Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Abemaciclib (Breast Cancer; in Combination with Fulvestrant)

of 2 May 2019

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

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

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

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient abemaciclib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 November 2018. 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 18 September 2018.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 February 2019 on the website of the G-BA (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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by 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 light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of 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 peri-menopausal women, the endocrine therapy should be combined with an LHRH agonist (LHRH = luteinising hormone-releasing hormone).

Indication:

This assessment relates exclusively to the assessment of the additional benefit abemaciclib in combination with fulvestrant. For the assessment of the additional benefit of abemaciclib with an aromatase inhibitor, reference is made to the separate benefit assessment procedure for this combination therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for abemaciclib in combination with an aromatase inhibitor in women with HR-positive, HER2-negative advanced or metastatic breast cancer is:

a1) for post-menopausal women who have not yet received initial endocrine therapy:

Anastrozole *or* letrozole *or* fulvestrant *or* possibly tamoxifen if aromatase inhibitors are not suitable,

a2) for pre- and peri-menopausal women who have not yet received initial endocrine therapy:

Tamoxifen in combination with an elimination of the ovarian function.

b1) for post-menopausal women with prior endocrine therapy:

Another endocrine therapy depending on the previous therapy with:

- tamoxifen *or*
- anastrozole *or*
- fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment *or*
- letrozole; only for patients with relapse or progress after anti-oestrogen treatment *or*
- exemestane; only for patients with progress after anti-oestrogen treatment *or*
- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

b2) for pre-/peri-menopausal women with prior endocrine therapy:

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

Endocrine therapy according to the doctor's instructions, taking into account the respective marketing authorisation.

Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone acetate are approved for the present therapeutic indication.

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

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

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

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

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

On 1. In addition to abemaciclib, medicinal products with the following active ingredients are approved for the present therapeutic indication: anastrozole, everolimus, exemestane, fulvestrant, goserelin, letrozole, leuprorelin, medroxyprogesterone acetate, megestrol acetate, palbociclib, ribociclib, tamoxifen, and toremifene.

Medicinal products with explicit marketing authorisation for hormone receptor-negative and HER2/neu-positive mammary carcinomas were not considered.

For the present therapeutic indication, it is assumed that an endocrine therapy is indicated for the patients and that there is no indication for chemotherapy.

On 2. As non-medicinal therapies, surgical resection and/or radiotherapy are generally considered for the treatment of mammary carcinoma. In the context of endocrine therapy, an ovariectomy to eliminate ovarian function may be considered.

For the present therapeutic indication, it is assumed that radiotherapy and/or (secondary) resection for curative purposes is not indicated. Therefore, (secondary) resection and/or radiotherapy were not included in the appropriate comparator therapy.

On 3. The following resolutions and guidelines of the G-BA have been issued on medicinal therapies in the present therapeutic indication:

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

Palbociclib: Resolution of 22 March 2019

Ribociclib: Resolution of 16 March 2018

Palbociclib: Resolution of 18 May 2017

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

National and international guidelines recommend aromatase inhibitors for initial endocrine therapy in advanced or metastatic stages in post-menopausal women (sub-population a1). As an alternative in the case of aromatase inhibitor intolerance, tamoxifen, which is also authorised, is an appropriate therapy.

In addition, the anti-oestrogen fulvestrant is another treatment option authorised for this indication. In the context of a Cochrane Review[2] and the FIRST study[3] included therein, an advantage of fulvestrant compared with the aromatase inhibitor anastrozole is described with regard to overall survival. Also in international guidelines, monotherapy with fulvestrant is a recommended treatment option for initial endocrine therapy.

For the initial endocrine therapy of pre- and peri-menopausal patients included in the present therapeutic indication (sub-population a2), tamoxifen in combination with an elimination of the ovarian function is recommended. Here, ovarian suppression by LHRH analogues or ovariectomy may be considered.

In the therapy situation of disease progression in post-menopausal patients after endocrine pre-treatment (sub-population b1), national and international guidelines unanimously recommend further endocrine therapy using an alternative active ingredient unless there is an indication for chemotherapy. With regard to the significance of gestagens, the corresponding statements in the guidelines are less clear than for 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 regard the gestagens as a regular treatment option for the present therapy situation and therefore does not include them in the appropriate comparator therapy. The restrictions to certain patient populations in the case of fulvestrant, letrozole, exemestane, and everolimus in combination with exemestane reflect the respective authorisation status.

For the sub-population pre- and peri-menopausal patients with progression after endocrine therapy (sub-population b2), there is a limited number of authorised treatment options. In accordance with the marketing authorisation, tamoxifen, medroxyprogesterone acetate, and megestrol acetate as well as the aromatase inhibitors exemestane and letrozole (in connection with an induced post-menopause) are possible candidates. The GnRH analogues leuprorelin and goserelin are also approved but are mainly used as add-on therapy for ovarian suppression. In this situation, however, tamoxifen will have been predominantly used as an initial therapy. As an alternative, an aromatase inhibitor may be considered (subject to marketing authorisation). The evidence available for the relevant progestins is not considered sufficient for a concrete recommendation.

It is assumed that ovarian suppression is continued with a GnRH analogue.

According to the guidelines, further endocrine therapy is unanimously recommended after initial endocrine therapy unless there is an indication for chemotherapy.

The endocrine therapy should be carried out according to the doctor's instructions in the respective treatment situation. The marketing authorisation and dosage data of the

[2] Lee CI, Goodwin A, Wilcken N. Fulvestrant for hormone-sensitive metastatic breast cancer. Cochrane Database Syst Rev. 2017 Jan 3; 1:CD011093.

[3] Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. J Clin Oncol. 2015 Nov 10; 33(32): 3781–7.

product information of the active ingredient shall be taken into account, and deviations shall be justified separately.

With the CDK 4/6 inhibitors abemaciclib (in combination with an aromatase inhibitor) and ribociclib (in combination with fulvestrant or with an aromatase inhibitor), two further treatment options are available. These are authorised in the present therapeutic indication and are still quite new in the field of care. Both active ingredients are currently undergoing a benefit assessment procedure.
Furthermore, for the CDK 4/6 inhibitor palbociclib in combination with an aromatase inhibitor as initial endocrine therapy, no additional benefit was found by the G-BA. The period of validity of the corresponding resolution of 18 May 2017 was limited. For palbociclib in combination with fulvestrant, no additional benefit was identified by resolution of 22 March 2019. Similarly, ribociclib in combination with an aromatase inhibitor as an initial endocrine therapy in post-menopausal women was found to have no additional benefit. The period of validity of the corresponding resolution of 16 March 2018 was limited.
Based on the benefit assessments carried out so far, the CDK 4/6 inhibitors mentioned in the respective combinations cannot be considered as appropriate comparator therapy.

