Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Abemaciclib (new therapeutic indication: breast cancer, HR+, HER2-, early at high risk of recurrence, adjuvant treatment, combination with endocrine therapy)

of 20 October 2022

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 the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient abemaciclib (Verzenios) was listed for the first time on 1 November 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 1 April 2022, abemaciclib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products (OJ L 334 of 12.12.2008, p. 7).

On 26 April 2022, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction

with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient abemaciclib with the new therapeutic indication (in combination with an endocrine therapy for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence).

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

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

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

2.1.1 Approved therapeutic indication of Abemaciclib (Verzenios) in accordance with the product information

Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence.

In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Therapeutic indication of the resolution (resolution of 20.10.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Premenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

Appropriate comparator therapy for abemaciclib in combination with an endocrine therapy:

- Tamoxifen (if necessary, in addition with cessation of ovarian function)

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

a2) Postmenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

Appropriate comparator therapy for abemaciclib in combination with an endocrine therapy:

- an aromatase inhibitor (anastrozole or letrozole) alone, or, if necessary, tamoxifen if aromatase inhibitors are unsuitable,

  or

- an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen

a3) Men with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

Appropriate comparator therapy for abemaciclib in combination with an endocrine therapy:

- Tamoxifen

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

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

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

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

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

On 1. In addition to abemaciclib, the active ingredients tamoxifen, anastrozole, exemestane and letrozole, leuprorelin, goserelin and triptorelin cyclophosphamide, docetaxel,

doxorubicin, epirubicin, fluorouracil, methotrexate, paclitaxel and vincristine are approved for the present therapeutic indication.

Medicinal products with explicit marketing authorisation for hormone receptor (HR)-negative breast cancer, HER2-positive breast cancer and advanced metastatic breast cancer were not considered.

On 2. In the present therapeutic indication, a radiotherapy is considered as non-medicinal treatment.

Adjuvant radiotherapy has a high significance in the present therapeutic indication, especially in case of a high risk of recurrence. Adjuvant radiotherapy can be given sequentially or in parallel with endocrine therapy. It is assumed that the patients have received prior radiotherapy. An adjuvant radiotherapy is therefore not part of the appropriate comparator therapy.

On 3. Guideline on examination and treatment methods in the hospital (guideline on inpatient treatment methods), entered into force on 20 March 2019

- Proton therapy for breast cancer

Annex VI to Section K of the Pharmaceuticals Directive - Active ingredients that cannot be prescribed in applications beyond the scope of the marketing authorisation (off-label use):

- Gemcitabine in monotherapy for breast cancer in women

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 therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

Based on this information, a differentiation was made according to menopausal status when determining the appropriate comparator therapy, as pre- and postmenopausal women differ physiologically as well as pathophysiologically, e.g., in the course of the disease and the symptom burden. In addition, there are separate therapy recommendations for both groups in the guidelines.

In addition, for the present therapeutic indication, it was assumed that adjuvant chemotherapy - if indicated - has been completed.

Premenopausal women

In the adjuvant treatment of hormone receptor (HR)-positive breast cancer in premenopausal women, tamoxifen is the standard. The available evidence based on meta-analyses does not show a clear additional therapeutic benefit for the additional cessation of ovarian function. However, the guidelines recommend additional

cessation of ovarian function for the group of patients with an increased risk of recurrence. This recommendation is made in the guidelines with low strength of recommendation, but is unanimous. Against the background that the present therapeutic indication explicitly includes patients with a high risk of recurrence, it is stated that, in addition to tamoxifen, cessation of ovarian function is included in the appropriate comparator therapy, if necessary.

Furthermore, the active ingredient triptorelin - a GnRH analogue - is approved in combination with an aromatase inhibitor in premenopausal women at high risk of recurrence. However, this treatment option clearly does not have the same significance as tamoxifen. In the German S3 guideline, triptorelin in combination with an aromatase inhibitor is recommended with only a low level of recommendation and is not mentioned at all in other guidelines. Therefore, this treatment option is not determined as a component of the appropriate comparator therapy.

Postmenopausal women

Aromatase inhibitors have a high significance in the adjuvant treatment of hormone receptor (HR)-positive breast cancer in postmenopausal women. For these active ingredients, there is extensive evidence at the level of systematic reviews as well as clear recommendations in guidelines. There is a marketing authorisation for the two non-steroidal aromatase inhibitors anastrozole and letrozole for the treatment of postmenopausal women. The steroidal aromatase inhibitor exemestane is only approved after progression under anti-oestrogen treatment and is therefore not considered for initial adjuvant treatment as an appropriate comparator therapy. In case of intolerance to an aromatase inhibitor, tamoxifen is the recommended alternative for (further) adjuvant treatment.

