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 (reassessment after the deadline: (breast cancer, HR+, HER2-, combination with aromatase inhibitor))

of 15 June 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. 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 pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient abemaciclib (Verzenios) to be assessed for the first time on 29 October 2018. For the resolution passed by the G-BA in this procedure on 2 May 2019, a time limit was set until 31 December 2022 for patient population a1) (postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy).

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Verzenios recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of

Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 22 December 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 03 April 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of abemaciclib compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of 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 is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In pre or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

Therapeutic indication of the resolution (resolution of 15 June 2023):

Verzenios is indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine therapy.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy

Appropriate comparator therapy for abemaciclib in combination with fulvestrant:

- Anastrozole

  or

- Letrozole

  or

- Fulvestrant

  or

- Tamoxifen, if necessary, if aromatase inhibitors are unsuitable

  or

- Exemestane (only for patients with progression after anti-oestrogen treatment)

  or

- Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- Ribociclib in combination with fulvestrant

  or

- Abemaciclib in combination with fulvestrant

  or

- Palbociclib in combination with fulvestrant

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 principle, medicinal products with the following active ingredients are approved in the therapeutic indication:

the anti-oestrogens tamoxifen, toremifene, fulvestrant; the non-steroidal aromatase inhibitors anastrozole and letrozole; the steroidal aromatase inhibitor exemestane; the progestogens megestrol acetate and medroxyprogesterone acetate; the protein kinase inhibitors everolimus, palbociclib, ribociclib and abemaciclib; and the PIK3 inhibitor alpelisib.

on 2. Both surgical resection and/or radiotherapy as well as ovariectomy for the cessation of ovarian function are generally considered as non-medicinal therapies for the treatment of breast carcinoma.

In the present therapeutic indication, it is assumed that radiotherapy and/or (secondary) resection with a curative objective is not indicated. The (secondary) resection and/or radiotherapy were therefore not included in the appropriate comparator therapy.

on 3. Resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are:

- Abemaciclib (in combination with fulvestrant) - resolution of 2 May 2019 and resolution of 3 September 2020 and resolution of 19 May 2022
- Abemaciclib (in combination with aromatase inhibitors): Resolution of 2 May 2019
- Palbociclib (in combination with fulvestrant): Resolution of 18 May 2017 and resolution of 22 March 2019
- Palbociclib (in combination with aromatase inhibitor): Resolution of 18 May 2017 and resolution of 15 December 2022
- Ribociclib (in combination with fulvestrant): Resolution of 4 July 2019 and resolution of 20 August 2020
- Ribociclib (in combination with aromatase inhibitor): Resolution of 4 July 2019 and resolution of 20 August 2020
- Alpelisib (in combination with fulvestrant): Resolution of 18 February 2021

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.

The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately.

For the present therapeutic indication, it is assumed that (possibly further) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative objectives.

In national and international guidelines, aromatase inhibitors are recommended for initial endocrine therapy in the advanced or metastatic stage in postmenopausal women. Considering the authorisation status, steroidal (exemestane) and non-steroidal aromatase inhibitors (anastrozole, letrozole) can be considered. For exemestane, according to the product information, the term "progress" can also include a relapse after anti-oestrogen treatment.

As an alternative in cases of aromatase inhibitor intolerance, tamoxifen, which is also approved, is an appropriate therapy.

In addition, the antiestrogen fulvestrant is another recommended treatment option for initial endocrine therapy.

<u>On the CDK4/6 inhibitors (ribociclib, abemaciclib, palbociclib) in the appropriate comparator therapy for patient population a1</u>

The CDK4/6 inhibitors (ribociclib, abemaciclib, palbociclib) in combination with a non-steroidal aromatase inhibitor or fulvestrant are also approved treatment options for postmenopausal women for initial endocrine therapy in the therapeutic indication.

The results of the benefit assessment procedures to date for the CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) for postmenopausal women with initial endocrine therapy in the therapeutic indication can be summarised as follows:

For postmenopausal women with initial endocrine therapy, a hint for a minor additional benefit was shown for ribociclib in combination with letrozole compared with letrozole and an indication of a minor additional benefit was shown for ribociclib in combination with fulvestrant compared with fulvestrant.

