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 carcinoma, HR+, HER2-, combination with fulvestrant)

of 19 May 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 pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient abemaciclib (Verzenios) for the first time on 16 March 2020. For the resolution of 3 September 2020 made by the G-BA in this procedure, a limitation up to 1 June 2021 was pronounced for patient populations a1 (postmenopausal women who have not yet received initial endocrine therapy) and b1 (postmenopausal women who have received prior endocrine therapy). At the pharmaceutical company's request, this limitation was extended until 1 December 2021 by the resolution of the G-BA of 1 April 2021.

In accordance with Section 4, paragraph 3, No. 5 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 1 of the Ordinance on the Benefit Assessment of

Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 November 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 March 2022, 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the 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 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 or fulvestrant 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 19 May 2022):

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 fulvestrant as initial endocrine therapy or in postmenopausal women who have received prior 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 not suitable

  or

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

  or

- Abemaciclib 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

- Palbociclib in combination with fulvestrant

b1) Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy

Appropriate comparator therapy for abemaciclib in combination with fulvestrant:

Another endocrine therapy with:

- Tamoxifen

  or

- Anastrozole

  or

- fulvestrant as monotherapy; only for patients with relapse or progression after antiestrogen treatment

or

- letrozole; only for patients with relapse or progression after antiestrogen treatment

  or

- exemestane; only for patients with progression after anti-oestrogen treatment

  or

- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis following progression after a non-steroidal aromatase inhibitor.

  or

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

  or

- Abemaciclib 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

- 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 substances are approved in the therapeutic indication:

the antiestrogens 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 to eliminate 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): resolutions of 2 May 2019 and 3 September 2020
- Abemaciclib (in combination with aromatase inhibitors): Resolution of 02 May 2019
- Palbociclib: resolutions of 18 May 2017 and 22 March 2019
- Ribociclib (in combination with fulvestrant): resolutions of 4 July 2019 and 20 August 2020
- Ribociclib (in combination with aromatase inhibitors): resolutions of 4 July 2019 and 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 systematic 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 health care provision.

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 the view of the G-BA, there are patient populations to be considered separately for the present indication according to the current state of medical knowledge, which differ with regard to the treatment situation after previous endocrine therapy (initial endocrine therapy / after previous endocrine therapy in the respective locally advanced or metastasised stage). Therefore, when determining the appropriate comparator therapy, a differentiation is made according to the following patient populations:

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 national and international guidelines, aromatase inhibitors are recommended for initial endocrine therapy in the advanced or metastatic stage in postmenopausal women. 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.

b1) postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy

In the treatment setting of disease progression in postmenopausal patients on previous endocrine therapy, national and international guidelines unanimously recommend further endocrine therapy, using an alternative agent, if there is no indication for chemotherapy. With regard to the importance of progestogens, the corresponding statements in the guidelines are less clear compared to the other therapy options mentioned. In addition, their use is described as a rather subordinate option in the treatment cascade, which is why the G-BA does not consider the progestogens to be a regular treatment option for the present treatment setting and therefore does not include them in the appropriate comparator therapy. The restrictions on specific patient populations for fulvestrant, letrozole, exemestane and everolimus in combination with exemestane reflect the respective authorisation status.

Fulvestrant is only approved for use in the therapeutic indication after previous antiestrogen treatment. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in care, which are based not only on previous therapy with antiestrogens, but also on previous therapy with aromatase inhibitors. This fact was also presented in the statements submitted by medical experts in the benefit assessment procedures already carried out in this therapeutic indication.

In this special therapy and medical treatment situation, the G-BA sees a sufficient medical factual reason that would justify considering fulvestrant as a sufficiently suitable comparator in the present case, despite remaining uncertainties.

It is assumed that a change of treatment has taken place with regard to the active ingredient used for the initial endocrine therapy.

On the CDK4/6 inhibitors (ribociclib, abemaciclib, palbociclib) in the appropriate comparator therapy for patient populations a1 and b1

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 or following previous 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 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. For postmenopausal women with previous endocrine therapy, a hint for a minor additional benefit was identified both for ribociclib in combination with fulvestrant and abemaciclib in combination with fulvestrant.