For the present therapeutic indication, it is assumed for all sub-populations that further endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative objectives. Furthermore, it is assumed that in pre- and peri-menopausal patients, the ovarian function is suppressed by ovariectomy or a GnRH analogue.

Division according to menopause status (pre-menopausal/peri-menopausal and post-menopausal patients):

The division according to menopause status results from the fact that pre-menopausal patients differ physiologically from post-menopausal patients and that there is a significant pathophysiological difference with regard to the hormone-dependent tumour biology presented here.

In the guidelines for endocrine therapy in advanced metastatic breast cancer, a clear and unanimous distinction is made between pre-menopausal and post-menopausal patients, each with distinct therapy recommendations.

In addition, for most of the medicinal products used in endocrine therapy in the respective approved therapeutic indications, the menopausal status of the patients is specifically taken into account, and restrictions are made in this regard.

The written statements of medical experts in the present benefit assessment procedure also refer to the special situation of pre-menopausal/peri-menopausal patients in contrast to post-menopausal patients, including the course of the disease and the burden of symptoms.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of abemaciclib in combination with fulvestrant is assessed as follows:

Description of the MONARCH-2 study

The pharmaceutical company submitted results from the randomised, double-blind MONARCH-2 Phase III study to demonstrate the additional benefit of abemaciclib in combination with fulvestrant.

This multinational study (N = 669) included pre-/peri-menopausal and post-menopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who

had not received endocrine therapy for treatment of the locally advanced or metastatic disease or who had been previously treated with endocrine therapy. The medicinal product combination abemaciclib + fulvestrant (N = 446) was compared with placebo + fulvestrant (N = 223). Pre-/peri-menopausal patients also received a GnRH agonist to suppress ovarian function.

With regard to previous therapy, patients who experienced disease progression either during a (neo)adjuvant endocrine therapy or within 12 months after completion of an adjuvant endocrine therapy were included. In addition, patients with progression after first-line endocrine therapy in the metastatic stage who were previously progressive or *de novo* in the metastatic stage later than 12 months after completion of adjuvant endocrine therapy were included.

At the start of study, patients who had never received endocrine therapy before were included until a protocol change was made. The results of these endocrine naïve patients were evaluated separately in the dossier of the pharmaceutical company. These are 44 patients who were recruited in addition to the 669 patients described above. Of these, 36 patients are post-menopausal and were assigned to sub-population a1. For the group of endocrine-naïve patients, however, only a selection of the endpoints have been evaluated, and only a summary of these evaluations is available for post- and pre-/peri-menopausal patients. The results for these patients can therefore not be used for the present assessment.

In MONARCH-2, stratification factors were disease type (visceral metastases vs only bone metastases vs others) and sensitivity to endocrine therapy (primary vs secondary vs prior to additional admission of endocrine-naïve patients: not endocrine treated). Primary resistance was defined as the disease-free interval of ≤ 24 months during adjuvant endocrine therapy or progression within 6 months during endocrine therapy for the advanced/metastatic stage. Secondary resistance applied to all patients who did not meet the criteria for primary resistance.

Treatment was continued until disease progression or discontinuation for other reasons. A change of treatment from the comparator arm to the intervention arm (cross-over) was not permitted in MONARCH-2.

In the MONARCH-2 study, according to the initial study protocol, a starting dose of 200 mg abemaciclib every 12 hours was prescribed. However, this dosage did not correspond to the final permitted dosage of 150 mg every 12 hours. As part of a protocol change, the starting dose was reduced to the later approved dosage. With regard to post-menopausal patients, 27% had already been included in the intervention arm and 26% in the control arm at this time. However, the patients in the MONARCH-2 study received abemaciclib at the higher dose of 200 mg only for a relatively short period of time compared with the median total treatment duration. The higher dose did not significantly influence the dose intensity. It is therefore assumed that the high starting dose does not significantly influence the study results.

The ongoing MONARCH-2 study started in August 2014 and is being conducted multi-centrically in 145 study centres in Asia, Australia, Europe and, North America.
For the benefit assessment, the data cut-off of 14 February 2017 was used.

For separate consideration of MONARCH-2 patients after initial endocrine therapy or with prior endocrine therapy in locally advanced or metastatic stage

The MONARCH-2 study included pre-/peri-menopausal and post-menopausal patients who had either not received endocrine therapy in an advanced or metastatic stage or had been previously treated with endocrine therapy in this stage. The results of the study were presented by the pharmaceutical company in the dossier for the benefit assessment as part of a summarised evaluation for all pre-menopausal/peri-menopausal patients and all post-menopausal patients, regardless of whether or not they had received previous endocrine therapy in the locally advanced or metastasised stage.

However, in determining the appropriate comparator therapy in relation to the previous endocrine therapy, the G-BA differentiated the patients into different groups depending on whether they had not received initial endocrine therapy in the locally advanced or metastatic stage or had already been treated with a prior endocrine therapy. This was done in particular against the background of the correspondingly differentiated recommendations in national and international guidelines and taking into account the authorisation status of the relevant medicinal products (see also Section 2.1.2 on appropriate comparator therapy).
In the MONARCH-2 study, the majority of patients received the last prior endocrine therapy in the (neo)adjuvant stage (54%). It should be noted that these patients showed a short disease-free interval according to the inclusion criteria and thus an early relapse. The remainder of the patients had already received prior endocrine therapy for the advanced or metastatic stage. In these patients, either a long disease-free interval and thus a late relapse had previously been observed after successful adjuvant endocrine therapy or they were already *de novo* in a locally advanced or metastatic stage.
In this context, it should be noted that these two patient populations with early or late relapse are to be differentiated from a clinical point of view. This is particularly true against the background that the characteristic of early or late relapse is a prognostic factor.
The written statements in the present benefit assessment procedure, including the opinions of medical experts, as well as in the statements in the dossier of the pharmaceutical company take the that all patients in the MONARCH-2 study can be described as “endocrine resistant” because of disease progression either during or shortly after (neo)adjuvant endocrine therapy or endocrine therapy in locally advanced or metastatic stages. This calls into question the subdivision according to therapy line in the advanced or metastatic stage. The choice of endocrine therapy would be made in the locally advanced or metastatic stage, particularly on the basis of the type of previous therapy and not according to therapy line. In addition, the MONARCH-2 study would be understood in relevant guidelines exclusively as a study that examines patients after endocrine therapy with respect to their advanced or metastatic stage.