In the benefit assessments of palbociclib in combination with a non-steroidal aromatase inhibitor or fulvestrant and of abemaciclib in combination with an fulvestrant, no additional benefit has been demonstrated in postmenopausal women with initial endocrine therapy.

According to the recommendations of the German S3 guideline of the AWMF (Association of the Scientific-Medical Societies),[2] the initial endocrine-based therapy in postmenopausal patients with a CDK4/6 inhibitor should be carried out either in combination with an aromatase inhibitor or with fulvestrant.

In the S3 guideline, all three currently approved CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) are equally recommended or no specific preference is stated. In contrast, the results of the respective benefit assessments differed with regard to the additional benefit.

In the overall review of the evidence, the three CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) in the respective approved combinations are also considered equally suitable appropriate comparator therapies.

[2] Interdisciplinary S3 guideline for early detection, diagnosis, therapy and follow-up of breast cancer of the AWMF (Association of the Scientific-Medical Societies); Version 4.4

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

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

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

Change of the appropriate comparator therapy

With the present resolution, the appropriate comparator therapy is supplemented by the treatment option "exemestane (only for patients with progression after anti-oestrogen treatment)".

The basis for this change is the consideration of the explanations in the product information on exemestane, according to which the term "progress" can also be considered to include a relapse after anti-oestrogen treatment.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

2.1.3 Extent and probability of the additional benefit

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

Hint for a minor additional benefit

Justification:

MONARCH 3 study:

For the proof of an additional benefit of abemaciclib in combination with anastrozole or letrozole over anastrozole or letrozole, the pharmaceutical company has presented results from the randomised, double-blind, controlled phase III MONARCH 3 study. This multinational study enrolled postmenopausal patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer who had not yet received endocrine therapy for the treatment of the locally advanced or metastatic disease.

With regard to prior therapy, patients with a previous (neo-)adjuvant endocrine therapy (e.g. anti-oestrogens or aromatase inhibitors) with a disease-free interval of ≤ 12 months after the end of treatment were excluded from the study. Patients had to have an ECOG-PS of 0 or 1 at study entry.

A total of 493 patients were enrolled in the study, randomised in the ratio 2:1 and allocated to treatment with abemaciclib + anastrozole or letrozole (N = 328) or placebo + anastrozole or letrozole (N = 165). Randomisation was stratified by type of disease (visceral metastases vs bone metastases only vs others) and previous (neo-)adjuvant endocrine therapy (aromatase inhibitors vs others vs none). The aromatase inhibitor was chosen by the doctor. In both study

arms, about 20% of the patients received anastrozole and about 80% of the patients received letrozole.

The primary endpoint of the MONARCH 3 study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, symptomatology, health status, health-related quality of life, and adverse events.

The still ongoing MONARCH 3 study began in November 2014. The multicentre study is being conducted in 158 study sites in Asia, Australia, Europe and North America. So far, 4 data cut-offs are available. The results of the 4th and most recent data cut-off from 02.07.2021 are relevant for the present benefit assessment. This is the data cut-off planned after 252 deaths according to the study documents. Besides this data cut-off, the pharmaceutical company plans another data cut-off for the final analysis of overall survival after 315 deaths.

MONARCH plus study:

The MONARCH plus study (cohort B) is a double-blind, randomised and controlled phase III study comparing abemaciclib in combination with anastrozole or letrozole with placebo in combination with anastrozole or letrozole. The study was conducted predominantly in Asia and is the label-enabling study for China. The cohort A of the study enrolled only postmenopausal women with HR-positive, HER2-negative locally relapsed or metastatic breast cancer who had not previously received endocrine therapy based on advanced disease stage.

Regarding prior therapy, patients were enrolled if disease progression occurred either within 12 months or later than 12 months after completion of an adjuvant endocrine therapy. In addition, patients with de novo metastatic disease and without any prior endocrine therapy were enrolled.