In the benefit assessments of palbociclib in combination with a non-steroidal aromatase inhibitor or fulvestrant, no additional benefit has been shown so far in postmenopausal women either with initial endocrine therapy or with previous endocrine therapy.

According to the updated recommendations of the German S3 guideline of the AWMF (Association of the Scientific-Medical Societies)[2] , 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, both in the initial endocrine therapy and after endocrine therapy has already taken place, if CDK4/6 inhibitors have not been used before.

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.

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

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

2.1.3 Extent and probability of the additional benefit

Evidence base:

MONARCH 2 study:

For the proof of an additional benefit of abemaciclib in combination with fulvestrant compared to fulvestrant, the pharmaceutical company has presented results from the randomised, double-blind, controlled phase III MONARCH 2 study. This multinational study included pre/perimenopausal and 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 or who had already been pre-treated with endocrine therapy.

Regarding prior therapy, patients were included if disease progression occurred either during (neo)adjuvant endocrine therapy or within 12 months after completion of adjuvant endocrine therapy. In addition, patients with progression after first-line endocrine therapy in the metastatic stage who had previously progressed later than 12 months after completion of adjuvant endocrine therapy or were de novo in the metastatic stage were included.

A total of 713 patients were included in the study and randomised in a 2:1 ratio to the two treatment arms. Of these, 374 patients are relevant for the evaluation of question a1 (postmenopausal women with initial endocrine therapy) and 210 patients are relevant for the evaluation of question b1 (postmenopausal women who have previously received endocrine therapy). The pharmaceutical company submits evaluations of these sub-populations in its dossier, analogous to the previous benefit assessment. These responder analyses are used for the benefit assessment.

The primary endpoint of the MONARCH 2 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 MONARCH 2 study, which is currently still ongoing, began in August 2014. Planned end of study is January 2024. The multicentre study is being conducted in 145 study sites in Asia, Australia, Europe and North America. So far, 3 data cut-offs are available. As in the previous benefit assessment, the results of the 3rd and most recent data cut-off from 20.06.2019 are relevant for the present benefit assessment. This is the final overall survival data cut-off planned according to the study documents. The pharmaceutical company has not provided any information on whether further evaluations are planned for the ongoing study.

MONARCH plus study:

The MONARCH plus study (cohort B) is a double-blind, randomised and controlled phase III study comparing abemaciclib in combination with fulvestrant to fulvestrant. The study was conducted predominantly in Asia and is the study justifying approval for China. The study included only postmenopausal women with HR-positive, HER2-negative locally recurrent or metastatic breast cancer who either had not previously received endocrine therapy or had already received endocrine therapy based on advanced disease stage.

A total of 157 patients were included in cohort B of the study, which is relevant for the benefit assessment, and randomised in a ratio of 2:1 to the two treatment arms. 104 patients were assigned to the intervention arm and 53 patients to the control arm.

For the present evaluation, the pharmaceutical company presents evaluations for the evaluation-relevant sub-populations a1 and b1 for the first time. For question a1, 121 (77.1 %) and for question b1, 36 (22.9 %) of the total of 157 patients are relevant.

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 (final analysis) are relevant.

Meta-analysis:

In accordance with the G-BA's time limitation requirement, the pharmaceutical company's dossier includes not only the study results of the MONARCH 2 study but also the study results of the MONARCH plus study, each differentiated according to the sub-populations a1 and b1. In addition, the pharmaceutical company shall examine the possibility of a meta-analytical summary of the studies.

In particular, there are differences between the studies for age, disease duration and ancestry for patient population a1 and for age and ancestry for patient population b1. However, the differences do not fundamentally 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, before meta-analyses are used or calculated for the individual endpoints, heterogeneity tests are used to check whether the two studies are sufficiently homogeneous for a statistical summary.

In summary, the additional benefit of Abemaciclib is assessed 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

Extent and probability of the additional benefit

An additional benefit is not proven.

Justification:

Mortality

Overall survival was defined in the MONARCH 2 and MONARCH plus studies as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups in the meta-analysis of the studies.