In addition to sole treatment with an aromatase inhibitor (anastrozole or letrozole), or with tamoxifen if aromatase inhibitors are unsuitable, sequential treatment with initial tamoxifen followed by an aromatase inhibitor ("switch therapy") is another option. The aromatase inhibitors anastrozole and exemestane are approved for this purpose after 2-3 years of initial adjuvant treatment with tamoxifen. The aromatase inhibitor letrozole is approved 5 years after prior completed tamoxifen treatment ("extended adjuvant treatment"). This option with letrozole also has relatively weak evidence of benefit, especially considering IQWiG's report[2], and is also less strongly recommended in the guidelines. Therefore, sequential treatment with tamoxifen followed by letrozole is not included in the appropriate comparator therapy. In addition, reverse sequential treatment - initially an aromatase inhibitor followed by tamoxifen - is not included in the appropriate comparator therapy as the evidence for this option, relative to the other options, is of less significance.

Men

[2] Institute for Quality and Efficiency in Health Care (IQWiG). Aromatase inhibitors in female breast cancer; final report; mandate A10-03. [online]. Cologne (GER): IQWiG; 2016. [Accessed: 08.05.2019]. (IQWiG Reports; Volume 437) URL: https://www.iqwig.de/download/A10-03_Abschlussbericht_Aromatasehemmer-beim-Mammakarzinom.pdf

Male breast cancer is a very rare disease; the incidence is about 0.5 - 1% of all diagnosed breast cancers. The evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men with breast cancer are predominantly based on the recommendations for the treatment of women. Aromatase inhibitors are only recommended for men with contraindications. The guidelines primarily recommend therapy with tamoxifen for men.

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

2.1.3 Extent and probability of the additional benefit

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

a1) Premenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

Hint for a minor additional benefit

a2) Postmenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

An additional benefit is not proven.

a3) Men with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

An additional benefit is not proven.

Justification:

For the evidence of additional benefit, the pharmaceutical company has submitted in the dossier the results of the still ongoing, open-label, randomised controlled trial MONARCH-E, in which abemaciclib in combination with standard endocrine therapy is compared with standard endocrine therapy.

Patients with node-positive, HR-positive, HER2-negative, definitely resected early-stage breast cancer without distant metastases and at a high risk of recurrence were enrolled in the study. The MONARCH-E study is divided into 2 cohorts. In cohort 1, high risk of recurrence is defined as ≥ 4 positive axillary lymph nodes (pALN) or 1 to 3 pALN in the presence of an additional grade 3 tumour and/or a tumour size of ≥ 5 cm (corresponding to stage IIA to IIIC at diagnosis). In cohort 2, a high risk of recurrence was determined primarily on the basis of the proliferation marker Ki-67. The definition of a high risk of recurrence for cohort 1 is considered adequate for the benefit assessment. Cohort 2 is not considered relevant for the

benefit assessment as the marketing authorisation was granted solely on the basis of the results for cohort 1.

Cohort 1 included a total of 5,120 patients who were randomised in a 1:1 ratio according to previous treatment (neoadjuvant chemotherapy vs adjuvant chemotherapy vs no chemotherapy), menopausal status (premenopausal vs postmenopausal), region (North America and Europe vs Asia vs others) to the intervention arm (N = 2555) and the comparator arm (N = 2565).

In both study arms, patients received standard adjuvant endocrine therapy according to the doctor's instructions. Only patients who received an endocrine therapy corresponding to the appropriate comparator therapy for the entire duration of the study were included in the benefit assessment. This corresponded to 1,088 premenopausal women (553 patients in the intervention arm and 535 patients in the comparator arm), 2,548 postmenopausal women (1,283 patients in the intervention arm and 1,265 patients in the comparator arm) and 19 men (10 patients in the intervention arm and 9 patients in the comparator arm).

The currently ongoing study is being conducted at 611 study sites in Asia, Australia, Europe, North America and South America. The primary endpoint of the study is invasive disease-free survival (IDFS, hereafter also referred to as recurrences). Relevant secondary endpoints are overall survival, symptoms, health-related quality of life, and adverse events (AE).

At the time of the benefit assessment, 4 data cut-offs were available:

- 1st data cut-off from 27.09.2019: planned interim analysis after 195 invasive disease-free survival events (IDFS events)
- 2nd data cut-off from 16.03.2020: planned interim analysis after 293 IDFS events
- 3rd data cut-off from 08.07.2020: planned final IDFS analysis after 390 IDFS events
- 4th data cut-off from 01.04.2021: post hoc interim analysis on overall survival required by the regulatory authorities

For the present benefit assessment, the results of the 4th data cut-off from 01.04.2021 are used, which is a post-hoc interim analysis on overall survival required by the regulatory authorities.

a1) Premenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

Mortality

Overall survival was defined in the MONARCH-E study as the time between randomisation and death from any cause.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment groups. At the time of the 4th data cut-off, 17 patients in the intervention arm and 11 patients in the comparator arm had died.