A total of 306 patients were included in cohort A of the study, which is relevant for the benefit assessment, and randomised in a ratio of 2:1 to the two treatment arms. 207 patients were assigned to the intervention arm and 99 patients to the control arm. Randomisation was stratified by type of disease (visceral metastases vs non-visceral metastases) and prior (neo-)adjuvant endocrine therapy (prior therapy with disease-free interval > 12 months after end of therapy vs prior therapy with disease-free interval ≤ 12 months after end of therapy vs no prior therapy). The aromatase inhibitor was chosen by the doctor. In both study arms, about 25% of the patients received anastrozole and about 75% of the patients received letrozole.

The primary endpoint of the MONARCH plus study is progression-free survival (PFS). Patient-relevant secondary endpoints include overall survival, symptomatology, health-related quality of life, and adverse events.

The study, which is currently still ongoing, began in December 2016. For the present benefit assessment, the results of the 2nd data cut-off from 18 May 2020 (final analysis) are relevant.

Meta-analysis:

There are differences between the studies, especially in terms of age, the percentage of patients with de novo metastasis and descent. In addition, patients with a disease-free interval ≤ 12 months after the end of adjuvant endocrine therapy or during adjuvant therapy were also enrolled in the MONARCH plus study. However, the differences between the used study populations do not call into question the feasibility of a meta-analysis, as the studies are considered sufficiently comparable for the research question investigated. For the benefit assessment, a fixed-effect model is therefore used to calculate meta-analyses.

Extent and probability of the additional benefit

Mortality

Overall survival was defined in the MONARCH 3 and MONARCH plus studies as the time between randomisation and death, regardless of the underlying cause of death.

Overall, the meta-analysis of the studies shows a significant prolongation in overall survival and thus, a benefit of treatment with abemaciclib in combination with letrozole or anastrozole compared to letrozole or anastrozole.

In the MONARCH 3 study, abemaciclib led to an prolongation in median overall survival by 12.6 months in postmenopausal patients after a longer observation period. The corresponding Kaplan-Meier curves of both treatment arms show a similar course until about the 30th month of observation; only after that does the advantage of abemaciclib in the MONARCH 3 study become clear.

So far, the MONARCH plus study has not shown a statistically significant prolongation in overall survival. The follow-up period is significantly shorter than in the MONARCH 3 study. The associated Kaplan-Meier curves also indicate a separation of the survival curves after about 30 months.

Morbidity

Progression-free survival (PFS)

Progression-free survival is the primary endpoint in both studies and was defined as the time between randomisation and disease progression (determined by the principal investigator using RECIST criteria version 1.1) or death regardless of the underlying cause of death.

PFS was statistically significantly prolonged in the abemaciclib treatment group compared to the control group.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component of mortality was assessed in the studies via the secondary endpoint of overall survival as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST criteria). Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The available data on morbidity and health-related quality of life are used to interpret the results on PFS. These results are relevant in the present case because radiologically disease progression may be associated to effects on morbidity and/or quality of life.

However, the prolonged PFS with abemaciclib was not associated with a benefit in terms of morbidity or quality of life in the meta-analysis of the two MONARCH 3 and MONARCH plus studies. In contrast, with regard to the endpoints on symptomatology, the available data show disadvantages of abemaciclib in combination with letrozole or anastrozole compared to letrozole or anastrozole.

It should be noted that the corresponding endpoints were only collected up to the point of progression and therefore only allow statements up to the point of progression. However, robust analysis of data before and after the time of radiologically determined progression are required to assess any impact of radiologically determined progression on quality of life as well as morbidity.

In summary, the available data do not indicate that the statistically significant increase in progression-free survival time with abemaciclib is associated with an improvement in morbidity or health-related quality of life. The results on the endpoint of progression-free survival are not therefore used in this assessment.

Time until the first subsequent chemotherapy

The endpoint time to first subsequent chemotherapy was only collected in the MONARCH 3 study and is defined as the time from randomisation to the start of first subsequent chemotherapy or death regardless of the underlying cause of death.

For patients who are in an early phase of the course of advanced/ metastatic breast cancer and have so far only been treated with endocrine therapy at this stage of the disease, the delay of treatment with cytotoxic (intravenous) chemotherapy, which may be associated with known relevant side effects, especially myelosuppressive, but also other relevant side effects, as well as intravenous treatment, may be relevant.

The pharmaceutical company's dossier lacks detailed information on post-progression therapies; furthermore, essential information on the circumstances of the treatment decision for or against chemotherapy is not described by the pharmaceutical company. Furthermore, the endpoint for MONARCH 3 was defined post-hoc in the context of the benefit dossier on abemaciclib.