Morbidity

Progression-free survival

Progression-free survival was 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 results 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, no meaningfully interpretable data on morbidity (health status (EQ-5D VAS) and symptomatology (EORTC QLQ-C30 and EORTC QLQ-BR23)) and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23) are available for the new benefit assessment. For justification, please refer to the explanations under the endpoints for the EORTC QLQ-C30 and EORTC QLQ-BR23 and the EQ-5D VAS in the endpoint categories morbidity and quality of life. With regard to the evaluations of pain (assessed by means of mBPI-SF) in the morbidity category, no statistically significant difference between the treatment groups was found.

On the basis of the available data, it is therefore not possible to adequately assess the extent to which radiologically determined progression is associated with a change in morbidity and/or quality of life. The results on the progression-free survival endpoint 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 2 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 2 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

For the endpoint pain (assessed by mBPI-SF and the use of analgesics), time-to-event analysis are available for the time from randomisation to the first deterioration. Deterioration is defined as either an increase of ≥2 points from start of the study (on the symptom scale "strongest pain in the last 24 hours") or an increase in use of analgesics by more than one step (according to the WHO 3-step cancer pain management system).

In this respect, the pharmaceutical company submits separate evaluations for both endpoints for the MONARCH 2 study and evaluations for the endpoint "strongest pain in the last 24 hours" (assessed using mBPI-SF) for the MONARCH plus study. The increase of at least 2 points corresponds to a threshold of > 15 % of the total scale range of 0-11 points.

For the endpoint pain (strongest pain in the last 24 hours and increase in use of analgesics), the studies show no statistically significant difference between the treatment groups, neither for the combined endpoint nor for its individual components.

Symptomatology

The disease symptomatology was assessed in both the MONARCH 2 and MONARCH plus studies using the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 until the end of treatment.

The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the “time to permanent deterioration” without subsequent improvement.

The so-called "time to permanent deterioration" was defined as an increase in score of ≥ 10 points from baseline without subsequent improvement to a score above this level. Death was excluded as an event. 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 "permanent deterioration" in this situation. Rather, it is a deterioration confirmed over the shortened observation period.

Furthermore, there are clear differences in observation times 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. Consequently, additional evaluations of first-time deterioration or once-confirmed deterioration would be necessary to interpret the presented data on patient-reported symptomatology endpoints in the present situation.

Despite corresponding criticism in IQWiG's benefit assessment, the pharmaceutical company did not subsequently submit these evaluations in the written statement procedure. The results for the endpoint symptomatology can therefore not be meaningfully interpreted and thus cannot be used for the benefit assessment.

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

Health status is assessed in the MONARCH 2 study using the EQ-5D visual analogue scale (VAS) up to 30 days after the end of treatment.

The pharmaceutical company shall submit responder analyses for the "time to confirmed deterioration" over the shortened observation period, defined as a decrease in the score by 15 points without subsequent improvement compared to the baseline value.

According to the above explanations on symptomatology, additional evaluations on first-time deterioration or once-confirmed deterioration would be necessary in order to be able to interpret the presented data on health status in the present situation.

Despite corresponding criticism in the IQWiG's benefit assessment, the pharmaceutical companydid not subsequently submit these evaluations in the written statement procedure. Theresults for the endpoint health status can therefore not be meaningfully interpreted and thus cannot be used for the benefit assessment.

Quality of life

Health-related quality of life was assessed in both studies 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 until the onset of disease progression.

The pharmaceutical company shall submit evaluations for the "time to confirmed deterioration" by ≥ 10 points over the shortened observation period up to 30 days after the end of treatment.

According to the above explanations on symptomatology, additional evaluations on first-time deterioration or once-confirmed deterioration would be necessary in order to be able to interpret the submitted quality-of-life data in the present situation.

Despite corresponding criticism in the IQWiG's benefit assessment, the pharmaceutical companydid not subsequently submit these evaluations in the written statement procedure. Theresults on quality of life can therefore not be meaningfully interpreted and thus cannot be used for the benefit assessment.

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 2 study, 98.8% of postmenopausal patients who had not yet received initial endocrine therapy experienced an adverse event in the intervention arm, compared to 91.4% of patients in the comparator arm.

In the MONARCH plus study, adverse events occurred in 100% of patients in the intervention arm and in 85.0% of patients in the control arm.