Morbidity

Recurrences (recurrence rate and disease-free survival)

The patients in the present therapeutic indication are treated with a curative therapy approach: adjuvant therapy after complete resection of the primary tumours and possibly affected lymph nodes. The remaining tumour cells can cause a recurrence in the further course. Recurrence means that the attempt at a cure by the curative therapeutic approach was unsuccessful. The occurrence of a recurrence is patient-relevant.

The combined endpoint recurrences include the following individual components:

- Local breast cancer recurrence
- Regional recurrence of invasive breast cancer
- Remote recurrence
- Contralateral invasive breast cancer
- Secondary primary cancer (not breast cancer)
- Death of any cause without previous recurrence

For the present assessment, the results of the operationalisations as the percentage of patients with recurrence (recurrence rate) and as disease-free survival are used for the endpoint of recurrence.

For the endpoint of recurrence, for the endpoint component of recurrence rate as well as for the endpoint component of disease-free survival, there was a statistically significant difference in each case to the advantage of abemaciclib in combination with endocrine therapy compared to endocrine therapy.

In the analysis of both endpoint components, a relevant advantage with regard to the avoidance of recurrences is determined overall for abemaciclib in combination with endocrine therapy.

Symptomatology (FACIT fatigue)

In the MONARCH-E study, the endpoint of fatigue was assessed using the validated survey instrument FACIT fatigue.

In the dossier, the pharmaceutical company submitted analyses using a mixed model for repeated measures (MMRM) on the course and change from baseline. In doing so, the pharmaceutical company assigned values that were collected at different times from randomisation to constructed time points. These time points were referred to as 30-day, 6-month and 12-month follow-up. The actual observation time point per patient is determined

by the individual time of the end of treatment plus the respective follow-up time (of 30 days, 6 months and 12 months) and not by the time period from the start of the study, so that there were no uniform evaluation times for all patients from the start of the study. These constructed time points, fixed relative to the end of treatment, can differ both within a treatment arm and between treatment arms, so the required equivalence of evaluation time points between arms was no longer given. Furthermore, no information was available in the dossier on the total number of patients included in the MMRM analyses.

As part of the written statement procedure, the pharmaceutical company submitted evaluations in which the follow-up observations for patients with premature therapy discontinuation were assigned to a visit if they could be assigned in a corresponding, undisclosed time frame according to the occurrence after randomisation. In addition, the pharmaceutical company stated in the written statement procedure that the numbers of patients with values at baseline given in the results tables correspond to the total number of patients who contributed data to the MMRM analyses.

As a result, there was a statistically significant difference in the endpoint of symptomatology, measured by FACIT fatigue, to the disadvantage of abemaciclib in combination with endocrine therapy. However, the 95% CI of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2 in each case. Thus, it cannot be inferred that the observed effect is relevant.

Health status (EQ-5D, visual analogue scale)

Health status was assessed in the MONARCH-E study using the EQ-5D visual analogue scale.

In the dossier, the pharmaceutical company presented MMRM analyses for the endpoint of health status - as outlined above for the endpoint of symptomatology (FACIT fatigue) - on the course and change from baseline, which were based on constructed evaluation time points, and did not provide information on the total number of patients included in the MMRM analyses.

As part of the written statement procedure, the pharmaceutical company submitted MMRM analyses with assignment of the follow-up observations for patients with therapy discontinuation to the visit at the relevant time. It also stated that the number of patients with values at the baseline reported in the results tables corresponds to the total number of patients included in the MMRM analyses.

As a result, for the endpoint of health status, assessed by means of the EQ-5D VAS, there was no statistically significant difference between the treatment groups.

In summary, in the endpoint category of morbidity, there is an advantage of abemaciclib in combination with endocrine therapy in the avoidance of recurrences. With regard to symptomatology, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effect is relevant. For health status, there is neither an advantage nor a disadvantage of abemaciclib in combination with endocrine therapy.

Quality of life

Functional Assessment of Cancer Therapy – Breast (FACT-B)

Health-related quality of life is assessed in the study using, among other things, the disease-specific FACT-B[3] questionnaire. The FACT-B questionnaire consists of the cross-tumour disease questionnaire (FACT-G[4]) and a breast cancer-specific subscale (BCS[5]). Only the FACT-B total score is included in the assessment of the additional benefit as it comprehensively considers the data on the health-related quality of life of the patients. The FACT-G questionnaire is therefore only presented additionally.

In the dossier, the pharmaceutical company presented MMRM analyses for the endpoint of health-related quality of life, assessed by means of the FACT-B questionnaire - as outlined above for the endpoint of symptomatology (FACIT fatigue) - on the course and change from baseline, which were based on constructed evaluation time points, and did not provide any information on the total number of patients included in the MMRM analyses.

As part of the written statement procedure, the pharmaceutical company submitted MMRM analyses with assignment of the follow-up observations for patients with therapy discontinuation to the visit at the relevant time. It also stated that the number of patients with values at the baseline reported in the results tables corresponds to the total number of patients included in the MMRM analyses.