Irrespective of the fundamental question of whether the endpoint "time to first subsequent chemotherapy" should also be reflected in other relevant endpoints in order to be assessed as patient-relevant, there are considerable uncertainties in the present case with regard to the significance of the results for this endpoint, which mean that no statements on additional benefit can be derived from the available data.

Pain (mBPI-SF)

The endpoint of pain was only assessed in the MONARCH plus study using mBPI-SF as the strongest pain in the last 24 hours.

For this endpoint, time-to-event analyses are available for the time from randomisation to the first deterioration. An increase of ≥ 2 points compared to the start of the study on the symptom scale "strongest pain in the last 24 hours" is considered to be deterioration. The increase of at least 2 points corresponds to a threshold of > 15 points of the total scale range of 0 - 10 points.

For the endpoint of strongest pain in the last 24 hours, there was no statistically significant difference between the treatment groups in the MONARCH plus study.

Symptomatology (EORTC QLQ-C30/ EORTC QLQ-BR23)

Disease symptomatology was assessed in the MONARCH 3 study using the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 each until 30 days after the end of treatment. In the MONARCH plus study, a corresponding assessment was only conducted with the EORTC QLQ-C30 questionnaire.

The pharmaceutical company submits responder analyses for the percentage of patients with a change of ≥ 10 points for the time to first deterioration and for the time to so-called "sustained" deterioration.

The so-called "time to sustained deterioration" was defined as deterioration by ≥ 10 points without subsequent improvement to a score of this level. The pharmaceutical company's data on the median observation durations for the endpoints regarding symptomatology submitted

with the reassessment show that the observation duration for these endpoints is significantly shorter compared to the median overall survival. Therefore, the observation period of the patient-reported endpoints on symptomatology covers only a very small percentage of the total observation time, whereby it is not considered appropriate to speak of a "sustained deterioration" in this situation. Rather, it is a deterioration confirmed over the truncated observation period. Furthermore, there are clear differences in observation duration between the treatment arms. Thus, sustained deterioration across all follow-up values is potentially more difficult to achieve in the longer observed intervention arm. In addition, it cannot be ruled out that the evaluation also included patients who had deteriorated once at the last survey time point and for whom no confirmed value was available. Although both operationalisations ("time to first deterioration" and "time to sustained deterioration") are considered patient-relevant, the time-to-event analysis for the first-time deterioration is used against the background of the uncertainties described for the sustained deterioration as it has a lower risk of bias than the analysis for the sustained deterioration.

In the analysis of the "time to first-time deterioration" by 10 points, statistically significant differences to the disadvantage of abemaciclib in combination with letrozole or anastrozole compared to letrozole or anastrozole are shown for the domains of fatigue, nausea and vomiting, appetite loss, diarrhoea and side effects of systemic therapy (only collected in the MONARCH 3 study). Based on this, a disadvantage can be derived in the overall analysis of the results for symptomatology.

General health status (EQ-5D VAS)

Health status is assessed only in the MONARCH 3 study using the EQ-5D visual analogue scale (VAS) up to 30 days after the end of treatment.

The pharmaceutical company submits responder analyses for the "time to first deterioration" and for the "time to sustained deterioration", each defined as a decrease in the score by ≥ 15 points compared to the baseline value.

The results for "time to sustained deterioration" are classified as having a potentially high risk of bias due to the uncertainties described under the comments on symptomatology. Therefore, the analyses for time to first deterioration are used for the endpoint of health status.

For this evaluation, no statistically significant difference could be identified between the treatment arms.

Quality of life

Health-related quality of life was assessed in the MONARCH 3 study using the functional scales and the global health status scale of the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 in each case up to 30 days after the end of treatment. In the MONARCH plus study, a corresponding assessment was only conducted with the EORTC QLQ-C30 questionnaire.

The pharmaceutical company submits evaluations for the "time to first deterioration" and for the "time to sustained deterioration" by ≥ 10 points over the truncated observation period up to 30 days after the end of treatment.