In principle, the G-BA can understand this argumentation. However, for the medical reasons already mentioned, it does not consider it appropriate to consider the two patient populations together.
The present approved therapeutic indication also differentiates between the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine therapy and women with prior endocrine therapy.

For these reasons, the present assessment differentiates the results of the MONARCH-2 study in accordance with the respective sub-populations according to the established appropriate comparator therapy. In the dossier evaluation of the IQWiG, the results for the relevant sub-populations were taken from the sub-group analyses in the dossier of the pharmaceutical company for the characteristic “prior endocrine therapy for metastatic/locally advanced disease” (yes vs no).

Implementation of the appropriate comparator therapy in the MONARCH-2 study in the b1 and b2 sub-populations:

In the MONARCH-2 study, monotherapy with fulvestrant was prescribed for the control group as per study protocol. The MONARCH-2 study was therefore limited to a single therapeutic option in the comparator arm with fulvestrant.

For sub-population b1, in addition to several approved therapy options recommended in the guidelines, the G-BA determined fulvestrant as an appropriate comparator therapy for post-menopausal patients with relapse or progress after anti-oestrogen treatment (in this context: tamoxifen or toremifen) only to a limited extent according to the marketing authorisation. In MONARCH-2, post-menopausal patients who can be assigned to sub-population b1 were included if they had received an aromatase inhibitor or an anti-oestrogen as prior endocrine therapy in the locally advanced or metastatic stage. Thus, only a part of these patients had received prior treatment with an anti-oestrogen.
The marketing authorisation of fulvestrant provides for its use in patients with relapse during or after adjuvant anti-oestrogen therapy or in the case of disease progression with anti-

oestrogen therapy. In 2010, the EMA[4] did not comply with a corresponding application for a marketing authorisation extension for fulvestrant even after pre-treatment with aromatase inhibitors because the risk-benefit ratio was judged to be unfavourable. On 29 May 2017, the EMA again rejected a repeated application for a corresponding extension of approval on the grounds that no new evidence had been submitted compared with the first application (see EPAR on fulvestrant[5,6]).

However, the guidelines explicitly recommend fulvestrant as a treatment option for post-menopausal women after pre-treatment with aromatase inhibitors in addition to other active ingredients (e.g. tamoxifen). This significance of fulvestrant in the reality of care was also emphasised in the corresponding written statements of medical societies in the present procedure, according to which fulvestrant is a therapy option regularly applied in the present treatment situation alongside other endocrine therapies.

For pre-/peri-menopausal patients with progression after endocrine therapy, the G-BA determined an "endocrine therapy according to the doctor's instructions, taking into account the respective marketing authorisation" to be the appropriate comparator therapy. In MONARCH-2, all pre-/peri-menopausal patients were also treated exclusively with fulvestrant (plus a GnRH agonist for ovarian suppression). Thus, the investigator did not have a choice of several therapy options that could be considered in the therapeutic indication in question. With regard to the present treatment situation, there is no information available as to how fulvestrant should be assessed as the appropriate endocrine therapy according to the doctor's instructions for all patients. In addition, fulvestrant is explicitly approved for post-menopausal patients only. However, according to the guidelines, fulvestrant is also an established therapeutic option for pre-/peri-menopausal patients in addition to other active ingredients such as tamoxifen together with elimination of ovarian function. This view is also supported in corresponding statements by medical experts in the present written statement procedure.

In the special therapy and medical treatment situation in the therapeutic indication in question and by acknowledging the corresponding written statements of medical experts in the procedure in question, the G-BA sees a sufficient medical reason that, despite remaining uncertainties, justifies assessing fulvestrant or fulvestrant alone as a sufficiently suitable comparator without taking into account further endocrine therapies indicated in accordance with the guidelines in the present treatment situation and also using the data from the MONARCH-2 study for the benefit assessment for sub-populations b1 and b2.

The G-BA points out that it will continue to adhere to the principles laid down in the provisions on benefit assessment in accordance with Section 35a SGB V (AM-NutzenV and Chapter 5 of the Rules of Procedure of the G-BA) and thus also to the requirement laid down in Chapter 5, Section 6, paragraph 3, sentence 2, No. 1 VerfO that comparative therapy be used in the clinical trial used for benefit assessment in compliance with the marketing authorisation.

If the fulvestrant used as comparator in this study has been used in a manner that is not compliant with marketing authorisation, it is not possible to draw any conclusions about its usefulness in the application form that exceeds the authorisation in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V.

Extent and probability of the additional benefit

a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally

[4] European Medicines Agency
[5] European Medicines Agency. Assessment report: Faslodex. 25 October 2010, pages 31 and 45
[6] European Medicines Agency. Assessment report: Faslodex. 29 May 2017, Page 40

advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

For post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy, an additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparative therapy is not proven.

Mortality

In the MONARCH-2 study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death. In MONARCH-2, overall survival was a secondary endpoint.
For overall survival, MONARCH-2 showed no statistically significant difference between study arms for post-menopausal patients who had not yet received initial endocrine therapy (HR: 0.76 [95% CI: 0.47; 1.23]; p-value = 0.279). Median survival has not yet been achieved because of the low number of events.

For the endpoint category mortality, there is no additional benefit from adding abemaciclib to therapy with fulvestrant based on the results available.

Morbidity

Progression-free survival (PFS)

In the MONARCH-2 study, progression-free survival was the primary endpoint and was defined as the time between randomisation and disease progression (determined by the investigator using RECIST criteria version 1.1) or death regardless of the underlying cause.
In the dossier of the pharmaceutical company, the results for these endpoints were also presented in the form of summarised evaluations for all post-menopausal patients. No differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received previous endocrine therapy or not.
For this endpoint, there are therefore no usable data for the relevant sub-population a1.

Health status (EQ-5D visual analogue scale) and symptomatology

In the endpoint category morbidity, health status (EQ-5D VAS), and symptomatology (mBPI-SFI, symptom scales of the EORTC QLQ-C30 and -BR23) were assessed.
In the dossier of the pharmaceutical company, the results for these endpoints were presented in the form of summarised evaluations for all post-menopausal patients. No differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received previous endocrine therapy or not.
In the course of the written statement procedure, the pharmaceutical company submitted additional evaluations with an adapted operationalisation for the aforementioned endpoints; however, this was also done only in the summarised presentation described above. There are therefore no usable data for the relevant sub-population a1.