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

For the endpoints serious adverse events, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs, the meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib and fulvestrant.

Specific AEs

For the specific AEs neutropenia (CTCAE grade ≥ 3), diarrhoea (CTCAE grade ≥ 3), anaemia (CTCAE grade ≥ 3), eye disorders (AEs), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) and renal and urinary disorders (AEs), there was a statistically significant difference to the disadvantage of abemaciclib and fulvestrant.

Overall assessment

For the assessment of the additional benefit of abemaciclib in combination with fulvestrant 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 are available from a meta-analysis compared to fulvestrant. The meta-analysis includes the randomised, controlled, double-blind studies MONARCH 2 and MONARCH plus.

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

The analyses presented on symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-BR23) and health status (collected using EQ 5D-VAS) cannot be meaningfully interpreted and are not used for the benefit assessment. Furthermore, for the endpoint pain (strongest pain in the last 24 hours as well as increase in use of analgesics), there is no statistically significant difference between the treatment groups in the studies, neither for the combined endpoint nor for its individual components.

With regard to health-related quality of life, assessed using the scales of the EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-BR23 (functional scales), there are no data that can be meaningfully interpreted and thus cannot be used for the benefit assessment.

In the overall results on side effects, there are statistically significant and meaningful disadvantages for abemaciclib in combination with fulvestrant compared to fulvestrant with regard to the endpoints serious AEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, the specific severe adverse events (CTCAE grade ≥ 3) diarrhoea, neutropenia and anaemia each show disadvantages of abemaciclib in combination with fulvestrant.

In a weighing decision, the G-BA comes to the conclusion that there is no evidence of an additional benefit for abemaciclib in combination with fulvestrant for the treatment of postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine therapy compared to fulvestrant.

b1) Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy

Extent and probability of the additional benefit

Indication of a minor additional benefit

Justification:

Mortality

Overall survival was defined in the MONARCH 2 and MONARCH plus studies as the time between randomisation and death, regardless of the underlying cause of death.

For the endpoint overall survival, the meta-analysis of the studies for postmenopausal patients with prior endocrine therapy showed a statistically significant difference in the benefit of abemaciclib in combination with fulvestrant compared to fulvestrant.

There is an effect modification by the characteristic "type of disease" for overall survival. Accordingly, for patients with visceral metastases, there is a statistically significant effect in favour of abemaciclib in combination with fulvestrant. For patients with non-visceral metastases, however, there was no significant difference between the treatment groups.

In the overall consideration of the available results from the MONARCH 2 and MONARCH plus studies, the effect modification observed for the endpoint overall survival due to the characteristic "type of disease" is not considered sufficient to derive corresponding separate statements on the additional benefit in the overall assessment. The data on the subgroups "visceral metastases" and "non-visceral metastases" are nevertheless considered a relevant outcome of the benefit assessment and are therefore shown in the study results.

Morbidity

Progression-free survival

Progression-free survival was 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 both 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 results 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.

No meaningfully interpretable data on morbidity (health status (EQ 5D VAS) and symptomatology (EORTC QLQ-C30 and BR23)) and health-related quality of life (EORTC QLQ-C30 and BR23) are available for the new benefit assessment. For justification, please refer to the explanations under the endpoints on the EORTC QLQ-C30 and BR23 and the EQ 5D VAS in the endpoint categories morbidity and quality of life. With regard to the evaluations of pain (assessed by means of mBPI-SF) in the morbidity category, no statistically significant difference between the treatment groups was found.

On the basis of the available data, it is therefore not possible to adequately assess the extent to which the radiologically determined progression in the meta-analysis is associated with a change in morbidity and/or quality of life. The results on the progression-free survival endpoint 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 2 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 2 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

For the endpoint pain (assessed by mBPI-SF and the use of analgesics), time-to-event analysis are available for the time from randomisation to the first deterioration. Deterioration is defined as either an increase of ≥2 points from start of the study (on the symptom scale "strongest pain in the last 24 hours") or an increase in use of analgesics by more than one step (according to the WHO 3-step cancer pain management system).