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

In the analysis for "time to first-time deterioration" by ≥ 10 points, a statistically significant difference to the disadvantage of abemaciclib in combination with letrozole or anastrozole compared to letrozole or anastrozole is only shown in the meta-analysis for the domain "body

image" of the breast cancer-specific additional module EORTC QLQ-BR23, which was collected in the Monarch 3 study alone. For the endpoints of global health status and social functioning, there is an effect modification by the age characteristic. For patients ≥ 65 years, the meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib in combination with letrozole or anastrozole, while for patients < 65 years, the meta-analysis shows no statistically significant difference. These effect modifications are not evident in other endpoints except for the endpoint "serious adverse events (SAE)". Overall, the significance of the available subgroup results is considered insufficient for the assessment of the additional benefit.

Overall, no disadvantage can be derived in the overall analysis of the results for health-related quality of life solely based on the disadvantage in the domain "body image" of the breast cancer-specific additional module EORTC QLQ-BR23, which was also surveyed only in the Monarch 3 study.

Thus, there are no relevant differences between the treatment arms with regard to health-related quality of life.

Side effects

Endpoints in the category side effects were assessed in both studies up to 30 days after the end of treatment.

Adverse events (AEs) in total

In the MONARCH 3 study, 98.8% of postmenopausal patients who had not yet received initial endocrine therapy experienced an adverse event in the intervention arm, compared to 94.4% of patients in the comparator arm.

In the MONARCH plus study, adverse events occurred in 99.5% of patients in the intervention arm and in 89.9% of patients in the control arm.

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

For the endpoints of serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, the meta-analysis shows in each case a statistically significant difference to the disadvantage of abemaciclib in combination with letrozole or anastrozole. For the endpoint of SAEs, there is an effect modification due to the age characteristic. For patients ≥ 65 years, the meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib in combination with letrozole or anastrozole, while for patients < 65 years, the meta-analysis shows no statistically significant difference.

This effect modification is not evident in other endpoints except for the endpoints "global health status" and "social functioning" of the EORTC QLQ-C30 in the category of health-related quality of life. Overall, the significance of the available subgroup results is considered insufficient for the assessment of the additional benefit.

Specific AEs

For the specific AEs of neutropenia (CTCAE grade ≥ 3), diarrhoea (CTCAE grade ≥ 3), blood and lymphatic system disorders (CTCAE grade ≥ 3), infections and infestations (CTCAE grade ≥ 3), metabolism and nutrition disorders (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) and eye disorders (AEs), there is a statistically significant difference, in detail, to the disadvantage of abemaciclib in combination with letrozole or anastrozole.

Overall assessment

For the assessment of the additional benefit of abemaciclib in combination with letrozole or anastrozole for the treatment of hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer in postmenopausal patients who have not yet received initial endocrine therapy, results on the endpoint categories mortality, morbidity, health-related quality of life and side effects compared to letrozole or anastrozole are available from a meta-analysis. The meta-analysis includes the randomised, controlled, double-blind studies MONARCH 3 and MONARCH plus.

For overall survival, meta-analysis shows an advantage of abemaciclib in combination with letrozole or anastrozole over letrozole or anastrozole.

The evaluations of symptomatology used for the benefit assessment (collected using EORTC QLQ-C30 and EORTC QLQ-BR23) in the endpoint category of morbidity show disadvantages of abemaciclib in combination with letrozole or anastrozole compared to letrozole or anastrozole, particularly for the domains of fatigue, nausea and vomiting and appetite loss, which is why a disadvantage is derived for symptomatology in the overall analysis.

With regard to health-related quality of life (assessed with EORTC QLQ-C30 / EORTC QLQ-BR23), there were no differences relevant for the benefit assessment.

In the overall assessment of the results of side effects, there are statistically significant and meaningful disadvantages of abemaciclib in combination with anastrozole or letrozole compared to anastrozole or letrozole with regard to the endpoints of serious AEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, the specific severe adverse events (CTCAE ≥ 3) of neutropenia, diarrhoea, blood and lymphatic system disorders, infections and infestations, metabolism and nutrition disorders and investigations each show disadvantages of abemaciclib in combination with letrozole or anastrozole.