Quality of life

The health-related quality of life was measured using the functional scales of the EORTC QLQ-C30 and -BR23 survey instruments.
Also for the endpoints in this category, no usable data for the relevant sub-population are available for all post-menopausal patients in the dossier of the pharmaceutical company and in the documents submitted in the written statement procedure because of the summarised evaluations described above.

Side effects

Adverse events (AE)

In MONARCH-2, of post-menopausal patients who had not yet received initial endocrine therapy, 99.1% in the intervention arm and 86.8% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

For the serious adverse events, there was a statistically significant effect to the detriment of abemaciclib in combination with fulvestrant (HR: 3.11 [95% CI: 1.59; 6.09]; $p < 0.001$).

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

When assessing the results on the serious adverse events, a risk of bias must be considered. In MONARCH-2, high and varying proportions of patients between the study arms discontinued treatment. This was essentially determined by the discontinuation because of progression and resulted in different median treatment durations between the study arms. Disease progression is potentially informative for the occurrence of events of this endpoint.

Severe AE (CTCAE grade 3 or 4)

In terms of time to the occurrence of severe adverse events with CTCAE grade 3 or 4, there was a statistically significant treatment effect to the disadvantage of abemaciclib in combination with fulvestrant (HR: 3.83 [95% CI: 2.54; 5.79]; $p < 0.001$).
As for the endpoint SAE, the results of the endpoint severe adverse events are considered potentially biased.

Discontinuation because of AE

For the present assessment, the evaluation of the discontinuation of one or both medications because of adverse events was used. For the median time to therapy discontinuation because of AE, a statistically significant effect was observed to the detriment of abemaciclib in combination with fulvestrant (HR: 4.04 [95% CI: 1.59; 10.23]; p-value = 0.002).
For the endpoint discontinuation because of AE, a low risk of bias can be assumed.

Specific AE

A selection of specific AEs based on the frequencies and differences between the treatment arms could not be made because there are no data on the frequent events from the endpoint category side effects for sub-population a1. Because specific AE can also be selected if they are particularly important for the clinical picture or the active ingredients used in the study, the specific AE neutropenia (CTCAE grade ≥ 3) was selected on this basis.

However, neither the dossier of the pharmaceutical company nor the documents submitted as part of the written statement procedure provide adequate evaluations of this endpoint for the relevant sub-population.

The side-effect profile of abemaciclib is qualitatively comparable to the side-effect profile of cytotoxic chemotherapy and differs significantly from the side-effect profile of endocrine therapy.

Overall assessment

For the assessment of the extent of the additional benefit of abemaciclib in combination with fulvestrant, results from the MONARCH-2 study in comparison to fulvestrant on mortality (overall survival), and side effects are available.

The data on overall survival are preliminary, and therefore no assessment of the effect on overall survival can as yet be drawn for the mortality endpoint category. Based on the available data, there is no statistically significant difference in overall survival between the study arms. Final analyses on the endpoint of overall survival are pending. Based on the data available, an additional benefit of abemaciclib in combination with fulvestrant is not proven for overall survival.

No usable data are available for the endpoints of the categories morbidity (symptomatology and health status) and quality of life for the relevant sub-population because the pharmaceutical company submitted summarised evaluations in the dossier and in the documents submitted within the framework of the written statement procedure for all post-menopausal patients in which no differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received a previous endocrine therapy or not. There are thus no usable data for the endpoint “progression-free survival” for the sub-population under consideration.

For the side effects, with regard to the endpoints serious adverse events (SAE), severe adverse events (CTCAE grade 3 or 4), and therapy discontinuation because of adverse events, statistically significant disadvantages for abemaciclib in combination with fulvestrant compared with fulvestrant can be identified. For relevant specific AE, in particular neutropenia (CTCAE grade 3 or 4), no evaluations were available for the sub-population under consideration.
The overall side effect profile of abemaciclib differs significantly from that of endocrine therapy. However, taking into account clinical relevance, the disadvantage in terms of side effects does not reach an extent that would justify a lesser benefit in the overall assessment.

In a balancing decision, the G-BA concluded that abemaciclib in combination with fulvestrant for the treatment of post-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer who did not yet receive initial endocrine therapy at this stage of the disease has no proven additional benefit compared with fulvestrant.

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

For pre-/peri-menopausal patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy, an additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparative therapy is not proven.

Justification:

For pre-/peri-menopausal patients who have not yet received initial endocrine therapy, no suitable data were provided to assess the additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparator therapy.

For pre-/peri-menopausal patients who have not yet received initial endocrine therapy, the G-BA has defined “tamoxifen in combination with an elimination of the ovarian function” as an appropriate comparator therapy. In MONARCH-2, all pre-/peri-menopausal patients were treated with fulvestrant in the comparator arm (as well as a GnRH agonist for ovarian

suppression). Fulvestrant is explicitly approved for post-menopausal patients only. For the treatment of pre-/peri-menopausal patients who have not yet received initial endocrine therapy, tamoxifen is an approved treatment option recommended in the guidelines. The appropriate comparator therapy was therefore not adequately implemented for sub-population a2.

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

For post-menopausal women with hormone receptor (HR)- HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy, an additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparative therapy is not proven.

Mortality

For overall survival, MONARCH-2 showed no statistically significant difference between study arms for post-menopausal patients with prior endocrine therapy (HR: 1.09 [95% CI: 0.57; 2.09]; p-value = 0.751). Median survival has not yet been achieved because of the low number of events.

For the endpoint category mortality, there is no additional benefit from adding abemaciclib to therapy with fulvestrant based on the results available.

Morbidity

Progression-free survival (PFS)

In the dossier of the pharmaceutical company, the results for the endpoint “progression-free survival” were presented in the form of summarised evaluations for all post-menopausal patients. No differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received previous endocrine therapy or not.
For this endpoint, there are therefore no usable data for the relevant sub-population b1.

Health status (EQ-5D visual analogue scale) and symptomatology

In the endpoint category morbidity, health status (EQ-5D VAS), and symptomatology (mBPI-SFI, symptom scales of the EORTC QLQ-C30 and -BR23) were assessed.

