Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Abemaciclib (Reassessment after the Deadline: Breast Cancer, HR+, HER2-, Combination with Fulvestrant)

of 3 September 2020

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The pharmaceutical company initially submitted a dossier for the early benefit assessment of the active ingredient abemaciclib (Verzenio®) on 18 September 2018. The validity of the resolution adopted on 2 May 2019 by the G-BA in the course of the present proceedings was limited until 31 December 2020 for the patient populations a1) postmenopausal women who have not received initial endocrine-based therapy, b1) postmenopausal women who have received prior endocrine therapy and b2) pre- or perimenopausal women who have received prior endocrine therapy. At the request of the pharmaceutical company, this limitation was extended to 15 March 2020 by a resolution of the G-BA dated 5 December 2019.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO, the benefit assessment procedure for the medicinal product Verzenio® shall start again on the day the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 16 March 2020.

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

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

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

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

2.1.1 Approved therapeutic indication of abemaciclib (Verzenio) 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 luteinising hormone-releasing hormone (LHRH) agonist.

Indication:

The resolution of 3 September 2020 relates exclusively to the assessment of the additional benefit of abemaciclib in combination with fulvestrant in the following sub-populations: a1) postmenopausal women as initial endocrine-based therapy, b1) postmenopausal women with endocrine therapy and b2) pre- or perimenopausal women previously treated with endocrine therapy.

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-based therapy:

- anastrozole or
- letrozole or
- fulvestrant or
- tamoxifen, if aromatase inhibitors are not appropriate

[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.

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

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

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 applications 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/newly-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 treatments, surgical resection and/or radiotherapy are generally considered for the treatment of mammary carcinoma. In the context of endocrine therapy, an oophorectomy 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 drug therapies in the present therapeutic indication:

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

Ribociclib (combination with an aromatase inhibitor):
Resolution of 20 August 2020

Ribociclib (combination with fulvestrant): Resolution of 20 August 2020

Ribociclib (combination with fulvestrant, combination with an aromatase inhibitor): Resolution of 4 July 2019

Abemaciclib (combination with an aromatase inhibitor): Resolution of 2 May 2019

Abemaciclib (combination with fulvestrant): Resolution of 2 May 2019

Palbociclib (combination with fulvestrant): Resolution of 22 March 2019

Palbociclib (combination with an aromatase inhibitor and combination with fulvestrant): Resolution of 18 May 2017

Eribulin: Resolution of 22 January 2015

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

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

In addition, the anti-oestrogen fulvestrant is another treatment option approved for this indication. In the context of a Cochrane Review[2] and the FIRST[3] study 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-based therapy. In this therapeutic scenario, fulvestrant is approved for postmenopausal patients who have not received previous endocrine therapy or who have relapsed during or after adjuvant anti-oestrogen therapy.

In the therapeutic scenario of disease progression in postmenopausal 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

[2] Lee CI, Goodwin A, Wilcken N. Fulvestrant for hormone-sensitive metastatic breast cancer. Cochrane Database Syst Rev. 2017 Jan 3; 1: CD011093.
[3] Elles 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 Cli Oncol. 2015 Nov 10; 33(32): 3781–7.

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 therapeutic scenario 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 perimenopausal patients with progression after endocrine therapy (sub-population b2), there is a limited number of approved 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-based 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 treatment should take information from the marketing authorisation into account, as well as the dosage instructions in the product information for the active ingredients, and any deviations should be justified separately.

For the CDK 4/6 inhibitor palbociclib in combination with an aromatase inhibitor as initial endocrine-based 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.

For ribociclib in combination with an aromatase inhibitor as an initial endocrine therapy in pre- or perimenopausal women (a2) and after previous endocrine therapy in both postmenopausal women (b1) and pre- or perimenopausal women (b2), no additional benefit was determined by the resolution of 4 July 2019.

For ribociclib in combination with an aromatase inhibitor as an initial endocrine therapy in both postmenopausal women, a hint of a minor additional benefit was determined in the reassessment after the deadline (resolution of 29 August 2020).

For ribociclib in combination with fulvestrant as an initial endocrine therapy and after previous endocrine therapy in pre- or perimenopausal women, no additional benefit was determined by the resolution of 4 July 2019.

In the reassessment after the deadline, with resolution of 29 August 2020, for ribociclib in combination with fulvestrant as an initial endocrine-based therapy in the patient population of postmenopausal women (a1) an indication of a minor additional benefit was established, and for the patient population of postmenopausal women who received prior endocrine therapy (b1) a hint for a minor additional benefit was established.

For abemaciclib in combination with an aromatase inhibitor, no additional benefit was determined by the G-BA. The period of validity of the corresponding resolution of 2 May 2019 was limited.

Based on the benefit assessments carried out so far, the CDK 4/6 inhibitors palbociclib and abemaciclib in their respective combinations cannot be considered as appropriate comparator therapy. This also applies to the CDK 4/6 inhibitor ribociclib in the respective

combinations in pre- or perimenopausal women. With regard to the results of the recently completed benefit assessment procedure for ribociclib in its respective combinations in postmenopausal women (resolutions of 20 August 2020), no new determination of the appropriate comparator therapy was made in the resolution under consideration.

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 perimenopausal patients, the ovarian function is suppressed by oophorectomy or a GnRH analogue.

Division according to menopausal status (pre- or perimenopausal and postmenopausal patients):

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

Regarding the detailed argumentation, reference is made to the prior benefit assessment procedure for abemaciclib in the resolution of 2 May 2019.

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

Basis of evidence

MONARCH-2 study

To demonstrate an additional benefit of abemaciclib in combination with fulvestrant compared with placebo in combination with fulvestrant, the pharmaceutical company presented the results of the most recent data cut-off of the randomised, double-blind controlled Phase III MONARCH-2 study, which is already known from the previous benefit assessment of abemaciclib in the present therapeutic indication.

