3) and discontinuation of therapy due to adverse events. In detail, the specific adverse events assessed reveal disadvantages.

In an overall assessment of the findings on the patient-relevant endpoints, the clear benefit in the present adjuvant therapy situation, in particular relevant prevention of relapses, is counterbalanced by significant negative effects on symptomatology, quality of life and side effects. Against the background of an expectation for curative treatment of early breast cancer, the detriments associated with symptomatology, quality of life and side effects must be weighed against the benefits for the prevention of relapses.

Weighing up these factors, the G-BA concludes that trastuzumab emtansine is associated with minor additional benefit compared to trastuzumab in the adjuvant treatment of adult patients with HER2-positive early breast cancer with a high risk of relapse who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

Reliability of data (probability of additional benefit)

The present evaluation is based on findings from the open, controlled, randomised parallel group study KATHERINE, in which trastuzumab emtansine is compared with the appropriate comparative therapy trastuzumab.

The benefit assessment is based on the results of only one study, hence, at best, only indications of an additional benefit can be derived with regard to the reliability of data.

At study level, the risk of bias is considered to be low.

At the endpoint level, the risk of bias for the endpoints overall survival, relapses, DFS, SAEs and severe AEs (CTCAE-grade ≥ 3) is estimated to be low.

In view of the overall low risk of bias at study and endpoint levels, the established additional benefit is classified as an “indication” for an additional benefit.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the present resolution on the benefit assessment of trastuzumab emtansine finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V, according to which the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V:

The presented findings on overall survival and relapses are based on the primary data cut-off of 25 July 2018 from the KATHERINE study, which was performed after the occurrence of 256 predefined iDFS events. At the time of the primary data cut-off, the median observed period for overall survival and relapses was approximately 3.4 years. Due to the low number of events recorded for overall survival, this finding is limited in its validity. The KATHERINE study plans collection of final overall survival data after 367 deaths or after 10 years of follow-up.

The pharmaceutical company is required to submit final data on overall survival to the European Medicines Agency (EMA) on 30 June 2024.

As the final data on overall survival from the KATHERINE study are expected to be relevant for assessing the benefits of the medicinal product, limiting the period of validity of the present resolution is justifiable.

Conditions of the limitation:

A renewed benefit assessment once the limitation deadline has expired will require submission of a dossier presenting all the endpoint results relevant to demonstrating an additional benefit from the ongoing KATHERINE study.

A limitation of the resolution until 30 September 2024 is considered to be appropriate.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, number 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product trastuzumab emtansine shall recommence when the period of limitation has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of trastuzumab emtansine in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). The possibility that a benefit assessment for the medicinal product trastuzumab emtansine can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Numbers 2–4 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient trastuzumab emtansine.

The therapeutic indication assessed here is as follows: trastuzumab emtansine, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.

The appropriate comparator therapy was determined by the G-BA as follows:

Continuation of anti-HER2 directed therapy with trastuzumab initiated preoperatively.

The pharmaceutical company has presented findings from the ongoing, open, controlled, randomised parallel group study KATHERINE, in which trastuzumab emtansine is compared to trastuzumab.

With regards to mortality, the available findings, based on an overall low number of events, do not reveal a statistically significant effect on the overall survival endpoint. Final data on overall survival are still pending.

Trastuzumab emtansine is associated with a clear benefit in prevention of relapses compared to trastuzumab. The prevention of relapses is an essential therapeutic goal in the present curative therapy situation.

With regards to symptomatology, a clear detriment for treatment with trastuzumab emtansine has been identified.

Trastuzumab emtansine treatment is associated with adverse effects on health-related quality of life.

With regards to side effects, an increase in serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation of therapy due to adverse events was observed with trastuzumab emtansine.

Due to the low number of events, there are uncertainties when interpreting the results on overall survival.

In an overall assessment of the findings, the clear benefit in prevention of relapses is counterbalanced by significant negative effects on symptoms, quality of life and side effects. The disadvantages are weighted against the background of the curative therapy claim.

Overall, there is an indication of a minor additional benefit for trastuzumab emtansine compared with trastuzumab.

The resolution is limited until 30 September 2024.

For the renewed benefit assessment after the expiration of the limitation, the dossier to demonstrate an additional benefit should include the results expected in 2024 from the final analysis on overall survival and other patient-relevant outcomes from the KATHERINE study.

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

approx. 1,980 patients

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The procedure of the pharmaceutical company is in part mathematically and methodically plausible. However, it should be noted that the patient numbers presented are an underestimate. This is due to the very small sample size used to determine the non-pCR rate.

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 Kadcyla® (active ingredient: trastuzumab emtansine) at the following publicly accessible link (last access: 10 March 2020):

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

Treatment with trastuzumab emtansine should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with breast cancer.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on trastuzumab emtansine:

- Information for healthcare professionals

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 June 2020).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number

of treatments/patient/year", time between individual treatments, and for the maximum treatment duration if specified in the product information. Use of trastuzumab emtansine as a single agent for adjuvant treatment in adult patients with HER2-positive early breast cancer is limited to 14 cycles.

Dosage recommendations refer to use in women, as breast cancer is relatively rare in men. For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average body weight adult women: 68.7 kg)[2].

Treatment duration:

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 emtansine	1 × every 21 days	14	1	14
Appropriate comparator therapy				
Trastuzumab	1 × every 21 days	17.4	1	17.4

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Trastuzumab emtansine	3.6 mg/kg = 247.32 mg	247.32 mg	1 × 100 mg + 1 × 160 mg	14	14 × 100 mg + 14 × 160 mg
Appropriate comparator therapy					
Trastuzumab IV	8 mg/kg = 549.6 mg	549.6 mg	1 × 420 mg + 1 × 150 mg	1	1 × 420 mg + 1 × 150 mg
	6 mg/kg = 412.2 mg	412.2 mg	1 × 420 mg	16.4	16.4 × 420 mg

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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 emtansine 100 mg	1 PIS	€ 2,038.09	€ 1.77	€ 113.12	€ 1,923.20
Trastuzumab emtansine 160 mg	1 PIS	€ 3,226.52	€ 1.77	€ 180.99	€ 3,043.76
Appropriate comparator therapy					
Trastuzumab 420 mg IV	1 PIS	€ 2,134.05	€ 1.77	€ 118.60	€ 2,013.68
Trastuzumab 150 mg IV	1 PIS	€ 776.08	€ 1.77	€ 42.36	€ 731.95
Abbreviations: PIS = powder for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 2020

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 assessed 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 standard expenditure in the course of the treatment are not shown.

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

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

4. Process sequence

At its session on 29 January 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 4 December 2019, the working group Section 35a reviewed the appropriate comparator therapy.

On 10 January 2020, the pharmaceutical company submitted a dossier for the benefit assessment of trastuzumab emtansine to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 2 VerfO.

By letter dated 14 January 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 emtansine.

The dossier assessment by the IQWiG was submitted to the G-BA on 14 April 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 April 2020. The deadline for submitting written statements was 6 May 2020.

The oral hearing was held on 26 May 2020.

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 were discussed at the session of the subcommittee on 23 June 2020, and the proposed resolution was approved.

On 2 July 2020, the Federal Joint Committee resolved by written statement to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	29 January 2019	Determination of the appropriate comparator therapy
Working group Section 35a	4 December 2019	Review of the appropriate comparator therapy
Working group Section 35a	19 May 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	26 May 2020	Conduct of the oral hearing
Working group Section 35a	4 June 2020 16 June 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	23 June 2020	Concluding discussion of the draft resolution
Plenum	2 July 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 July 2020

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

Prof. Hecken