In the dossier of the pharmaceutical company, the results for these endpoints were presented in the form of summarised evaluations for all post-menopausal patients. No differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received previous endocrine therapy or not.
In the course of the written statement procedure, the pharmaceutical company submitted additional evaluations with an adapted operationalisation for the aforementioned endpoints; however, this was also done only in the summarised presentation described above. There are therefore no usable data for the relevant sub-population b1.

Quality of life

The health-related quality of life was measured using the functional scales of the EORTC QLQ-C30 and -BR23 survey instruments.
Also for the endpoints in this category, no usable data for the relevant sub-population are available for all post-menopausal patients in the dossier of the pharmaceutical company and in the documents submitted in the written statement procedure because of the summarised evaluations described above.

Side effects

Adverse events (AE)

In MONARCH-2, of post-menopausal patients with prior endocrine therapy, 97.9% in the intervention arm and 89.4% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

For the serious adverse events, there was no statistically significant difference between the study arms.

When assessing the results on the serious adverse events, a risk of bias must be considered. In MONARCH-2, high and varying proportions of patients between the study arms discontinued treatment. This was essentially determined by the discontinuation because of progression and resulted in different median treatment durations between the study arms. Disease progression is potentially informative for the occurrence of events of this endpoint.

Severe AE (CTCAE grade 3 or 4)

In terms of time to the occurrence of severe adverse events with CTCAE grade 3 or 4, there was a statistically significant treatment effect to the disadvantage of abemaciclib in combination with fulvestrant (HR: 2.70 [95% CI: 1.64; 4.43]; p < 0.001).
As for the endpoint SAE, the results of the endpoint severe adverse events are considered potentially biased.

Discontinuation because of AE

For the present assessment, the evaluation of the discontinuation of one or both medications because of adverse events was used. For the median time to therapy discontinuation because of AE, a statistically significant effect was observed to the detriment of abemaciclib in combination with fulvestrant (HR: 5.42 [95% CI: 1.29; 22.85]; p-value = 0.008).
For the endpoint discontinuation because of AE, a low risk of bias can be assumed.

Specific AE

A selection of specific AEs based on the frequencies and differences between the treatment arms could not be made because there are no data on the frequent events from the endpoint category side effects for sub-population b1. Because specific AE can also be selected if they are particularly important for the clinical picture or the active ingredients used in the study, the specific AE neutropenia (CTCAE grade ≥ 3) was selected on this basis.

However, neither the dossier of the pharmaceutical company nor the documents submitted as part of the written statement procedure provide adequate evaluations of this endpoint for the relevant sub-population.

The side-effect profile of abemaciclib is qualitatively comparable to the side-effect profile of cytotoxic chemotherapy and differs significantly from the side-effect profile of endocrine therapy.

Overall assessment

For the assessment of the extent of the additional benefit of abemaciclib in combination with fulvestrant, results from the MONARCH-2 study in comparison to fulvestrant on mortality (overall survival), and side effects are available.

The data on overall survival are preliminary, and therefore no assessment of the effect on overall survival can as yet be drawn for the mortality endpoint category. Based on the available data, there is no statistically significant difference in overall survival between the study arms. Final analyses on the endpoint of overall survival are pending. Based on the data available, an additional benefit of abemaciclib in combination with fulvestrant is not proven for overall survival.

No usable data are available for the endpoints of the categories morbidity (symptomatology and health status) and quality of life for the relevant sub-population because the pharmaceutical company submitted summarised evaluations in the dossier and in the documents submitted within the framework of the written statement procedure for all post-menopausal patients in which no differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received a previous endocrine therapy or not. There are thus no usable data for the endpoint “progression-free survival” for the sub-population under consideration.

For the side effects, with regard to the endpoints severe adverse events (CTCAE grade 3 or 4), and therapy discontinuation because of adverse events, statistically significant disadvantages for abemaciclib in combination with fulvestrant compared with fulvestrant can be identified. For relevant specific AE, in particular neutropenia (CTCAE grade 3 or 4), no evaluations were available for the sub-population under consideration.
The overall side effect profile of abemaciclib differs significantly from that of endocrine therapy. However, taking into account clinical relevance, the disadvantage in terms of side effects does not reach an extent that would justify a lesser benefit in the overall assessment.

In a balancing decision, the G-BA concluded that abemaciclib in combination with fulvestrant for the treatment of post-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy has no proven additional benefit compared with fulvestrant.

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

For pre-/peri-menopausal patients with hormone receptor (HR)- HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy, an additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparative therapy is not proven.

Justification:

Mortality

For the overall survival of pre-/peri-menopausal patients with prior endocrine therapy in the MONARCH-2 study, there are no data on event time analysis because of the small number of events in the small sub-population of 46 patients (the pharmaceutical company did not carry out an evaluation if there were fewer than 10 events).

Morbidity

Progression-free survival (PFS)

In the dossier of the pharmaceutical company, the results for the endpoint “progression-free survival” were presented in the form of summarised evaluations for all pre-/peri-menopausal

patients. No differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received previous endocrine therapy or not.
For this endpoint, there are therefore no usable data for the relevant sub-population b2.

Health status (EQ-5D visual analogue scale) and symptomatology

In the endpoint category morbidity, health status (EQ-5D VAS), and symptomatology (mBPI-SFI, symptom scales of the EORTC QLQ-C30 and -BR23) were assessed.

In the dossier of the pharmaceutical company, the results for these endpoints were presented in the form of summarised evaluations for all post-menopausal patients. No differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received previous endocrine therapy or not.
In the course of the written statement procedure, the pharmaceutical company submitted additional evaluations with an adapted operationalisation for the aforementioned endpoints; however, this was also done only in the summarised presentation described above. There are therefore no usable data for the relevant sub-population b2.

Quality of life

The health-related quality of life was measured using the functional scales of the EORTC QLQ-C30 and -BR23 survey instruments.
Also for the endpoints in this category, no usable data for the relevant sub-population are available for all post-menopausal patients in the dossier of the pharmaceutical company and in the documents submitted in the written statement procedure because of the summarised evaluations described above.

Side effects

Adverse events (AE)

In MONARCH-2, of pre-/peri-menopausal patients with prior endocrine therapy, 96.2% in the intervention arm and 95.0% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

For the serious adverse events, there are no data on event time analysis because of the small number of events (the pharmaceutical company did not carry out an evaluation if there were fewer than 10 events).

Severe AE (CTCAE grade 3 or 4)

In terms of time to the occurrence of severe adverse events with CTCAE grade 3 or 4, there was a statistically significant treatment effect to the disadvantage of abemaciclib in combination with fulvestrant (HR: 6.55 [95% CI: 1.93; 22.30]; $p < 0.001$).