This multinational study (N = 713) included pre- or perimenopausal patients and postmenopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who, to treat locally advanced or metastatic disease, had received no prior endocrine therapy or who had previously been treated with endocrine therapy. The medicinal product combination abemaciclib + fulvestrant (N = 446) was compared with placebo + fulvestrant (N = 223). Pre- or perimenopausal patients received, in addition, a GnRH agonist to suppress ovarian function.

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

At the start of the study, patients who had never previously received endocrine therapy were enrolled, until the protocol was amended. In the PC's analysis, the endocrine-naive patients (n=44) who had already been enrolled at this time were not included in the intention-to-treat population or in the initial assessment, but they were included in the current assessment.

The stratification factors considered in the MONARCH-2 study were the type of disease (visceral metastases vs solely bone metastases vs others) and sensitivity to endocrine therapy

(primary vs secondary vs before enrolment of endocrine-naive patients was suspended: not endocrine pre-treated). It defined primary resistance as a disease-free interval of ≤ 24 months during adjuvant endocrine therapy or progression within 6 months during endocrine therapy for the advanced/metastatic stage. All patients who did not meet the criteria for primary resistance were considered to be secondarily resistant.

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.

The ongoing MONARCH-2 study was started in August 2014 and is being conducted in 145 study centres in Asia, Australia, Europe, and North America.

The benefit assessment is based on the 3rd data cut-off of 20 June 2019, which forms the basis of the planned final analysis.

Regarding the separate examination of patients in MONARCH-2 after initial endocrine therapy or with prior endocrine therapy in locally advanced or metastasized stages

The MONARCH-2 study included pre- or perimenopausal and postmenopausal patients who had either not received endocrine therapy in an advanced or metastatic stage or who had been pretreated with at most one line of endocrine therapy at this stage.

On the basis of this study, the pharmaceutical company once again assesses the additional benefit for all patients, without distinguishing between the therapy lines as described in research questions A and B. However, the pharmaceutical company presents the findings separately for research questions A1, B1 and B2 as a supplement. 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 previous 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. The rationale underlying this decision finds its basis in the benefit assessment procedure for abemaciclib (in combination with fulvestrant) in the resolution of 2 May 2019. The current assessment is therefore based on the evaluations of each sub-population.

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

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.

Against the background of the special therapy and care situation in the present therapeutic indication, fulvestrant (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 medical treatment situation.

With regard to the reasoning underlying this assessment, reference is made to the past benefit assessment procedures for palbociclib in the resolution of 22 March 2019 and abemaciclib in the resolution of 2 May 2019.

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.

MONARCH plus study

The MONARCH plus study is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant (+ placebo). The study included postmenopausal women with HR-positive, HER2-negative, locally-relapsed or metastatic breast cancer who, considering the advanced stage of the disease, either had not yet received endocrine therapy or had received prior endocrine therapy.

A total of 157 patients were included in cohort B (abemaciclib plus fulvestrant versus placebo plus fulvestrant) of the trial, which is relevant for the benefit assessment, and randomised to the two treatment arms at a 2:1 ratio. The study includes patients who are relevant to either research question A1 or research question B1. It is not clear how the included patients are distributed between the two sub-populations. Separate evaluations are not available.

The primary endpoint of the MONARCH plus study is PFS. Patient-relevant secondary endpoints are overall survival, symptomatology, quality of life, and adverse events.

The MONARCH plus study is an ongoing study. So far, the results of the first data cut-off of 29 March 2019 have been made available. The end of the study and thus also the final results are planned for November 2020.

In the dossier for the benefit assessment, the pharmaceutical company identifies the MONARCH plus study, but does not include it in the pool of studies deemed relevant to the assessment. Hence, no results for the MONARCH plus study have been submitted in Module 4 of the dossier. The pharmaceutical company has included the corresponding study report solely in Module 5, but this does not contain any differential analyses for the sub-populations a1 and b1, which are required for the present assessment.

The pharmaceutical company justifies the exclusion of the MONARCH plus study on the grounds that it is an ongoing study for which final results are not yet available and that the data of this study with almost exclusively Asian patients would not provide any additional relevant evidence for the present benefit assessment. In its dossier evaluation, the IQWiG states that it does not consider the pharmaceutical company's justification to be sound, as an initial data cut-off had already been assessed and published, and the origin of the patients was not *per se* a reason for exclusion. The IQWIG considers the MONARCH plus study to be relevant for the benefit assessment in the sub-populations a1 and b1 and thus concludes that the study pool submitted by the pharmaceutical company in the dossier is incomplete. Consequently, both the MONARCH-2 study and the MONARCH plus study were included in the IQWiG's benefit assessment.

Despite the clear criticism of the exclusion of the MONARCH plus study in the IQWiG's assessment of the dossier, the pharmaceutical company did not submit any differential analyses of the sub-populations a1 and b1 from the MONARCH plus study that would have enabled a more detailed analysis for the present assessment, even during the written statement procedure.

In principle, the G-BA agrees with the IQWiG's criticism of the processing of the available evidence by the pharmaceutical company. Taking into account the scope and significance of the available data, in particular the final analysis of the MONARCH-2 study, which is now available, the G-BA does not entirely rule out that an appropriate evaluation of the additional benefit in the sub-populations a1 and b1 is feasible, despite the lack of relevant analyses from the MONARCH plus study. However, the missing analyses are cause for a relevant uncertainty in the assessment of the available findings for the sub-populations a1 and b1, and this is reflected in reduced confidence in the assessment.

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-based therapy:

An additional benefit is not proven

Justification:

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.

Regarding overall survival, MONARCH-2 showed no statistically significant difference between the treatment arms for postmenopausal patients who had not yet received initial endocrine-based therapy.

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.
PFS was statistically significantly longer 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. In the MONARCH-2 study, the mortality endpoint component was calculated as an independent endpoint via the secondary endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

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

The morbidity data show statistically significant differences in the endpoints health status (EQ-5D VAS) and the endpoints nausea, vomiting, constipation, arm symptoms, breast symptoms and diarrhoea (EORTC QLQ-C30; QLQ-BR23). The data on health-related quality of life (EORTC QLQ-C30; QLQ-BR23) reveal statistically significant differences only for the social functioning endpoint.