In a weighing decision, the G-BA comes to the conclusion that due to the advantage in overall survival, the improvement of the therapy-relevant benefit outweighs the significant disadvantages in terms of side effects and other disadvantages in terms of disease symptomatology. In the overall assessment, a minor additional benefit of abemaciclib in combination with letrozole or anastrozole over letrozole or anastrozole is identified for the treatment of postmenopausal patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the two randomised, controlled, double-blind MONARCH 3 and MONARCH plus studies.

The risk of bias across endpoints is classified as low at study level.

From the present planned and most current data cut-off of 2 July 2021 (4th interim analysis after 252 deaths) of the MONARCH 3 study, data are available for the endpoint of overall survival, based on a follow-up duration of approx. 6 years. With regard to the hazard ratio of overall survival, however, a rather wide 95% confidence interval is still noticeable even at this advanced data cut-off, which results in uncertainty in the interpretation of the effect estimator.

For the MONARCH plus study, the final data cut-off for overall survival is available. However, the follow-up time of 2.5 years is significantly shorter than in the MONARCH 3 study. Accordingly, the hazard ratio estimate for overall survival is based on a significantly lower

number of events compared to the MONARCH 3 study. The data on overall survival according to the Kaplan-Meyer analysis show an advantage of abemaciclib in the MONARCH 3 study only after approximately 2.5 years after randomisation. In the MONARCH plus study, a similar picture of the Kaplan-Meyer curves emerges. According to this, the short follow-up time of the MONARCH plus study results in relevant limitations to the reliability of data for overall survival. This also corresponds to the assessment of the medical experts in the written statement procedure.

Overall, this results in relevant uncertainties in the interpretation of the results on overall survival in the meta-analytic summary of the data from the MONARCH 3 and MONARCH plus studies.

In view of the decisive importance of the result on overall survival for the above-mentioned weighing decision in the overall assessment of the additional benefit, the uncertainties presented justify that the reliability of data for the identified additional benefit is classified in the category "hint".

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient abemaciclib due to the expiry of the limitation of the resolution of 2 May 2019. The assessment relates only to the use of abemaciclib in combination with aromatase inhibitor for the treatment of hormone receptor (HR-)positive, HER2-negative locally advanced or metastatic breast cancer in the following patient population:

a1) postmenopausal women with hormone receptor (HR)-positive HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy.

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

- Anastrozole

  or

- Letrozole

  or

- Fulvestrant

  or

- Tamoxifen, if necessary, if aromatase inhibitors are unsuitable

  or

- Exemestane (only for patients with progression after anti-oestrogen treatment)

  or

- Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

  or

- Ribociclib in combination with fulvestrant

or

- Abemaciclib in combination with fulvestrant

  or

- Palbociclib in combination with fulvestrant

For the assessment of the additional benefit of abemaciclib in combination with letrozole or anastrozole for the treatment of hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer in postmenopausal patients who have not yet received initial endocrine therapy (sub-population a1), results on the endpoint categories mortality, morbidity, health-related quality of life and side effects compared to letrozole or anastrozole are available from a meta-analysis. The meta-analysis includes the randomised, controlled, double-blind studies MONARCH 3 and MONARCH plus.

For overall survival, abemaciclib in combination with letrozole or anastrozole shows an advantage over letrozole or anastrozole.

For the category of morbidity (pain, symptomatology and general health status), overall analysis results in a disadvantage for symptomatology.

With regard to the health-related quality of life, there are no differences relevant for the benefit assessment.

In the overall assessment of the results on side effects, there are statistically significant and meaningful disadvantages of abemaciclib in combination with letrozole or anastrozole compared to letrozole or anastrozole.

In a weighing decision, the G-BA comes to the conclusion that due to the advantage in overall survival, the improvement of the therapy-relevant benefit outweighs the significant disadvantages in terms of side effects and other disadvantages in terms of disease symptomatology. In the overall assessment, a minor additional benefit of abemaciclib in combination with letrozole or anastrozole over letrozole or anastrozole is identified for the treatment of postmenopausal patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy.

The reliability of data of the additional benefit identified is classified in the "hint" category.

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).

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of abemaciclib (resolution of 19 May 2022).

The above range takes into account the existing uncertainties in the data basis and reflects the minimum and maximum values obtained in the derivation.