When assessing the results on the severe adverse events, a risk of bias must be considered. In MONARCH-2, high and varying proportions of patients between the study arms discontinued treatment. This was essentially determined by the discontinuation because of progression and resulted in different median treatment durations between the study arms. Disease progression is potentially informative for the occurrence of events of this endpoint.

Discontinuation because of AE

Also for the median time to therapy discontinuation because of AE, there are no data on event time analysis because of the small number of events (the pharmaceutical company did not carry out an evaluation if there were fewer than 10 events).

Specific AE

A selection of specific AEs based on the frequencies and differences between the treatment arms could not be made because there are no data on the frequent events from the endpoint

category side effects for sub-population b2. Because specific AE can also be selected if they are particularly important for the clinical picture or the active ingredients used in the study, the specific AE neutropenia (CTCAE grade ≥ 3) was selected on this basis.

However, neither the dossier of the pharmaceutical company nor the documents submitted as part of the written statement procedure provide adequate evaluations of this endpoint for the relevant sub-population.

The side-effect profile of abemaciclib is qualitatively comparable to the side-effect profile of cytotoxic chemotherapy and differs significantly from the side-effect profile of endocrine therapy.

Overall assessment

For the assessment of the extent of the additional benefit of abemaciclib in combination with fulvestrant, results from the MONARCH-2 study in comparison to fulvestrant on mortality (overall survival), and side effects are available.

In the mortality endpoint category, there are no data on event time analysis for overall survival in pre-/peri-menopausal patients with prior endocrine therapy because of the low number of events in the small sub-population of 46 patients. Thus, the preliminary data for this endpoint do not allow a conclusive assessment of the effects on overall survival. Final analyses on the endpoint of overall survival are pending. Based on the data available, an additional benefit of abemaciclib in combination with fulvestrant is not proven for overall survival.

No usable data are available for the endpoints of the categories morbidity (symptomatology and health status) and quality of life for the relevant sub-population because the pharmaceutical company submitted summarised evaluations in the dossier and in the documents submitted within the framework of the written statement procedure for all pre-/peri-menopausal patients in which no differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received a previous endocrine therapy or not. There are thus no usable data for the endpoint “progression-free survival” for the sub-population under consideration.

For the side effects, with regard to the endpoint severe adverse events (CTCAE grade 3 or 4), statistically significant disadvantage for abemaciclib in combination with fulvestrant compared with fulvestrant can be identified.
Because of the small number of events, no data on event time analyses are available for serious adverse events and therapy discontinuation because of adverse events. For relevant specific AE, in particular neutropenia (CTCAE grade 3 or 4), no evaluations were available for the sub-population under consideration.
The overall side effect profile of abemaciclib differs significantly from that of endocrine therapy. However, taking into account clinical relevance, the disadvantage in terms of side effects does not reach an extent that would justify a lesser benefit in the overall assessment.

In a balancing decision, the G-BA concluded that abemaciclib in combination with fulvestrant for the treatment of pre-/peri-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy has no proven additional benefit compared with fulvestrant.

2.1.4 Limitation of the period of validity of the resolution

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

therapy:

and

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

and

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy:

The limitation of the period of validity of the resolution on the benefit assessment of abemaciclib (in combination with fulvestrant) has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

For this assessment, the overall survival data from the MONARCH-2 study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending.

Against the background, that clinical data on overall survival that may be relevant for the assessment of the benefit of the medicinal product are expected, it is justified to temporarily limit the resolution until further scientific evidence is available for the assessment of the additional benefit of abemaciclib in combination with fulvestrant. The limitation allows the expected final results from the MONARCH-2 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

For this purpose, the G-BA considers a limitation of the resolution until 31 December 2020 to be appropriate.

Conditions of the limitation:

After the deadline, the final study results for all endpoints from the currently ongoing MONARCH-2 study used to demonstrate an additional benefit should be submitted in the dossier for the renewed benefit assessment.

For sub-population a1, it must be taken into account that the relevant sub-population of patients who had never previously received endocrine therapy (endocrine-naïve patients) included at the start of the MONARCH-2 study up to a protocol amendment is included in the submission of the final study results.

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

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product abemaciclib in combination with fulvestrant shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of abemaciclib in combination with fulvestrant in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

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

2.1.5 Summary of the assessment

The present evaluation is the benefit assessment of the new medicinal product Verzenios containing the active ingredient abemaciclib.

The assessment relates exclusively to the use of abemaciclib in combination with fulvestrant for the treatment of the following patient populations:

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

a2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy

b2) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy

<u>On patient group a1)</u>

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

Anastrozole *or* letrozole *or* fulvestrant *or* possibly tamoxifen if aromatase inhibitors are not suitable.

For this patient group, the pharmaceutical company presents the results of the currently ongoing randomised controlled study MONARCH-2 in which abemaciclib plus fulvestrant is compared with placebo plus fulvestrant. MONARCH-2 included women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who had either not received endocrine therapy at this stage or who had received previous endocrine therapy. Here, the results of MONARCH-2 are relevant for the sub-population of post-menopausal women without initial endocrine therapy from the data cut-off of 14 February 2017.

The data on overall survival are preliminary, and therefore no assessment of the effect on overall survival could be drawn for the mortality endpoint category. Based on the available data, there was no statistically significant difference in overall survival between the study arms. Final analyses on the endpoint of overall survival are pending.

No usable data were available for the endpoints of the categories morbidity (symptomatology and health status) and quality of life for the relevant sub-population because the pharmaceutical company submitted only summarised evaluations for all post-menopausal patients in which no differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received a previous endocrine therapy or not.

In the side effects category, disadvantages of abemaciclib plus fulvestrant were found with regard to serious and severe adverse events as well as therapy discontinuations because of adverse events. For relevant specific AE, in particular neutropenia (CTCAE grade 3 or 4), no evaluations were available for the sub-population under consideration.
However, taking into account clinical relevance, the disadvantage in terms of side effects did not reach an extent that would justify a lesser benefit in the overall assessment.

In a balancing decision, the G-BA concluded that abemaciclib in combination with fulvestrant does not have any additional benefit over the appropriate comparator therapy.

The resolution is limited to 31 December 2020 for this patient group. For this assessment, the overall survival data from the ongoing MONARCH-2 study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending. After the deadline, the final study results for all endpoints from the

MONARCH-2 study used to demonstrate an additional benefit should be submitted in the dossier for the renewed benefit assessment.