The observation period for the relevant endpoints in the MONARCH-2 study covers the period of treatment with the study medication (an additional 30 days). However, in order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required. However, based on the available data, the extent to which radiologically determined progression in the MONARCH-2 study is associated with changes in morbidity and/or quality of life cannot be adequately assessed. The results on the progression-free survival endpoint are not used in this assessment.

Time to first subsequent chemotherapy

The endpoint “time to first subsequent chemotherapy” was defined as the period from randomisation to the start of first subsequent chemotherapy or death regardless of the underlying cause.

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

The dossier of the pharmaceutical company does not contain detailed information on the post-progression therapies; moreover, the pharmaceutical company does not describe essential information on the circumstances of the treatment decision for or against chemotherapy. Furthermore, the endpoint for MONARCH-2 was defined *post hoc* in the benefit dossier for abemaciclib.

Irrespective of the fundamental question whether the “time to first subsequent chemotherapy” endpoint should also be reflected in other relevant endpoints in order to be assessed as patient-relevant, in the present case, it is clearly uncertain whether the results for this endpoint are meaningful, and, as a result, no conclusions can be drawn regarding additional benefit from the available data.

Health status (EQ-5D visual analogue scale)

The general health status was assessed using the visual analogue scale of the EQ-5D. For the benefit assessment, the pharmaceutical company presented in the dossier responder analyses for the time until deterioration by ≥ 7 points and by ≥ 10 points of the VAS score compared with baseline for the sub-population under consideration. Analyses of differences in mean values were not made available.

The IQWiG made no use of the responder analyses, because the study on which the derivation of minimal important difference (MID) is based (Pickard *et al.*, 2007) is no longer considered suitable by the IQWiG to demonstrate the validity of MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine MID, which is assumed in the current scientific discussion on deriving valid MID figures. However, the evaluations submitted by the PC are presented as supplementary information in the benefit assessment.

Because responder analyses based on MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and because the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status.

The responder analyses for the endpoint health status reveal a statistically significant difference for both a 7-point and a 10-point MID to the benefit of abemaciclib in combination with fulvestrant compared to fulvestrant. The time to deterioration was statistically significantly longer by ≥ 7 points and by ≥ 10 points in the abemaciclib treatment group than in the control group.

Consequently, a benefit exists with respect to health status.

Symptomatology

In the MONARCH-2 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the additional module EORTC QLQ-BR23.

For the present assessment, the evaluation of the time until permanent deterioration of the symptomatology is used (the increase of the score by at least 10 points compared with baseline without subsequent improvement to a score below this level).

For the endpoints nausea/vomiting, constipation, arm symptoms and breast symptoms, a statistically significant difference has been demonstrated to the benefit of abemaciclib + fulvestrant. Age is an effect modifier for the endpoint arm symptoms. For patients < 65 years, there is a statistically significant effect to the benefit of abemaciclib plus fulvestrant compared to fulvestrant. For patients ≥ 65 years, there was no statistically significant difference between the treatment groups.

For the endpoint diarrhoea, there was a statistically significant difference to the detriment of abemaciclib + fulvestrant.

For the endpoint "burden due to hair loss", there is no usable data. For all further endpoints, there was no statistically significant difference between the treatment groups.

Quality of life

Health-related quality of life was investigated by means of the functional scales of the EORTC QLQ-C30 QLQ-C30.

For the present assessment, the evaluation of the time until permanent deterioration of quality of life is used (defined as the decrease of the score by at least 10 points compared with baseline without subsequent improvement to a score above this level).

For the endpoint social functioning, there was a statistically significant difference to the benefit of abemaciclib with fulvestrant.

In the endpoint category health-related quality of life, a benefit could be established in only one scale.

Side effects

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

Adverse events (AEs)

In MONARCH-2, 98.8 % of postmenopausal patients in the intervention arm who had received no initial endocrine therapy experienced an adverse event, compared to 91.4 % in the control arm.

Serious adverse events

For the serious adverse events, a statistically significant effect to the detriment of abemaciclib in combination with fulvestrant was observed.

Severe AEs (CTCAE grade ≥ 3)

With regards to the occurrence of severe adverse events of CTCAE grade ≥ 3, a statistically significant treatment effect was observed to the detriment of abemaciclib with fulvestrant.

Discontinuation due to AEs

In MONARCH-2, therapy discontinuation was defined as the termination of therapy with abemaciclib or placebo. In the study, discontinuing treatment with fulvestrant only was not permitted. For the median time to therapy discontinuation due to AEs, a statistically significant effect was observed to the detriment of abemaciclib in combination with fulvestrant.

Specific AEs

Due to the fact that the pharmaceutical company did not present any time-to-event analyses that would have been required to adequately assess specific AEs, only information provided on the number of patients experiencing each type of event and the percentage of patients calculated on the basis of this information can be drawn upon. Regarding the specific AEs neutropoenia and diarrhoea, both classified as CTCAE grade ≥ 3, a significantly larger proportion of patients in the treatment group abemaciclib in combination with fulvestrant experienced AEs than in the control group fulvestrant and placebo.

Overall assessment

To assess the additional benefit of abemaciclib in combination with fulvestrant compared to fulvestrant in the sub-population a1, results are available on mortality (overall survival), morbidity (symptomatology and health status), quality of life, and side effects from the MONARCH-2 study.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups.

In the morbidity category, a benefit has been demonstrated for the endpoint health status for treatment with abemaciclib in combination with fulvestrant compared to fulvestrant. Regarding symptomatology, benefits can be deduced for the endpoints nausea/vomiting, constipation, arm symptoms and breast symptoms as well as detriments for the endpoint diarrhoea for treatment with abemaciclib in combination with fulvestrant compared to fulvestrant.