In this respect, the pharmaceutical company submits separate evaluations for both endpoints for the MONARCH 2 study and evaluations for the endpoint "strongest pain in the last 24 hours" (assessed using mBPI-SF) for the MONARCH plus study. The increase of at least 2 points corresponds to a threshold of > 15 % of the total scale range of 0-11 points.

For the endpoint pain (strongest pain in the last 24 hours and increase in use of analgesics), the studies show no statistically significant difference between the treatment groups, neither for the combined endpoint nor for its individual components. In addition, for the endpoint "strongest pain in the last 24 hours", an effect modification by the characteristic age is shown. For patients aged ≥ 65 years, there was a statistically significant difference in the benefit of abemaciclib in combination with fulvestrant compared to fulvestrant, whereas for patients aged < 65 years there was no statistically significant difference. The significance of the available subgroup results is not considered sufficient for the overall assessment of the additional benefit.

Symptomatology

The disease symptomatology was assessed in both the MONARCH 2 and MONARCH plus studies using the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module EORTC QLQ-BR23 until the end of treatment.

The pharmaceutical company submitted responder analyses for the percentage of patients with a change of ≥ 10 points for the “time to permanent deterioration” without subsequent improvement.

The so-called "time to permanent deterioration" was defined as an increase in score of ≥ 10 points from baseline without subsequent improvement to a score above this level. Death was excluded as an event. 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 "permanent deterioration" in this situation. Rather, it is a deterioration confirmed over the shortened observation period.

Furthermore, there are clear differences in observation times 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. Consequently, additional evaluations of first-time deterioration or once-confirmed deterioration would be necessary to interpret the presented data on patient-reported symptomatology endpoints in the present situation.

Despite corresponding criticism in IQWiG's benefit assessment, the pharmaceutical company did not subsequently submit these evaluations in the written statement procedure. The results for the endpoint symptomatology can therefore not be meaningfully interpreted and thus cannot be used for the benefit assessment.

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

Health status is assessed in the MONARCH 2 study using the EQ-5D visual analogue scale (VAS) up to 30 days after the end of treatment.

The pharmaceutical company shall submit responder analyses for the "time to confirmed deterioration" over the shortened observation period, defined as a decrease in the score by 15 points without subsequent improvement compared to the baseline value.

According to the above explanations on symptomatology, additional evaluations on first-time deterioration or once-confirmed deterioration would be necessary in order to be able to interpret the presented data on health status in the present situation.

Despite corresponding criticism in the IQWiG's benefit assessment, the pharmaceutical companydid not subsequently submit these evaluations in the written statement procedure. Theresults for the endpoint health status can therefore not be meaningfully interpreted and thus cannot be used for the benefit assessment.

Quality of life

Health-related quality of life was assessed in both studies 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 until the onset of disease progression.

The pharmaceutical company shall submit evaluations for the "time to confirmed deterioration" by ≥ 10 points over the shortened observation period up to 30 days after the end of treatment.

According to the above explanations on symptomatology, additional evaluations on first-time deterioration or once-confirmed deterioration would be necessary in order to be able to interpret the submitted quality-of-life data in the present situation.

Despite corresponding criticism in the IQWiG's benefit assessment, the pharmaceutical companydid not subsequently submit these evaluations in the written statement procedure. Theresults on quality of life can therefore not be meaningfully interpreted and thus cannot be used for the benefit assessment.

Side effects

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

Adverse events (AEs)

In the MONARCH 2 study, 97.9% of postmenopausal patients with prior endocrine therapy experienced an adverse event in the intervention arm, compared to 89.4% of patients in the comparator arm.

In the MONARCH plus study, adverse events occurred in 100% of patients in the intervention arm and in 69.2% of patients in the control arm.

Serious adverse events (SAE)

For the endpoint of serious adverse events, no statistically significant difference was detected between the treatment arms.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

For the endpoints severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, the meta-analysis showed a statistically significant difference to the disadvantage of abemaciclib in combination with fulvestrant.

Specific AEs

For the specific AEs neutropenia (severe AE) and diarrhoea (severe AE), the MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib in combination with fulvestrant compared to fulvestrant. As no events occurred in the control arm of the MONARCH plus study, the effect estimator cannot be calculated and a meta-analysis is therefore not feasible in a meaningful way.