On patient group a2)

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

tamoxifen in combination with an elimination of the ovarian function.

For pre-/peri-menopausal patients who have not yet received initial endocrine therapy, no suitable data were provided to assess the additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparator therapy.

For pre-/peri-menopausal patients who have not yet received initial endocrine therapy, the G-BA has defined “tamoxifen in combination with an elimination of the ovarian function” as an appropriate comparator therapy.
In MONARCH-2, all pre-/peri-menopausal patients were treated with fulvestrant in the comparator arm (as well as a GnRH agonist for ovarian suppression). Fulvestrant is explicitly approved for post-menopausal patients only. The appropriate comparator therapy was therefore not adequately implemented for sub-population a2.

An additional benefit of abemaciclib in combination with fulvestrant compared with the appropriate comparator therapy is not proven.

On patient group b1)

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

Another endocrine therapy depending on the previous therapy with:

- tamoxifen *or*
- anastrozole *or*
- fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment *or*
- letrozole; only for patients with relapse or progress after anti-oestrogen treatment *or*
- exemestane; only for patients with progress after anti-oestrogen treatment *or*
- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

For this patient group, the pharmaceutical company presents the results of the currently ongoing randomised controlled study MONARCH-2 in which abemaciclib plus fulvestrant is compared with placebo plus fulvestrant. MONARCH-2 included women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who had either not received endocrine therapy at this stage or who had received previous endocrine therapy. Here, the results of MONARCH-2 are relevant for the sub-population of post-menopausal women with prior endocrine therapy from the data cut-off of 14 February 2017.

Against the background of the special therapy and care situation in the present therapeutic indication, fulvestrant or fulvestrant alone is exceptionally assessed as a sufficiently suitable comparator despite remaining uncertainties and without consideration of further endocrine therapies indicated in the guidelines of the present treatment situation.
From this, no conclusions can be drawn about the usefulness of fulvestrant in the form of application beyond the scope of authorisation in the standard care of insured persons in the SHI system.

The data on overall survival are preliminary, and therefore no assessment of the effect on overall survival could be drawn for the mortality endpoint category. Based on the available

data, there was no statistically significant difference in overall survival between the study arms. Final analyses on the endpoint of overall survival are pending.

No usable data were available for the endpoints of the categories morbidity (symptomatology and health status) and quality of life for the relevant sub-population because the pharmaceutical company submitted only summarised evaluations for all post-menopausal patients in which no differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received a previous endocrine therapy or not.

In the side effects category, disadvantages of abemaciclib plus fulvestrant were found with regard to severe adverse events as well as therapy discontinuations because of adverse events. For relevant specific AE, in particular neutropenia (CTCAE grade 3 or 4), no evaluations were available for the sub-population under consideration.
However, taking into account clinical relevance, the disadvantage in terms of side effects did not reach an extent that would justify a lesser benefit in the overall assessment.

In a balancing decision, the G-BA concluded that abemaciclib in combination with fulvestrant does not have any additional benefit over the appropriate comparator therapy.

The resolution is limited to 31 December 2020 for this patient group. For this assessment, the overall survival data from the ongoing MONARCH-2 study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending. After the deadline, the final study results for all endpoints from the MONARCH-2 study used to demonstrate an additional benefit should be submitted in the dossier for the renewed benefit assessment.

<u>On patient group b2)</u>

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

endocrine therapy according to the doctor’s instructions, taking into account the respective marketing authorisation.

Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone acetate are approved for the present therapeutic indication.

For this patient group, the pharmaceutical company presents the results of the currently ongoing randomised controlled study MONARCH-2 in which abemaciclib plus fulvestrant is compared with placebo plus fulvestrant. MONARCH-2 included women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who had either not received endocrine therapy at this stage or who had received previous endocrine therapy. Here, the results of MONARCH-2 are relevant for the sub-population of pre-/peri-menopausal women with prior endocrine therapy from the data cut-off of 14 February 2017.

Against the background of the special therapy and care situation in the present therapeutic indication, fulvestrant or fulvestrant alone is exceptionally assessed as a sufficiently suitable comparator despite remaining uncertainties and without consideration of further endocrine therapies indicated in the guidelines of the present treatment situation.
From this, no conclusions can be drawn about the usefulness of fulvestrant in the form of application beyond the scope of authorisation in the standard care of insured persons in the SHI system.

In the mortality endpoint category, there were no data for median overall survival in pre-/peri-menopausal patients with prior endocrine therapy because of the low number of events. Thus, the preliminary data for this endpoint did not allow a conclusive assessment of the effects on overall survival. Final analyses on the endpoint of overall survival are pending.

No usable data were available for the endpoints of the categories morbidity (symptomatology and health status) and quality of life for the relevant sub-population because the pharmaceutical company submitted only summarised evaluations for all post-menopausal patients in which no differentiation was made as to whether the patients in the locally advanced or metastasised stage had already received a previous endocrine therapy or not.

In the category side effects, abemaciclib plus fulvestrant showed a disadvantage in terms of severe adverse events. Because of the small number of events, no data on event time analyses were available for serious adverse events and therapy discontinuation because of adverse events. For relevant specific AE, in particular neutropenia (CTCAE grade 3 or 4), no evaluations were available for the sub-population under consideration.
However, taking into account clinical relevance, the disadvantage in terms of side effects did not reach an extent that would justify a lesser benefit in the overall assessment.

In a balancing decision, the G-BA concluded that abemaciclib in combination with fulvestrant does not have any additional benefit over the appropriate comparator therapy.

The resolution is limited to 31 December 2020 for this patient group. For this assessment, the overall survival data from the ongoing MONARCH-2 study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending. After the deadline, the final study results for all endpoints from the MONARCH-2 study used to demonstrate an additional benefit should be submitted in the dossier for the renewed benefit assessment.

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 patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used in the resolution on the benefit assessment of palbociclib (resolution of 18 May 2017).

This range takes into account the existing uncertainties in the data basis and reflects the minimum and maximum values obtained during 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: 13 March 2019):

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

Treatment with abemaciclib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with 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 April 2019).