In the morbidity endpoint category, overall assessment of the available findings on symptomatology and health status reveals a benefit for abemaciclib in combination with fulvestrant.

In totality, neither a benefit nor a detriment for treatment with abemaciclib in combination with fulvestrant can be deduced from the findings on health-related quality of life.

Overall, the results on side effects reveal statistically significant and meaningful detriments for abemaciclib in combination with fulvestrant compared with fulvestrant with regard to the endpoints serious AEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs In detail, the specific adverse events diarrhoea and neutropoenia, both classified as CTCAE grade ≥ 3, reveal detriments associated with abemaciclib in combination with fulvestrant. The overall side effect profile of abemaciclib differs significantly from that of endocrine therapy. In studies of patients who received abemaciclib in combination with fulvestrant, the side effects, in particular diarrhoea and neutropoenia, often led to a delay or interruption in taking the medication.

In a balancing decision taking into account benefits in the morbidity endpoint category versus detriments in side effects, the G-BA concludes that in treatment of postmenopausal women with HR+ and HER2- advanced or metastatic breast cancer who have received initial endocrine-based therapy, no additional benefit has been demonstrated for abemaciclib in combination with fulvestrant 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

Hint for a minor additional benefit

Justification:

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.

With regard to overall survival, for patients at a locally advanced or metastatic stage who had received prior endocrine therapy a statistically significant difference has been demonstrated to the benefit of abemaciclib in combination with fulvestrant compared to fulvestrant.

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.

PFS was statistically significantly longer 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. In the MONARCH-2 study, the mortality endpoint component was calculated as an independent endpoint via the secondary endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

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

The morbidity data reveal statistically significant differences in the nausea, vomiting, and pain endpoints (EORTC QLQ-C30). The data on health-related quality of life (EORTC QLQ-C30; QLQ-BR23) reveal statistically significant differences in the global health status, and emotional and physical functioning endpoints.

The observation period for the relevant endpoints in the MONARCH-2 study covers the period of treatment with the study medication (an additional 30 days). However, in order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required. However, based on the available data, the extent to which radiologically determined progression in the MONARCH-2 study is associated with changes in morbidity and/or quality of life cannot be adequately assessed. The results on the progression-free survival endpoint are not used in this assessment.

Time to first subsequent chemotherapy

The endpoint “time to first subsequent chemotherapy” was defined as the period from randomisation to the start of first subsequent chemotherapy or death regardless of the underlying cause.

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

The dossier of the pharmaceutical company does not contain detailed information on the post-progression therapies; moreover, the pharmaceutical company does not describe essential information on the circumstances of the treatment decision for or against chemotherapy. Furthermore, the endpoint for MONARCH-2 was defined *post hoc* in the benefit dossier for abemaciclib.

Irrespective of the fundamental question whether the "time to first subsequent chemotherapy" endpoint should also be reflected in other relevant endpoints in order to be assessed as patient-relevant, in the present case, it is clearly uncertain whether the results for this endpoint are meaningful, and, as a result, no conclusions can be drawn regarding additional benefit from the available data.

Health status (EQ-5D visual analogue scale)

The general health status was assessed using the visual analogue scale of the EQ-5D.

For the benefit assessment, the pharmaceutical company presented in the dossier responder analyses for the time until deterioration by ≥ 7 points and by ≥ 10 points of the VAS score compared with baseline for the sub-population under consideration. Analyses of differences in mean values were not made available.

The IQWiG made no use of the responder analyses, because the study on which the derivation of the minimal important difference MID is based (Pickard *et al.*, 2007) is no longer considered suitable by the IQWiG to demonstrate the validity of MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. However, the evaluations submitted by the PC are presented as supplementary information in the benefit assessment.

Because responder analyses based on MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and because the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status.

The responder analyses for the endpoint health status reveal a statistically significant difference for both a 7-point and a 10-point MID to the benefit of abemaciclib in combination with fulvestrant compared to fulvestrant.

Consequently, a benefit exists with respect to health status.

Symptomatology

In the MONARCH-2 study, symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the additional module EORTC QLQ-BR23.

For the present assessment, the evaluation of the time until permanent deterioration of the symptomatology is used (the increase of the score by at least 10 points compared with baseline without subsequent improvement to a score below this level).

For the endpoints nausea/vomiting and pain, a statistically significant difference has been demonstrated to the benefit of abemaciclib + fulvestrant.

For the insomnia endpoint, there was no statistically significant difference between the treatment groups. However, age is an effect modifier for this endpoint. For patients ≥ 65 years, there is a statistically significant effect to the benefit of abemaciclib plus fulvestrant compared to fulvestrant. For patients < 65 years, there was no statistically significant difference between the treatment groups.

For the endpoint “suffering due to hair loss”, there is no usable data. For all further endpoints, there was no statistically significant difference between the treatment groups.

Quality of life

Health-related quality of life was investigated by means of the functional scales of the EORTC QLQ-C30 QLQ-C30.

For the present assessment, the evaluation of the time until permanent deterioration of quality of life is used (defined as the decrease of the score by at least 10 points compared with baseline without subsequent improvement to a score above this level).

The time to deterioration in global health status and to deterioration in physical and emotional functioning was statistically significantly extended in the abemaciclib treatment group compared to the control group.

Side effects

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

Adverse events (AEs)

In MONARCH-2, 97.9 % of postmenopausal patients in the intervention arm who had received no initial endocrine therapy experienced an adverse event, compared to 89.4 % in the control arm.

Serious adverse events

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

Severe AE (CTCAE grade ≥ 3)

With regards to the occurrence of severe adverse events of CTCAE grade ≥ 3, a statistically significant treatment effect was observed to the detriment of abemaciclib with fulvestrant.

Discontinuation due to AEs

In MONARCH-2, therapy discontinuation was defined as the termination of therapy with abemaciclib or placebo. In the study, it was not allowed to discontinue treatment with fulvestrant only.