As a result, for the endpoint of health-related quality of life, assessed using the FACT-B, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, the 95% CI of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

In summary, in the quality of life category, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effect is relevant.

Side effects

Adverse events (AEs)

In the MONARCH-E study, an adverse event occurred in 98.2% of premenopausal patients in the intervention arm and 86.9% thereof in the comparator arm. The results were only presented additionally.

[3] Functional Assessment of Cancer Therapy – Breast

[4] Functional Assessment of Cancer Therapy – General

[5] Breast Cancer Subscale

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

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, there was a statistically significant disadvantage of abemaciclib in combination with endocrine therapy compared to endocrine therapy alone.

Specific adverse events

For the specific AEs of neutropenia (severe AEs), general disorders and administration site conditions (AEs), eye disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), gastrointestinal disorders (AEs), diarrhoea (severe AEs), skin and subcutaneous tissue disorders (AEs), blood and lymphatic system disorders (severe AEs) and hepatic events (severe AEs), there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy.

In summary, due to the disadvantages in the endpoints of SAEs, severe AEs and discontinuation due to AEs, a significant overall disadvantage in side effects can be determined for treatment with abemaciclib in combination with endocrine therapy . With regard to specific adverse events, there were in detail disadvantages of abemaciclib in combination with an endocrine therapy.

Overall assessment

For the benefit assessment of abemaciclib in combination with endocrine therapy for the treatment of hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence in premenopausal patients, results of the still ongoing, open-label, randomised controlled trial MONARCH-E are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

In the endpoint category of mortality, the present results for the endpoint of overall survival show no statistically significant difference between the study arms. Only small numbers of events are available for the endpoint of overall survival.

In the morbidity category, the endpoint of recurrence, expressed as recurrence rate and disease-free survival, shows statistically significantly fewer recurrences for patients treated with abemaciclib in combination with endocrine therapy. In the present adjuvant treatment setting, the avoidance of recurrences is a specially relevant therapeutic goal.

With regard to symptomatology, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effect is relevant. For health status, there is neither an advantage nor a disadvantage of abemaciclib in combination with endocrine therapy.

In the quality of life category, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effect is relevant.

With regard to side effects, there are statistically significant disadvantages for the endpoints of serious adverse events (SAEs), severe adverse events (AE) and discontinuation due to AEs for treatment with abemaciclib in combination with an endocrine therapy and in detail also for the specific AEs.

In the overall analysis, the relevant advantage with regard to the avoidance of recurrences is offset by significant disadvantages in terms of side effects. The disadvantages in terms of side effects are weighted against the background that the avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

In a weighing decision, the G-BA comes to the conclusion that the advantage of recurrences outweighs the disadvantages of side effects and that overall there is a moderate and not only minor improvement in the therapy-relevant benefit. Abemaciclib in combination with endocrine therapy is therefore found to be of minor additional benefit compared to sole endocrine therapy in the adjuvant treatment of premenopausal patients with HER2-positive early breast cancer at high risk of recurrence.

Reliability of data (probability of additional benefit)

The underlying MONARCH-E study is a randomised, controlled, open-label study.

The risk of bias across endpoints is rated high for the sub-population of premenopausal patients, as a significant percentage (14.3%) of premenopausal patients were not included in the analyses because the patients concerned switched to an endocrine therapy that did not correspond to the appropriate comparator therapy during the study.

In addition, the significance of the available results on the endpoint of recurrence is limited in the present treatment setting, as the median duration of observation in the study is only approx. 28 months.

Thus, the reliability of data for the additional benefit determined is classified in the category "hint" overall.

a2) Postmenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

Mortality

Overall survival was defined in the MONARCH-E study as the time between randomisation and death from any cause.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment groups. At the time of the 4th data cut-off, 54 patients in the intervention arm and 58 patients in the comparator arm had died.

Morbidity

Recurrences

The patients in the present therapeutic indication are treated with a curative therapy approach: adjuvant therapy after complete resection of the primary tumours and possibly affected lymph nodes. The remaining tumour cells can cause a recurrence in the further course. Recurrence means that the attempt at a cure by the curative therapeutic approach was unsuccessful. The occurrence of a recurrence is patient-relevant.

The combined endpoint recurrences include the following individual components:

- Local breast cancer recurrence
- Regional recurrence of invasive breast cancer
- Remote recurrence
- Contralateral invasive breast cancer
- Secondary primary cancer (not breast cancer)
- Death of any cause without previous recurrence

For the present assessment, the results of the operationalisations as the percentage of patients with recurrence (recurrence rate) and as disease-free survival are used for the endpoint of recurrence.

For the endpoint of recurrence, for the endpoint component of recurrence rate as well as for the endpoint component of disease-free survival, there was a statistically significant difference in each case to the advantage of abemaciclib in combination with endocrine therapy compared to endocrine therapy.