In addition, for the endpoints "gastrointestinal disorders" (AE) and "skin and subcutaneous tissue disorders" (AE), the meta-analysis shows a statistically significant difference in detail to the disadvantage of abemaciclib + fulvestrant compared to fulvestrant. In addition, for the endpoint "skin and subcutaneous tissue disorders", the subgroup analysis showed a statistically significant difference to the disadvantage of abemaciclib in combination with fulvestrant for patients ≥ 65 years in the MONARCH 2 study, whereas there was no statistically significant difference for patients < 65 years in the meta-analysis. The significance of the available subgroup results for the assessment of the additional benefit is considered insufficient overall.

Overall assessment

For the assessment of the additional benefit of abemaciclib in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer in postmenopausal patients with previous endocrine therapy (sub-population b1), results on the endpoint categories mortality, morbidity, health-related quality of life and side effects are available from a meta-analysis compared to fulvestrant. The meta-analysis includes the randomised, controlled, double-blind studies MONARCH 2 and MONARCH plus.

For overall survival, the meta-analysis shows an advantage of abemaciclib in combination with fulvestrant over fulvestrant.

The analyses presented on symptomatology (collected using EORTC QLQ-C30 and EORTC QLQ-BR23) and health status (collected using EQ 5D-VAS) in the endpoint category morbidity cannot be interpreted meaningfully. Furthermore, in the morbidity category for the endpoint pain (strongest pain in the last 24 hours as well as increase in use of analgesics), there is no statistically significant difference between the treatment groups in the studies, neither for the combined endpoint nor for its individual components.

With regard to health-related quality of life, surveyed using the scales of the EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-BR23 (functional scales), no meaningful interpretable data are available.

In the overall results on side effects, there are statistically significant and meaningful disadvantages for abemaciclib in combination with fulvestrant compared to fulvestrant with regard to the endpoints severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, the specific severe adverse events (CTCAE grade ≥ 3) diarrhoea and neutropenia each show disadvantages of abemaciclib in combination with fulvestrant.

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. Abemaciclib in combination with fulvestrant for the treatment of postmenopausal patients with HR+ and HER2- advanced or metastatic breast

carcinoma who have received previous endocrine therapy is found to have overall a minor additional benefit compared with fulvestrant.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on two randomised, double-blind and direct-comparison phase III studies, MONARCH 2 and MONARCH plus.

The risk of bias at the study level is rated as low.

The risk of bias for the results for the endpoint overall survival is also classified as low.

Uncertainties relevant to the reassessment after the deadline result from the fact that no evaluable data on morbidity (except pain) and quality of life are available for sub-population b1.

These uncertainties justify downgrading the reliability of data for the overall assessment, which could be categorised as "proof" if two randomised, double-blind and direct-comparison phase III studies were available. Thus, the reliability of data for the additional benefit determined is classified in the category “indication”.

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 01.04.2021. The assessment relates only to the use of abemaciclib in combination with fulvestrant for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in the following patient populations:

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

b1) Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy.

to sub-population a1)

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 not suitable

  or

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

  or

- abemaciclib 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

- palbociclib in combination with fulvestrant

For the assessment of the additional benefit of abemaciclib in combination with fulvestrant for the treatment of patients in sub-population a1, results of the meta-analysis on the endpoint categories mortality, morbidity, health-related quality of life and side effects compared to fulvestrant are available. The meta-analysis includes the randomised, controlled, double-blind studies MONARCH 2 and MONARCH plus.

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

The evaluations presented on morbidity (except pain) and quality of life cannot be interpreted in a meaningful way.

In the overall results on side effects, there are significant disadvantages for abemaciclib in combination with fulvestrant compared to fulvestrant.

In a weighing decision, the G-BA comes to the conclusion that there is no evidence of an additional benefit for abemaciclib in combination with fulvestrant for the treatment of postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine therapy compared to fulvestrant.