For the median time to therapy discontinuation due to AE, a statistically significant effect was observed to the detriment of abemaciclib in combination with fulvestrant.

Specific AEs

Due to the fact that the pharmaceutical company did not present any time-to-event analyses that would have been required to adequately assess specific AEs, only information provided on the number of patients experiencing each type of event and the percentage of patients

calculated on the basis of this information can be drawn upon. Regarding the specific AEs neutropoenia and diarrhoea, both classified as CTCAE grade ≥ 3, a significantly larger proportion of patients in the treatment group abemaciclib in combination with fulvestrant experienced AEs than in the control group fulvestrant and placebo.

Overall assessment

To assess the additional benefit of abemaciclib in combination with fulvestrant compared to fulvestrant in the sub-population b1, results are available on mortality (overall survival), morbidity (symptomatology, health status and pain), quality of life, and side effects from the MONARCH-2 study.

With regards to overall survival, the MONARCH-2 study reveals a benefit for abemaciclib in combination with fulvestrant compared to fulvestrant.

In the morbidity category, a statistically significant and meaningful benefit has been demonstrated for abemaciclib in combination with fulvestrant compared to fulvestrant for the nausea/vomiting and pain endpoints. Overall, a benefit has been determined for the morbidity endpoint category, taking into account the results of all the endpoints in the category.

Based on the statistically significant differences to the benefit of abemaciclib and fulvestrant compared to placebo and fulvestrant in the global health, and emotional and physical functioning endpoints, an overall benefit has been derived for the quality of life endpoint category.

Overall, the results on side effects reveal statistically significant and meaningful detriments for abemaciclib in combination with fulvestrant compared with fulvestrant with regard to the endpoints severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. In detail, the specific adverse events diarrhoea and neutropoenia, both classified as CTCAE grade ≥ 3, reveal detriments associated with abemaciclib in combination with fulvestrant. The overall side effect profile of abemaciclib differs significantly from that of endocrine therapy. In studies of patients who received abemaciclib in combination with fulvestrant, the side effects, in particular diarrhoea and neutropoenia, often led to a delay or interruption in taking the medication.

In a balancing decision, the G-BA concludes that, due to the benefits in overall survival, and supported by the positive effects in the endpoint categories morbidity and quality of life, the improvement in therapy-relevant benefit outweighs the significant detriments associated with side effects. Overall, in treatment of postmenopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have received prior endocrine therapy, a minor additional benefit has been established for abemaciclib in combination with fulvestrant compared to fulvestrant.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, double-blind phase III MONARCH-2 study. The risk of bias at the study level is classified as low.

Uncertainties relevant to the assessment arise from the fact that corresponding analyses of the sub-population b1 from the MONARCH plus study are missing (see comments above on the MONARCH plus study).

Taking this uncertainty into account, the finding of an additional benefit must therefore be classified as a “hint”.

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy

An additional benefit is not proven.

Justification:

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.

With regard to overall survival, MONARCH-2 revealed no statistically significant difference between the study arms for pre- or perimenopausal patients who had received prior endocrine therapy.

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.

PFS was statistically significantly longer 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. In the MONARCH-2 study, the mortality endpoint component was calculated as an independent endpoint via the secondary endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

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

The morbidity data reveal statistically significant differences in the endpoints constipation and side effects of systemic treatment (EORTC QLQ-C30; QLQ-BR23). The data on health-related quality of life reveal no statistically significant differences.

The observation period for the relevant endpoints in the MONARCH-2 study covers the period of treatment with the study medication (an additional 30 days). However, in order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required. However, based on the available data, the extent to which radiologically determined progression in the MONARCH-2 study is associated with changes in morbidity and/or quality of life cannot be adequately assessed. The results on the progression-free survival endpoint are not used in this assessment.

Time to first subsequent chemotherapy

The endpoint “time to first subsequent chemotherapy” was defined as the period from randomisation to the start of first subsequent chemotherapy or death regardless of the underlying cause.

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

The dossier of the pharmaceutical company does not contain detailed information on the post-progression therapies; moreover, the pharmaceutical company does not describe essential information on the circumstances of the treatment decision for or against chemotherapy. Furthermore, the endpoint for MONARCH-2 was defined *post hoc* in the benefit dossier for abemaciclib.

Irrespective of the fundamental question whether the "time to first subsequent chemotherapy" endpoint should also be reflected in other relevant endpoints in order to be assessed as patient-relevant, in the present case, it is clearly uncertain whether the results for this endpoint are meaningful, and, as a result, no conclusions can be drawn regarding additional benefit from the available data.

Health status (EQ-5D visual analogue scale)

The general health status was assessed using the visual analogue scale of the EQ-5D. The survey was conducted regularly during treatment, at the end of treatment, and 30 days after the end of treatment (when the side effects were followed up). Furthermore, if the treatment was discontinued before progression, data were collected beyond the end of treatment until progression.

For the benefit assessment, the pharmaceutical company presented in the dossier responder analyses for the time until deterioration by ≥ 7 points and by ≥ 10 points of the VAS score compared with baseline for the sub-population under consideration. Analyses of differences in mean values were not made available.

The IQWiG made no use of the responder analyses, because the study on which the derivation of minimal important difference (MID) is based (Pickard *et al.*, 2007) is no longer considered suitable by the IQWiG to demonstrate the validity of MID. This is justified by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. However, the evaluations submitted by the PC are presented as supplementary information in the benefit assessment.

Because responder analyses based on MID have general advantages for a clinical evaluation of effects compared with analysis of standardised mean differences and because the validation study in question has already been used in earlier assessments, the G-BA has decided to draw on responder analyses in the current assessment to determine the effects on health status.

The responder analyses for the endpoint health status reveal a statistically significant difference for both a 7-point and a 10-point MID to the benefit of abemaciclib in combination with fulvestrant compared to fulvestrant.

Consequently, a benefit exists with respect to health status.