In the consideration of both endpoint components, an overall advantage with regard to the avoidance of recurrences is found for abemaciclib in combination with endocrine therapy.

Symptomatology (FACIT fatigue)

In the MONARCH-E study, the endpoint of fatigue was assessed using the validated survey instrument FACIT fatigue.

In the dossier, the pharmaceutical company submitted analyses using a mixed model for repeated measures (MMRM) on the course and change from baseline. In doing so, the pharmaceutical company assigned values that were collected at different times from randomisation to constructed time points. These time points were referred to as 30-day, 6-month and 12-month follow-up. The actual observation time point per patient is determined by the individual time of the end of treatment plus the respective follow-up time (of 30 days, 6 months and 12 months) and not by the time period from the start of the study, so that there were no uniform evaluation times for all patients from the start of the study. These constructed time points, fixed relative to the end of treatment, can differ both within a treatment arm and between treatment arms, so the required equivalence of evaluation time points between arms was no longer given. Furthermore, no information was available in the dossier on the total number of patients included in the MMRM analyses.

As part of the written statement procedure, the pharmaceutical company submitted evaluations in which the follow-up observations for patients with premature therapy discontinuation were assigned to a visit if they could be assigned in a corresponding, undisclosed time frame according to the occurrence after randomisation. In addition, the pharmaceutical company stated in the written statement procedure that the numbers of

patients with values at baseline given in the results tables correspond to the total number of patients who contributed data to the MMRM analyses.

As a result, there was a statistically significant difference in the endpoint of symptomatology, measured by FACIT fatigue, to the disadvantage of abemaciclib in combination with endocrine therapy. However, the 95% CI of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2 in each case. Thus, it cannot be inferred that the observed effect is relevant.

Health status (EQ-5D, visual analogue scale)

Health status was assessed in the MONARCH-E study using the EQ-5D visual analogue scale.

In the dossier, the pharmaceutical company presented MMRM analyses for the endpoint of health status - as outlined above for the endpoint of symptomatology (FACIT fatigue) - on the course and change from baseline, which were based on constructed evaluation time points, and did not provide information on the total number of patients included in the MMRM analyses.

As part of the written statement procedure, the pharmaceutical company submitted MMRM analyses with assignment of the follow-up observations for patients with therapy discontinuation to the visit at the relevant time. It also stated that the number of patients with values at the baseline reported in the results tables corresponds to the total number of patients included in the MMRM analyses.

The result shows a statistically significant difference in the endpoint of health status, measured by the EQ-5D VAS, to the disadvantage of abemaciclib in combination with endocrine therapy. However, the 95% CI of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2 in each case. Thus, it cannot be inferred that the observed effect is relevant.

In summary, in the endpoint category of morbidity, there is an advantage of abemaciclib in combination with endocrine therapy in the avoidance of recurrences. With regard to symptomatology and health status, there are statistically significant differences to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effects are relevant.

Quality of life

Functional Assessment of Cancer Therapy – Breast (FACT-B)

Health-related quality of life is assessed in the study using, among other things, the disease-specific FACT-B questionnaire. The FACT-B questionnaire consists of the cross-tumour disease questionnaire (FACT-G[4]) and a breast cancer-specific subscale (BCS[5]). Only the FACT-B total score is included in the assessment of the additional benefit as it comprehensively considers the data on the health-related quality of life of the patients. The FACT-G questionnaire is therefore only presented additionally.

In the dossier, the pharmaceutical company presented MMRM analyses for the endpoint of health-related quality of life, assessed by means of the FACT-B questionnaire - as outlined above for the endpoint of symptomatology (FACIT fatigue) - on the course and change from baseline, which were based on constructed evaluation time points, and did not provide any information on the total number of patients included in the MMRM analyses.

As part of the written statement procedure, the pharmaceutical company submitted MMRM analyses with assignment of the follow-up observations for patients with therapy discontinuation to the visit at the relevant time. It also stated that the number of patients with values at the baseline reported in the results tables corresponds to the total number of patients included in the MMRM analyses.

As a result, for the endpoint of health-related quality of life, assessed using the FACT-B, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, the 95% CI of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

In summary, in the quality of life category, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effect is relevant.

Side effects

Adverse events (AEs)

In the MONARCH-E study, an adverse event occurred in 98.2% of postmenopausal patients in the intervention arm and 88.5% thereof in the comparator arm. The results were only presented additionally.

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

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, there was a statistically significant disadvantage of abemaciclib in combination with endocrine therapy compared to endocrine therapy alone.

Specific adverse events

For the specific AEs of neutropenia (severe AEs), alopecia (AEs), dizziness (AEs), eye disorders (AEs), gastrointestinal disorders (AEs), diarrhoea (severe AEs), fatigue (severe AEs), hypocalcaemia (severe AEs), blood and lymphatic system disorders (severe AEs), and hepatic events (severe AEs) and interstitial lung disease (ILD)/ pneumonitis (SAE), there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy.