<u>to sub-population b1)</u>

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

Another endocrine therapy with:

- Tamoxifen

  or

- anastrozole

  or

- fulvestrant as monotherapy; only for patients with relapse or progression after antiestrogen treatment

  or

- letrozole; only for patients with relapse or progression after antiestrogen treatment

  or

- exemestane; only for patients with progression after anti-oestrogen treatment

  or

- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis following progression after a non-steroidal aromatase inhibitor.

  or

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

  or

- abemaciclib 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

- palbociclib in combination with fulvestrant

For the assessment of the additional benefit of abemaciclib in combination with fulvestrant for the treatment of patients in sub-population b1, results of the meta-analysis on the endpoint categories mortality, morbidity, health-related quality of life and side effects compared to fulvestrant are available. The meta-analysis includes the randomised, controlled, double-blind studies MONARCH 2 and MONARCH plus.

For overall survival, abemaciclib in combination with fulvestrant shows an advantage over fulvestrant.

The evaluations presented on morbidity (except pain) and quality of life cannot be interpreted in a meaningful way.

In the overall view of the results on side effects, there are statistically significant and meaningful disadvantages for abemaciclib in combination with fulvestrant compared to fulvestrant.

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. Abemaciclib in combination with fulvestrant for the treatment of postmenopausal patients with HR+ and HER2- advanced or metastatic breast carcinoma who have received previous endocrine therapy is found to have overall a minor additional benefit compared with fulvestrant.

The reliability of data of the additional benefit identified is classified in the "indication" 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 palbociclib (resolution of 18 May 2017).

The minor deviations in patient numbers compared to the named palbociclib resolution result only from the use of more current data on the incidence and prevalence of breast cancer in Germany and from the consideration of the current percentage of patients in the SHI target population of 87.7%.

The above range takes into account the existing uncertainties in the data 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: 18 February 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, 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: 1 May 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				
Abemaciclib in combination with fulvestrant				
Abemaciclib	continuously, 2 x daily	365	1	365
Fulvestrant	continuously, cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12[3]	1 - 2	13
Appropriate comparator therapy				
Patient population a1)				
Non-steroidal aromatase inhibitors				
Anastrozole	continuously, 1 x daily	365	1	365
or				
Letrozole	continuously, 1 x daily	365	1	365
Antiestrogens				
Fulvestrant	continuously, cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12[3]	1 - 2	13
or				
Tamoxifen if necessary[4]	continuously, 1 x daily	365	1	365
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Ribociclib	continuously, 1 x on day 1 – 21 of a 28 day cycle	13.0	21	273

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

[4] If aromatase inhibitors are not suitable

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Abemaciclib	continuously, 2 x daily	365	1	365
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
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
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
ribociclib in combination with fulvestrant				
Ribociclib	continuously, 1 x on day 1 – 21 of a 28 day cycle	13.0	21	273
Fulvestrant	continuously, cycle 1: 1 x on day 1, 15 and 29 from cycle 2 onwards: 1 x monthly	12[3]	1 - 3	14
Palbociclib in combination with fulvestrant				
Palbociclib	continuously, 1 x on day 1 – 21 of a 28 day cycle	13.0	21	273
Fulvestrant	continuously, cycle 1: 1 x on day 1, 15 and 29	12	1 - 3	14

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	from cycle 2 onwards: 1 x monthly			
Patient population b1)				
Antiestrogens				
Tamoxifen	continuously, 1 x daily	365	1	365
or				
Fulvestrant[5]	continuously, cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12[3]	1 - 2	13
Non-steroidal aromatase inhibitors				
Anastrozole	continuously, 1 x daily	365	1	365
or				
Letrozole[6]	continuously, 1 x daily	365	1	365
Steroidal aromatase inhibitors				
Exemestane[7]	continuously, 1 x daily	365	1	365
Everolimus in combination with exemestane[8]				
Everolimus	continuously, 1 x daily	365	1	365
Exemestane	continuously, 1 x daily	365	1	365
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Ribociclib	continuously, 1 x on day 1 – 21 of a 28 day cycle	13.0	21	273

[5] Fluvastatnt as monotherapy; only for patients with relapse or progression after antiestrogen treatment