Symptomatology

In the MONARCH-2 study, symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the additional module EORTC QLQ-BR23.

For the present assessment, the evaluation of the time until permanent deterioration of the symptomatology is used (the increase of the score by at least 10 points compared with baseline without subsequent improvement to a score below this level).

For the endpoints constipation and side effects of systemic treatment, a statistically significant difference to the benefit of abemaciclib + fulvestrant has been demonstrated. However, the extent of the effect is small and based on only a small number of events in total, and, hence, solely based on this effect, no benefit can be deduced overall with regard to symptomatology.

For the endpoint “durden due to hair loss”, there is no usable data. For all further endpoints, there was no statistically significant difference between the treatment groups.

Quality of life

Health-related quality of life was investigated by means of the functional scales of the EORTC QLQ-C30 QLQ-C30.

For the present assessment, the evaluation of the time until permanent deterioration of quality of life is used (defined as the decrease of the score by at least 10 points compared with baseline without subsequent improvement to a score above this level).

For all presented endpoints, there was no statistically significant difference between the treatment groups.

Side effects

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

Adverse events (AEs)

In MONARCH-2, 96.2 % of postmenopausal patients in the intervention arm who had received no initial endocrine therapy experienced an adverse event, compared to 95.0 % in the control arm.

Serious adverse events

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

Severe AEs (CTCAE grade ≥ 3)

With regards to the occurrence of severe adverse events of CTCAE grade ≥ 3, a statistically significant treatment effect was observed to the detriment of abemaciclib with fulvestrant.

Discontinuation due to AEs

In MONARCH-2, therapy discontinuation was defined as the termination of therapy with abemaciclib or placebo. In the study, it was not allowed to discontinue treatment with fulvestrant only.

For the endpoint discontinuation because of AE, there was no statistically significant difference between the treatment groups.

Specific AEs

Due to the fact that the pharmaceutical company did not present any time-to-event analyses that would have been required to adequately assess specific AEs, only information provided on the number of patients experiencing each type of event and the percentage of patients calculated on the basis of this information can be drawn upon. Regarding the specific AEs neutropoenia and diarrhoea, both classified as CTCAE grade ≥ 3, a significantly larger

proportion of patients in the treatment group abemaciclib in combination with fulvestrant experienced AEs than in the control group fulvestrant and placebo.

Overall assessment

To assess the additional benefit of abemaciclib in combination with fulvestrant compared to fulvestrant in the sub-population b2, results are available on mortality (overall survival), morbidity (symptomatology, pain and health status), quality of life, and side effects from the MONARCH-2 study.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups.

Regarding the endpoint categories morbidity and health-related quality of life, neither benefits nor detriments can be deduced overall for treatment with abemaciclib in combination with fulvestrant compared with fulvestrant.

Overall, the results on side effects reveal statistically significant and meaningful detriments for abemaciclib in combination with fulvestrant compared with fulvestrant with regard to the endpoint severe AEs (CTCAE grade ≥ 3). In detail, the specific adverse events diarrhoea and neutropoenia, both classified as CTCAE grade ≥ 3, reveal detriments associated with abemaciclib in combination with fulvestrant. The overall side effect profile of abemaciclib differs significantly from that of endocrine therapy. In studies of patients who received abemaciclib in combination with fulvestrant, the side effects, in particular diarrhoea and neutrpoenia, often led to a delay or interruption in taking the medication.

In a balancing decision, the G-BA concludes that in treatment of pre- or perimenopausal women with HR+ and HER2- advanced or metastatic breast cancer who have received prior endocrine therapy, no additional benefit has been demonstrated for abemaciclib in combination with fulvestrant compared to fulvestrant.

2.1.4 Limitation of the period of validity of the resolution

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

and

b1) Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received 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 the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The MONARCH plus study does not analyse the existing evidence for the sub-populations a1 and b1, i.e. there is no differential analysis for these sub-populations. In addition, final results on overall survival from the ongoing MONARCH plus study are still pending; these are expected in November 2020.

In view of the fact that clinical data on overall survival relevant for the benefit assessment of the medicinal product are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific evidence on the additional benefit of abemaciclib in combination with fulvestrant is available. The limitation allows the expected final results from the MONARCH plus study to be rapidly included in the benefit assessment of the medicinal product according to Section 35 a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 01 June 2021 to be appropriate.

Conditions of the limitation:

Reassessment of benefit after the deadline expires will be contingent on the dossier including the results of the final evaluation of the ongoing MONARCH plus study, addressing all endpoints used to demonstrate an additional benefit and differentiated according to sub-populations a1 and b1. In line with the dossier template, a meta-analytical summary of the results of the studies should be reviewed, and, unless there are strong reasons not to do so, an additional meta-analysis should be provided. The dossier should include results from the most recent data cut-off from the MONARCH 2 study.

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

In accordance with Section 3, number 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product 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, number 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 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, numbers 2–4 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient abemaciclib because of the expiry of the limitation of the resolution of 2 May 2019. The assessment refers exclusively 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-based therapy

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

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy.

<u>On sub-population 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 appropriate.

For this patient group, the pharmaceutical company presents results from the randomised controlled MONARCH-2 study comparing abemaciclib plus fulvestrant with placebo plus fulvestrant. This multinational study (N = 713) included pre- or perimenopausal patients and postmenopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who, to treat locally advanced or metastatic disease, had received no prior endocrine therapy or who had previously been treated with endocrine therapy. For this benefit assessment the results of MONARCH2 are relevant for the sub-population of postmenopausal women without initial endocrine therapy from the data cut-off of 20 June 2019.

The pharmaceutical company did not present any differential analyses for the MONARCH plus study, a double-blind RCT that includes the sub-populations relevant for the benefit assessment in which abemaciclib in combination with fulvestrant is compared with fulvestrant. However, these analyses would have been indispensable for a more detailed assessment of the results from the MONARCH plus study, and, hence, the assessment is subject to uncertainty.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups.