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 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.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments per patient	Treatment days per patient per year
Medicinal product to be assessed			
Abemaciclib	continuous	2 × daily	365
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Additionally for patient populations a2 and b2)			
Goserelin	continuous	every 28 days	13
Leuprorelin	continuous	1 × every 3 months	4
Appropriate comparator therapy			
Patient population a1)			
Aromatase inhibitor			
Anastrozole	continuous	1 × daily	365
Letrozole	continuous	1 × daily	365
Anti-oestrogens			
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Tamoxifen	continuous	1 × daily	365
Patient population a2)			
Anti-oestrogens			
Tamoxifen	continuous	1 × daily	365
LHRH[7] analogue			
Goserelin	continuous	every 28 days	13

[7] Luteinising Hormone Releasing Hormone

Leuprorelin	continuous	1 × every 3 months	4
Patient population b1)			
Aromatase inhibitor			
Anastrozole	continuous	1 × daily	365
Exemestane	continuous	1 × daily	365
Letrozole	continuous	1 × daily	365
Anti-oestrogens			
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Tamoxifen	continuous	1 × daily	365
Protein kinase inhibitors			
Everolimus	continuous	1 × daily	365
Patient population b2)			
Aromatase inhibitor			
Exemestane	continuous	1 × daily	365
Letrozole	continuous	1 × daily	365
Anti-oestrogens			
Tamoxifen	continuous	1 × daily	365
Gestagens			
Medroxyprogesterone acetate	continuous	1 × daily	365
Megestrol acetate	continuous	1 × daily	365
LHRH analogue			
Goserelin	continuous	every 28 days	13
Leuprorelin	continuous	1 × every 3 months	4

Usage and consumption:

Designation of the therapy	Potency	Cost per patient per treatment day	Quantity per package	Annual mean consumption according to potency
Medicinal product to be assessed				
Abemaciclib	150 mg	300 mg	56 Tablets	730 Tablets
Fulvestrant	250 mg	500 mg	6 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Additionally for patient population a2 and b2)				
Goserelin	3.6 mg	3.6 mg	3 prefilled syringes	13 prefilled syringes
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes
Appropriate comparator therapy				
Patient population a1)				
Aromatase inhibitor				
Anastrozole	1 mg	1 mg	100 Tablets	365 Tablets
Letrozole	2.5 mg	2.5 mg	120 Tablets	365 Tablets
Anti-oestrogens				
Fulvestrant	250 mg	500 mg	6 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Tamoxifen	20 mg	20 mg	100 Tablets	365 Tablets
Patient population a2)				
Anti-oestrogens				
Tamoxifen	20 mg	20 mg	100 Tablets	365 Tablets
LHRH analogue				
Goserelin	3.6 mg	3.6 mg	3 prefilled syringes	13 prefilled syringes
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes

Designation of the therapy	Potency	Cost per patient per treatment day	Quantity per package	Annual mean consumption according to potency
Patient population b1)				
Aromatase inhibitor				
Anastrozole	1 mg	1 mg	100 Tablets	365 Tablets
Exemestane	25 mg	25 mg	100 Tablets	365 Tablets
Letrozole	2.5 mg	2.5 mg	120 Tablets	365 Tablets
Anti-oestrogens				
Fulvestrant	250 mg	500 mg	6 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Tamoxifen	20 mg	20 mg	100 Tablets	365 Tablets
Protein kinase inhibitors				
Everolimus	10 mg	10 mg	90 Tablets	365 Tablets
Patient population b2)				
Aromatase inhibitor				
Exemestane	25 mg	25 mg	100 Tablets	365 Tablets
Letrozole	2.5 mg	2.5 mg	120 Tablets	365 Tablets
Anti-oestrogens				
Tamoxifen	20 mg	20 mg	100 Tablets	365 Tablets
Gestagens				
Medroxyprogesterone acetate	500 mg	300–1,000 mg	100 Tablets	365–730 tablets
Megestrol acetate	160 mg	160 mg	30 Tablets	365 Tablets
LHRH analogue				
Goserelin	3.6 mg	3.6 mg	3 prefilled	13 prefilled syringes

Designation of the therapy	Potency	Cost per patient per treatment day	Quantity per package	Annual mean consumption according to potency
			syringes	
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Cost (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abemaciclib	150 mg, 56 tablets	€ 3,334.84	€ 1.77	€ 187.18	€ 3,145.89
Anastrozole	1 mg, 100 tablets	€ 77.93[8]	€ 1.77	€ 5.29	€ 70.87
Everolimus	10 mg, 90 tablets	€ 6,083.30[9]	€ 1.77	€ 294.98	€ 5,786.55
Exemestane	25 mg, 100 tablets	€ 127.20[8]	€ 1.77	€ 9.19	€ 116.24
Fulvestrant	250 mg, 6 prefilled syringes	€ 2,351.83	€ 1.77	€ 112.32	€ 2,237.74
Goserelin	3.6 mg, 3 prefilled syringes	€ 547.46	€ 1.77	€ 29.70	€ 515.99
Letrozole	2.5 mg, 120 tablets	€ 83.15[8]	€ 1.77	€ 5.71	€ 75.67
Leuprorelin	11.25 mg, 2 prefilled syringes	€ 948.89	€ 1.77	€ 51.93	€ 895.19
Medroxyproges terone acetate	500 mg, 100 tablets	€ 345.66	€ 1.77	€ 18.53	€ 325.36
Megestrol acetate	160 mg, 30 tablets	€ 471.89	€ 1.77	€ 25.52	€ 444.60
Tamoxifen	20 mg, 100 tablets	€ 22.13[8]	€ 1.77	€ 0.88	€ 19.48

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2019

[8] Fixed amount Level I

[9] The costs are presented on the basis of low-cost medicinal product also taking into account the requirements of Section 129 SGB V and the possibility of prescribing medicinal products under their active ingredient designation. The corresponding medicinal products must nevertheless be prescribed taking into account the respective approved therapeutic indications.

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

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

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 October 2017.

On 29 October 2018, the pharmaceutical company submitted a dossier for the benefit assessment of abemaciclib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 October 2018 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 January 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 February 2019. The deadline for submitting written statements was 22 March 2019.

The oral hearing was held on 11 March 2019.

By letter dated 11 March 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 11 April 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 April 2019, and the proposed resolution was approved.

At its session on 2 May 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 October 2017	Determination of the appropriate comparator therapy
Working group Section 35a	5 March 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 March 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 March 2019 2 April 2019 16 April 2019	Consultation on the dossier evaluation by the IQWiG and the evaluation of the written statement procedure
Subcommittee Medicinal products	24 April 2019	Concluding discussion of the proposed resolution
Plenum	2 May 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 May 2019

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

Prof Hecken