For the endpoint of venous thromboembolism (severe AEs), there is a significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. For this endpoint, there is an effect modification due to the age characteristic. There is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy only in patients ≥ 65 years. In patients < 65 years, there is no statistically significant difference between the treatment groups.

For the endpoint of arthralgia (AEs), there is a significant difference in favour of abemaciclib in combination with endocrine therapy.

In summary, due to the disadvantages in the endpoints of SAEs, severe AEs and discontinuation due to AEs, a significant overall disadvantage in side effects can be identified for treatment with abemaciclib in combination with endocrine therapy. With regard to specific

adverse events, there are, in detail, predominantly disadvantages of abemaciclib in combination with an endocrine therapy.

Overall assessment

For the benefit assessment of abemaciclib in combination with endocrine therapy for the treatment of hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence in postmenopausal patients, results of the still ongoing, open-label, randomised controlled trial MONARCH-E are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects.

In the endpoint category of mortality, the present results for the endpoint of overall survival show no statistically significant difference between the study arms. Only small numbers of events are available for the endpoint of overall survival.

In the morbidity category, the endpoint of recurrence, expressed as recurrence rate and disease-free survival, shows statistically significantly fewer recurrences for patients treated with abemaciclib in combination with endocrine therapy. In the present adjuvant treatment setting, the avoidance of recurrences is a specially relevant therapeutic goal.

With regard to symptomatology and health status, there are statistically significant differences to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effects are relevant.

In the quality of life category, there is a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. However, it cannot be inferred that the observed effect is relevant.

With regard to side effects, there are statistically significant disadvantages for the endpoints of serious adverse events (SAEs), severe adverse events (AE) and discontinuation due to AEs for treatment with abemaciclib in combination with an endocrine therapy and in detail also predominantly for the specific AEs.

In the overall analysis, the advantage with regard to the avoidance of recurrences is offset by significant disadvantages in terms of side effects. The disadvantages in terms of side effects are weighted against the background that the avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

In a weighing decision, the G-BA comes to the conclusion, against the background of the observed effect intensity for the endpoint of recurrence, that the significant disadvantages of the side effects question the advantage of the endpoint of recurrence. It was taken into account that the significance of the available results on the endpoint of recurrence is limited in the present treatment setting, as the median duration of observation in the study is only approx. 28 months.

Thus, overall, it is concluded that there is no evidence of additional benefit of abemaciclib in combination with endocrine therapy compared to endocrine therapy alone in the adjuvant treatment of postmenopausal patients with HER2-positive early breast cancer at high risk of recurrence.

a3) Men with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

No interpretable data are available to assess the additional benefit of abemaciclib in combination with endocrine therapy compared with the appropriate comparator therapy in men with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence.

The pharmaceutical company presented results on a total of 19 patients, of which 10 patients were treated with abemaciclib in combination with endocrine therapy and 9 patients with endocrine therapy. Thus, there is no sufficient data basis to assess the additional benefit.

2.1.4 Limitation of the period of validity of the resolution

a1) Premenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

and

a2) Postmenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

The limitation of the period of validity of the resolution on the benefit assessment of abemaciclib (in combination with endocrine therapy) finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present 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 significance of the results for the endpoint of overall survival and for the endpoint of recurrence is limited, as the median duration of observation in the MONARCH-E study at the time of the 4th data cut-off of 1 April 2021 was only 28 months.

Further interim analyses of overall survival are planned 2 and 3 years after final invasive disease-free survival (IDFS) analysis. The final analysis of overall survival is planned after 650 events or 10 years after randomisation of the last patient, whichever comes first.

Since further clinical data from the MONARCH-E study are expected, which may be relevant for the assessment of the benefits of the medicinal product, it is justified to limit the validity of the present resolution.

Conditions of the limitation:

For the renewed benefit assessment of abemaciclib in combination with endocrine therapy after the deadline, the results on all patient-relevant endpoints from the MORNACH-E study, in particular on overall survival and recurrences, must be presented in the dossier at the final data cut-off, differentiated according to sub-populations a1 and a2.

For this purpose, the G-BA considers a limitation for the resolution until 01.07.2025 to be appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 No. 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product abemaciclib in combination with endocrine therapy recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove an additional benefit of abemaciclib in combination with endocrine therapy in comparison with the appropriate comparator therapy (Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product abemaciclib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 to 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient abemaciclib in combination with endocrine therapy. The therapeutic indication assessed here is as follows:

Abemaciclib in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive early-stage breast cancer at high risk of recurrence. In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

In the therapeutic indication to be considered, three patient groups were distinguished:

a1) Premenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

The G-BA determined tamoxifen (if necessary, additionally with cessation of ovarian function) to be the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the RCT MONARCH-E, in which abemaciclib + endocrine therapy was compared with endocrine therapy alone. Only patients in whom the appropriate comparator therapy was adequately implemented were considered in the assessment.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment groups.