In the morbidity endpoint category, overall assessment of the available findings on symptomatology and health status reveals a benefit for abemaciclib in combination with fulvestrant.

In totality, neither a benefit nor a detriment for treatment with abemaciclib in combination with fulvestrant can be deduced from the findings on health-related quality of life.

Overall, the results on side effects reveal meaningful detriments for abemaciclib in combination with fulvestrant compared with fulvestrant with regard to the endpoints serious AEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs as well as in detail detriments for specific adverse events.

In a balancing decision taking into account benefits in the morbidity endpoint category versus detriments in side effects, the G-BA concludes that in treatment of post- menopausal women with HR+ and HER2- advanced or metastatic breast cancer who have received initial endocrine therapy, no additional benefit has been demonstrated for abemaciclib in combination with fulvestrant compared to fulvestrant.

Due to the absence of differential analyses for the MONARCH plus study between the sub-populations a1 and b1, the assessment is subject to uncertainty with regard to the findings for sub-population a1. This relevant uncertainty prevents a final assessment of the findings, and, hence, the resolution is limited in time until 1 June 2021. Reassessment of benefit after the deadline expires will be contingent on the dossier including the results of the final evaluation of the ongoing MONARCH plus study, addressing all endpoints used to demonstrate an additional benefit and differentiated according to sub-populations a1 and b1. In line with the dossier template, a meta-analytical summary of the results of the studies should be reviewed and, unless there are strong reasons not to do so, an additional meta-analysis should be provided. The dossier should include results from the most recent data cut-off from the MONARCH 2 study.

On sub-population b1)

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

A further endocrine therapy depending on the previous therapy with:

- tamoxifen or
- analstrozole 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 results from the randomised controlled MONARCH-2 study comparing abemaciclib plus fulvestrant with placebo plus fulvestrant. This multinational study (N = 713) included pre- or perimenopausal patients and postmenopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who, to treat locally advanced or metastatic disease, had received no prior endocrine therapy or who had previously been treated with endocrine therapy. For this benefit assessment the results of MONARCH2 are relevant for the sub-population of postmenopausal women who received prior endocrine therapy from the data cut-off of 20 June 2019.

The pharmaceutical company did not present any differential analyses for the MONARCH plus study, a double-blind RCT that includes the sub-populations relevant for the benefit assessment in which abemaciclib in combination with fulvestrant is compared with fulvestrant. However, these analyses would have been indispensable for a more detailed assessment of the results from the MONARCH plus study, and, hence, the assessment is subject to uncertainty.

With regards to overall survival, the MONARCH-2 study reveals a benefit for abemaciclib in combination with fulvestrant compared to fulvestrant.

In the morbidity endpoint category, a benefit has been established for abemaciclib and fulvestrant compared to fulvestrant.

For the endpoint category quality of life, overall a significant benefit has been identified.

Overall, the results on adverse events show significant detriments for abemaciclib in combination with fulvestrant compared to fulvestrant with regard to the endpoints severe AEs (CTCAE grade ≥ 3) and discontinuation of therapy due to AEs, as well as, in detail, detriments regarding specific adverse events.

In a balancing decision, the G-BA concludes that, due to the benefits in overall survival, and supported by the positive effects in the endpoint categories morbidity and quality of life, the improvement in therapy-relevant benefit outweighs the significant detriments associated with side effects.

Overall, in treatment of postmenopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have received prior endocrine therapy, a minor additional benefit has been established for abemaciclib in combination with fulvestrant compared to fulvestrant.

In particular, due to assessment-relevant uncertainties arising from the lack of appropriate analyses of sub-population b1 from the MONARCH plus study, the finding of an additional benefit must be classified as a “hint”.

Due to the absence of differential analyses for the MONARCH plus study between the sub-populations a1 and b1, the assessment is subject to uncertainty with regard to the findings for sub-population b1. This relevant uncertainty prevents a final assessment of the findings, and, hence, the resolution is limited in time until 1 June 2021. Reassessment of benefit after the deadline expires will be contingent on the dossier including the results of the final evaluation of the ongoing MONARCH plus study, addressing all endpoints used to demonstrate an additional benefit and differentiated according to sub-populations a1 and b1. In line with the dossier template, a meta-analytical summary of the results of the studies should be reviewed and, unless there are strong reasons not to do so, an additional meta-analysis should be provided. The dossier should include results from the most recent data cut-off from the MONARCH 2 study.

<u>On sub-population 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 results from the randomised controlled MONARCH-2 study comparing abemaciclib plus fulvestrant with placebo plus fulvestrant. This multinational study (N = 713) included pre- or perimenopausal patients and postmenopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who, to treat locally advanced or metastatic disease, had received no prior endocrine therapy or who had previously been treated with endocrine therapy. For this benefit assessment the results of MONARCH2 are relevant for the sub-population of pre- or perimenopausal women who received prior endocrine therapy from the data cut-off of 20 June 2019.

In the endpoint category mortality, for the endpoint overall survival, there was no statistically significant difference between treatment groups.

Regarding the endpoint categories morbidity and health-related quality of life, neither benefits nor detriments can be deduced overall for treatment with abemaciclib in combination with fulvestrant compared with fulvestrant.

Overall, the results on adverse events show significant detriments for abemaciclib in combination with fulvestrant compared to fulvestrant with regard to the endpoint severe AEs (CTCAE grade ≥ 3) and, in detail, detriments regarding specific adverse events.

In a balancing decision, the G-BA concludes that in treatment of pre- or perimenopausal women with HR+ and HER2- advanced or metastatic breast cancer who have received prior endocrine therapy, no additional benefit has been demonstrated for abemaciclib in combination with fulvestrant compared to fulvestrant.

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).

The slight differences in patient numbers compared with the palbociclib resolution are due only to the use of more recent data on the incidence and prevalence of breast cancer in Germany as well as the consideration of the current proportion of patients in the SHI target population (87.7%).