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: 21 March 2023):

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, obstetrics and gynaecology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with locally advanced or metastatic breast cancer.

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 May 2023).

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

Treatment period

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Abemaciclib	Continuously, 2 x daily	365.0	1	365.0
plus aromatase inhibitor:				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Non-steroidal aromatase inhibitors				
Anastrozole	Continuously,	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x daily			
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Anti-oestrogens				
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12.0[3]	Cycle 1: 2 From cycle 2 onwards: 1	13.0
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Ribociclib	on day 1 - 21 of a 28-day cycle	13.0	21	273.0
plus aromatase inhibitor:				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
plus aromatase inhibitor:				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Ribociclib in combination with fulvestrant				
Ribociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 from cycle 2 onwards: 1 x monthly	12.0[3]	Cycle 1: 3 From cycle 2 onwards: 1	14.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Abemaciclib in combination with fulvestrant				
Abemaciclib	Continuously, 2 x daily	365.0	1	365.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12.0[3]	Cycle 1: 2 From cycle 2 onwards: 1	13.0
Palbociclib in combination with fulvestrant				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 from cycle 2 onwards: 1 x monthly	12.0[3]	Cycle 1: 3 From cycle 2 onwards: 1	14.0

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

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					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
plus aromatase inhibitor:					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg

[3] Consistent with the presentation of the treatment mode for fulvestant in combination with ribociclib, as well as palbociclib, where fulvestrant is given, amongst others, on day 29 of the 1st cycle, fulvestrant is based on months (and not days), in contrast to the other active ingredients in this procedure.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Aromatase inhibitors					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Anti-oestrogens					
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole):					
Ribociclib	600 mg	600 mg	3 x 200 mg	273.0	819 x 200 mg
plus aromatase inhibitor:					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
plus aromatase inhibitor:					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 x 200 mg	273.0	819 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Abemaciclib in combination with fulvestrant					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Palbociclib in combination with fulvestrant					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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	€ 2.00	€ 559.04	€ 5,206.68
Anastrozole 1 mg[4]	120 FCT	€ 65.06	€ 2.00	€ 4.25	€ 58.81
Letrozole 2.5 mg[4]	120 FCT	€ 61.64	€ 2.00	€ 3.98	€ 55.66
Exemestane 25 mg[4]	100 FCT	€ 127.50	€ 2.00	€ 9.19	€ 116.31
Appropriate comparator therapy					
Anastrozole 1 mg[4]	120 FCT	€ 65.06	€ 2.00	€ 4.25	€ 58.81
Letrozole 2.5 mg[4]	120 FCT	€ 61.64	€ 2.00	€ 3.98	€ 55.66
Abemaciclib 150 mg	168 FCT	€ 5,767.72	€ 2.00	€ 559.04	€ 5,206.68
Fulvestrant 250 mg[4]	1 SFIPFS	€ 175.64	€ 2.00	€ 13.00	€ 160.64
Tamoxifen 20 mg[4]	100 FCT	€ 22.43	€ 2.00	€ 0.88	€ 19.55
Ribociclib 200 mg	189 FCT	€ 6,846.11	€ 2.00	€ 276.92	€ 6,567.19
Palbociclib 125 mg	21 HC	€ 2,461.87	€ 2.00	€ 235.38	€ 2,224.49
Abbreviations: FCT = film-coated tablets, SFIPFS = solution for injection in a pre-filled syringe, HC = hard capsules					

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<u>Costs for additionally required SHI services:</u>

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 need to be taken into account.

[4] Fixed reimbursement rate

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Abemaciclib

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

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 8 December 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 28 September 2021.

On 22 December 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 5 VerfO.

By letter dated 22 December 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 30 March 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 April 2023. The deadline for submitting statements was 24 April 2023.

The oral hearing was held on 2 May 2023.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 June 2023, and the proposed resolution was approved.

At its session on 15 June 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 December 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	28 September 2021	New implementation of the appropriate comparator therapy
Subcommittee Medicinal products	2 May 2023	Conduct of the oral hearing
Working group Section 35a	9 May 2023 16 May 2023 30 May 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 June 2023	Concluding discussion of the draft resolution
Plenum	15 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 June 2023

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

Prof. Hecken