For the endpoint of recurrence, presented as recurrence rate and disease-free survival, there are statistically significantly fewer recurrences for abemaciclib + endocrine therapy.

With regard to symptomatology and quality of life, there are statistically significant differences to the disadvantage of abemaciclib + endocrine therapy. However, it cannot be inferred that the observed effects are relevant. There is neither an advantage nor a disadvantage for the endpoint of health status.

The relevant advantage in recurrence is offset by significant disadvantages of abemaciclib + endocrine therapy in the category of side effects, particularly in the endpoints of serious adverse events (SAEs), severe adverse events (AEs, CTCAE grade ≥ 3) and discontinuation due

to AEs, which, however, do not fundamentally call into question the advantages in the endpoint of recurrence against the background of the essential importance of avoiding recurrences in the curative treatment setting.

The risk of bias at study level is considered high due to the significant percentage of patients who were not included in the analyses. In addition, the short median duration of observation in the study results in a relevant uncertainty with regard to the reliability of data, which is why this is classified as a hint.

In the overall assessment, therefore a hint for a minor additional benefit of abemaciclib in combination with endocrine therapy over endocrine therapy is found.

The resolution for this group of patients is limited until 01.07.2025.

a2) Postmenopausal women with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

The G-BA determined an aromatase inhibitor (anastrozole or letrozole) alone, possibly tamoxifen, if aromatase inhibitors are unsuitable, or an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen as an appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the RCT MONARCH-E, in which abemaciclib + endocrine therapy was compared with endocrine therapy alone. Only patients in whom the appropriate comparator therapy was adequately implemented were considered in the assessment.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment groups.

For the endpoint of recurrence, presented as recurrence rate and disease-free survival, there are statistically significantly fewer recurrences for abemaciclib + endocrine therapy.

With regard to symptomatology, health status and quality of life, there are statistically significant differences to the disadvantage of abemaciclib + endocrine therapy. However, it cannot be inferred that the effects are relevant.

The advantage in recurrences contrasts with the disadvantages of abemaciclib + endocrine therapy in the category of side effects, especially in the endpoints of serious adverse events (SAEs), severe adverse events (AEs, CTCAE grade ≥ 3) and discontinuation due to AEs. Against the background of the observed effect intensity for the endpoint of recurrence, the significant side effects question the advantage of the endpoint of recurrence. It was taken into account that the significance of the results for the endpoint of recurrence in the present treatment setting is limited due to the short median duration of observation.

Overall, it is therefore concluded that an additional benefit of abemaciclib in combination with endocrine therapy compared to endocrine therapy is not proven.

The resolution for this group of patients is limited until 01.07.2025.

a3) Men with hormone receptor-positive, HER2-negative early-stage breast cancer at high risk of recurrence

The G-BA determined tamoxifen as the appropriate comparator therapy.

Due to the small number of patients in the MONARCH-E study, there is no sufficient data basis to assess the additional benefit.

Thus, an additional benefit of abemaciclib in combination with endocrine therapy 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).

The resolution is based on the information from the dossier of the pharmaceutical company. However, the numbers of pre- and postmenopausal patients estimated by the pharmaceutical company are subject to uncertainties, as the initial population includes prevalent patients for whom adjunctive therapy with abemaciclib in combination with endocrine therapy is no longer an option in the majority of cases. In addition, it is unclear to what extent the results of the IQVIA database used can be transferred to the total population of patients in Germany.

Since the derivation of the patient numbers of men is based on those of women, these are also subject to uncertainties. In addition, it is unclear to what extent the percentage of all new cases of breast cancer in men is transferable to new cases of HR-positive, HER2-negative breast cancer in the early stage at high risk of recurrence.

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 Verzenios (active ingredient: abemaciclib) at the following publicly accessible link (last access: 27 June 2022):

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

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

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: 1 October 2022).

Treatment period:

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

The annual treatment costs shown refer to the first year of treatment.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Patient population a1)				
Abemaciclib + tamoxifen				
Abemaciclib	continuously, 2 x daily	365	1	365
Tamoxifen	continuously, 1 x daily	365	1	365
+ GnRH agonist[6]				
Leuprorelin	continuously, 1 x every 3 months	4	1	4
Goserelin	continuously, 1 x every 28 days	13	1	13.0
Patient population a2)				
Abemaciclib + anastrozole				
Abemaciclib	continuously, 2 x daily	365	1	365
Anastrozole	continuously, 1 x daily	365	1	365
Abemaciclib + letrozole				
Abemaciclib	continuously, 2 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
Abemaciclib + tamoxifen[7]				

[6] Leuprorelin or goserelin

[7] If aromatase inhibitors are unsuitable.