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: 2 June 2020):

https://www.ema.europa.eu/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, 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 August 2020).

Treatment duration:

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

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	continuously, 2 × daily	365	1	365
plus fulvestrant				
Fulvestrant	continuous, Cycle 1: 1 × on days 1 and 15 From Cycle 2: 1 × monthly	13	1	13
b2) in addition LHRH analogue				
Goserelin	1 × every 28 days	13	1	13
Leuprorelin	1 × every 3 months	4	1	4
Appropriate comparator therapy				
Patient population a1)				
Anastrozole	continuously, 1 × daily	365	1	365
Letrozole	continuously, 1 × daily	365	1	365
Fulvestrant	continuous, Cycle 1: 1 × on days 1 and 15 From Cycle 2: 1 × monthly	13	1	13
Tamoxifen	continuously, 1 × daily	365	1	365
Patient population b1)				
Tamoxifen	continuously, 1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Anastrozole	continuously, 1 × daily	365	1	365
Fulvestrant	continuous, Cycle 1: 1 × on days 1 and 15 From Cycle 2: 1 × monthly	13	1	13
Letrozole	continuously, 1 × daily	365	1	365
Exemestane	continuously, 1 × daily	365	1	365
Everolimus + exemestane				
Everolimus	continuously, 1 × daily	365	1	365
Exemestane	continuously, 1 × daily	365	1	365
Patient population b2)				
Tamoxifen	continuously, 1 × daily	365	1	365
Letrozole	continuously, 1 × daily	365	1	365
Exemestane	continuously, 1 × daily	365	1	365
Megestrol	continuously, 1 × daily	365	1	365
Medroxyprogesterone	continuously, 1 × daily	365	1	365
In addition LHRH analogue				
Goserelin	1 × every 28 days	13	1	13
Leuprorelin	1 × every 3 months	4	1	4

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Abemaciclib	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
plus fulvestrant					
Fulvestrant	500 mg	500 mg	2 × 250 mg	13	26 × 250 mg
b2) in addition LHRH analogue					
Goserelin	3.6 mg	3.6 mg	1 × 3.6 mg	13	13 × 3.6 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Appropriate comparator therapy					
Patient population a1)					
Anastrozole	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Fulvestrant	500 mg	500 mg	2 × 250 mg	13	26 × 250 mg
Tamoxifen	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg –
Patient population b1)					
Tamoxifen	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg
Anastrozole	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Fulvestrant	500 mg	500 mg	2 × 250 mg	13	26 × 250 mg
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Exemestane	25 mg	25 mg	1 × 25 mg	365	365 × 25 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
Everolimus + exemestane					
Everolimus	1 0 mg	1 0 mg	1 × 10 mg	365	365 × 10 mg
Exemestane	25 mg	25 mg	1 × 25 mg	365	365 × 25 mg
Patient population b2)					
Tamoxifen	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Exemestane	25 mg	25 mg	1 × 25 mg	365	365 × 25 mg
Megestrol	160 mg	160 mg	1 × 160 mg	365	365 × 160 mg
Medroxyprogesterone	300 mg – 1000 mg	300 mg – 1000 mg	1 × 500 mg – 2 × 500 mg	365	365 × 500 mg – 730 × 500 mg
In addition LHRH analogue					
Goserelin	3.6 mg	3.6 mg	1 × 3.6 mg	13	13 × 3.6 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Abemaciclib	168 FCT	€ 7,086.87	€ 1.77	€ 411.92	€ 6,673.18
Fulvestrant	6 SFI	€ 2,024.98	€ 1.77	€ 98.88	€ 1,924.33
b2) in addition LHRH analogue					
Goserelin	3 IMP	€ 533.72	€ 1.77	€ 29.70	€ 502.25
Leuprorelin	2 RMS	€ 951.72	€ 1.77	€ 53.44	€ 896.51
Appropriate comparator therapy					
Anastrozole[4]	100 FCT	€ 55.83	€ 1.77	€ 3.66	€ 50.40
Letrozole[4]	120 FCT	€ 59.86	€ 1.77	€ 3.98	€ 54.11
Exemestane[4]	100 FCT	€ 124.05	€ 1.77	€ 9.19	€ 113.09
Tamoxifen[4]	100 FCT	€ 21.63	€ 1.77	€ 0.88	€ 18.98
Letrozole[4]	120 FCT	€ 59.86	€ 1.77	€ 3.98	€ 54.11
Fulvestrant	6 SFI	€ 2,024.98	€ 1.77	€ 98.88	€ 1,924.33
Everolimus	90 TAB	€ 4,449.81	€ 1.77	€ 220.66	€ 4,227.38
Megestrol	30 TAB	€ 481.50	€ 1.77	€ 26.74	€ 452.99
Medroxyprogesterone	100 TAB	€ 346.53	€ 1.77	€ 19.07	€ 325.69
Goserelin	3 IMP	€ 533.72	€ 1.77	€ 29.70	€ 502.25
Leuprorelin	2 RMS	€ 951.72	€ 1.77	€ 53.44	€ 896.51
Abbreviations: FCT = film-coated tablets; IMP = implant; SFI = solution for injection; TAB = tablets; RMS = retard microcapsules and suspending agent					

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

Costs for additionally required SHI services:

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

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

[4] Fixed reimbursement rate

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

At its session on 10 December 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 16 March 2020, 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, no. 5 VerfO.

By letter dated 17 March 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient abemaciclib.

The dossier assessment by the IQWiG was submitted to the G-BA on 10 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2020. The deadline for submitting written statements was 06 July 2020.

The oral hearing was held on 27 July 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 25 August 2020, and the proposed resolution was approved.

At its session on 3 September 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 December 2019	Determination of the appropriate comparator therapy
Working group Section 35a	21 July 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 July 2020	Conduct of the oral hearing
Working group Section 35a	4 August 2020 18 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 August 2020	Concluding discussion of the draft resolution
Plenum	3 September 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 3 September 2020

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

Prof. Hecken