[6] only for patients with relapse or progression after antiestrogen treatment

[7] Exemestane only for patients with progression after antiestrogen treatment

[8] Everolimus in combination with exemestane only for patients without symptomatic visceral metastasis following progression after a non-steroidal aromatase inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Abemaciclib	continuously, 2 x daily	365	1	365
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
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
Anastrozole	continuously, 1 x daily	365	1	365
Letrozole	continuously, 1 x daily	365	1	365
Ribociclib in combination with fulvestrant				
Ribociclib	continuously, 1 x on day 1 – 21 of a 28 day cycle	13.0	21	273
Fulvestrant	continuously, cycle 1: 1 x on day 1, 15 and 29 from cycle 2 onwards: 1 x monthly	12[3]	1 - 3	14
Palbociclib in combination with fulvestrant				
Palbociclib	continuously, 1 x on day 1 – 21 of a 28 day cycle	13.0	21	273
Fulvestrant	continuously, cycle 1: 1 x on day 1, 15 and 29	12[3]	1 - 3	14

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	from cycle 2 onwards: 1 x monthly			

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 in combination with fulvestrant					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13	26x 250 mg
Appropriate comparator therapy					
Patient population a1)					
Non-steroidal aromatase inhibitors					
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
or					
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
Antiestrogens					
Fulvestrant	500 mg	500 mg	2 x 250 mg	13	26 x 250 mg
or					
Tamoxifen, if necessary[3]	20 mg	1 x 20 mg	365	365 x 20 mg	20 mg
ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Ribociclib	600 mg	600 mg	3 x 200 mg	273	819 x 200 mg
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

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 in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
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
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	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	273 x 125 mg
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
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 x 200 mg	273	819 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14	28x 250 mg
Palbociclib in combination with fulvestrant					
Palbociclib	125 mg	125 mg	1 x 125 mg	273	273 x 125 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14	28x 250 mg
Patient population b1)					
Antiestrogens					
Tamoxifen	20 mg	1 x 20 mg	365	365 x 20 mg	20 mg
or					
Fulvestrant[4]	500 mg	500 mg	2 x 250 mg	13	26 x 250 mg
Non-steroidal aromatase inhibitors					
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
or					
Letrozole[5]	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
Steroidal aromatase inhibitors					
Exemestane[6]	25 mg	25 mg	1 x 25 mg	365	365 x 25 mg
Everolimus in combination with exemestane[7]					
Everolimus	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Exemestane	25 mg	25 mg	1 x 25 mg	365	365 x 25 mg
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Ribociclib	600 mg	600 mg	3 x 200 mg	273	819 x 200 mg
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
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
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
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	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	273 x 125 mg
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
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 x 200 mg	273	819 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14	28 x 250 mg
Palbociclib in combination with fulvestrant					
Palbociclib	125 mg	125 mg	1 x 125 mg	273	273 x 125 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14	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	€ 1.77	€ 326.11	€ 5,439.84
Fulvestrant 250 mg	2 SFI	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Appropriate comparator therapy					
Abemaciclib 150 mg	168 FCT	€ 5,767.72	€ 1.77	€ 326.11	€ 5,439.84
Anastrozole 1 mg[9]	100 FTA	€ 57.51	€ 1.77	€ 3.66	€ 52.08
Everolimus 10 mg[9]	30 TAB	€ 769.86	€ 1.77	€ 36.00	€ 732.09
Exemestane 25 mg[9]	100 FCT	€ 127.50	€ 1.77	€ 9.19	€ 116.54
Fulvestrant 250 mg	2 SFI	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Letrozole 2.5 mg[9]	100 FCT	€ 53.44	€ 1.77	€ 3.33	€ 48.34
Palbociclib 125 mg	21 FCT	€ 2,461.87	€ 1.77	€ 137.31	€ 2,322.79
Ribociclib 200 mg	189 FCT	€ 6,846.11	€ 1.77	€ 0.00	€ 6,844.34
Tamoxifen 20 mg[9]	100 TAB	€ 22.43	€ 1.77	€ 0.88	€ 19.78
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; TAB = tablets					

LAUER-TAXE® last revised: 1 May 2022

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.

[9] Fixed reimbursement rate

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.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 28 September 2021.

On 30 November 2021, 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, number 5 VerfO.

By letter dated 2 December 2021 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 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 11 April 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 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, 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 determination of the appropriate comparator therapy
Working group Section 35a	6 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 April 2022	Conduct of the oral hearing, if necessary: Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	21 April 2022 4 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

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

Prof. Hecken