Abemaciclib	continuously, 2 x daily	365	1	365
Tamoxifen	continuously, 1 x daily	365	1	365
Abemaciclib + anastrozole in sequence after abemaciclib + tamoxifen[8]				
Abemaciclib + tamoxifen				
Abemaciclib	continuously, 2 x daily	365	1	365
Tamoxifen	continuously, 1 x daily	365	1	365
Abemaciclib + exemestane in sequence after abemaciclib + tamoxifen[8]				
Abemaciclib + tamoxifen				
Abemaciclib	continuously, 2 x daily	365	1	365
Tamoxifen	continuously, 1 x daily	365	1	365
Patient population a3)				
Abemaciclib + tamoxifen				
Abemaciclib	continuously, 2 x daily	365	1	365
Tamoxifen	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Patient population a1)				
Tamoxifen	continuously, 1 x daily	365	1	365
+ GnRH agonist[6]				
Leuprorelin	continuously, 1 x every 3 months	4	1	4
Goserelin	1 x every 28 days	13	1	13.0
Patient population a2)				
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
Tamoxifen[7]	continuously, 1 x daily	365	1	365

[8] According to the marketing authorisations, the switch to anastrozole and exemestane is indicated after 2 to 3 years of initial adjuvant therapy with tamoxifen. Treatment with abemaciclib should be given for 2 years. Accordingly, no costs are presented for anastrozole and exemestane.

Anastrozole in sequence after tamoxifen[8]				
Tamoxifen	continuously, 1 x daily	365	1	365
Exemestane in sequence after tamoxifen[8]				
Tamoxifen	continuously, 1 x daily	365	1	365
Patient population a3)				
Tamoxifen	continuously, 1 x daily	365	1	365

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					
Patient population a1)					
Abemaciclib + tamoxifen					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13	13 x 3.6 mg
Patient population a2)					
Abemaciclib + anastrozole					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Abemaciclib + letrozole					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
Abemaciclib + tamoxifen[7]					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Abemaciclib + anastrozole in sequence after abemaciclib + tamoxifen[8]					
Abemaciclib + tamoxifen					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Abemaciclib + exemestane in sequence after abemaciclib + tamoxifen[8]					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Abemaciclib + tamoxifen					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Patient population a3)					
Abemaciclib + tamoxifen					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Appropriate comparator therapy					
Patient population a1)					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4	4 x 11.25 mg
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13	13 x 3.6 mg
Patient population a2)					
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
Tamoxifen[7]	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Anastrozole in sequence after tamoxifen[8]					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Exemestane in sequence after tamoxifen[8]					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Patient population a3)					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Abemaciclib 150 mg	168 FCT	€ 5,767.72	€ 1.77	€ 326.11	€ 5,439.84

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
Anastrozole 1 mg[9]	100 FCT	€ 57.51	€ 1.77	€ 3.66	€ 52.08
Exemestane 25 mg[9]	100 FCT	€ 127.50	€ 1.77	€ 9.19	€ 116.54
Goserelin 3.8 mg	3 IMP	€ 547.76	€ 1.77	€ 29.70	€ 516.29
Letrozole 2.5 mg[9]	100 FCT	€ 53.44	€ 1.77	€ 3.33	€ 48.34
Leuprorelin 11.25 mg	2 IMP	€ 981.40	€ 1.77	€ 53.71	€ 925.92
Tamoxifen 20 mg[9]	100 TAB	€ 22.43	€ 1.77	€ 0.88	€ 19.78
Appropriate comparator therapy					
Anastrozole 1 mg	100 FCT	€ 57.51	€ 1.77	€ 3.66	€ 52.08
Exemestane 25 mg[9]	100 FCT	€ 127.50	€ 1.77	€ 9.19	€ 116.54
Goserelin 3.8 mg	3 IMP	€ 547.76	€ 1.77	€ 29.70	€ 516.29
Letrozole 2.5 mg[9]	100 FCT	€ 53.44	€ 1.77	€ 3.33	€ 48.34
Leuprorelin 11.25 mg	2 IMP	€ 981.40	€ 1.77	€ 53.71	€ 925.92
Tamoxifen 20 mg[9]	100 TAB	€ 22.43	€ 1.77	€ 0.88	€ 19.78
Abbreviations: FCT = film-coated tablets, IMP = implant, TAB = tablets					

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Costs for additionally required SHI services:

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

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

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

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.

[9] Fixed reimbursement rate

4. Process sequence

At its session on 6 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 26 April 2022, the pharmaceutical company submitted a dossier for the benefit assessment of abemaciclib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 April 2022 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 abemaciclib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 July 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2022. The deadline for submitting written statements was 22 August 2022.

The oral hearing was held on 5 September 2022.

By letter dated 6 September 2022, 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 23 September 2022.

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 October 2022, and the proposed resolution was approved.

At its session on 20 October 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 October 2020	Determination of the appropriate comparator therapy
Working group Section 35a	30 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 September 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 September 2022 20 September 2022 4 October 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 October 2022	Concluding discussion of the draft resolution
Plenum	20 October 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 October 2022

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

Prof. Hecken