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– Ribociclib (new therapeutic indication: breast cancer; in combination with fulvestrant)

of 4 July 2019

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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 active ingredient ribociclib was listed for the first time on 15 September 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 17 December 2018, ribociclib received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2, number 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 14 January 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ribociclib with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication “Kisqali 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)".

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 April 2019, 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 ribociclib 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 addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of ribociclib.

In the light of the above and taking into account the comments 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 ribociclib (Kisqali®) in accordance with product information

Kisqali 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 of ribociclib in combination with fulvestrant. For the assessment of the additional benefit of ribociclib 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 ribociclib in combination with fulvestrant was determined as follows:

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:

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

[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.

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:

- Tamoxifen in combination with an elimination of the ovarian function,
- possibly letrozole in combination with an elimination of ovarian function in women previously treated with anti-oestrogens

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer 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) Pre-/peri-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with 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 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 ribocicilb, medicinal products with the following active ingredients are approved for the present therapeutic indication: abemaciclib, anastrozole, everolimus, exemestane, fulvestrant, goserelin, letrozole, leuprorelin, medroxyprogesterone acetate, megestrol acetate, palbociclib, 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 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:

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

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

Palbociclib: Resolution of 22 March 2019

Ribociclib: Resolution of 16 March 2018

Palbociclib: 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 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

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

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. In this treatment situation, fulvestrant is authorised for post-menopausal patients who have not received previous endocrine therapy or who have relapsed during or after adjuvant anti-oestrogen 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. The use of aromatase inhibitors in combination with the elimination of ovarian function can also be considered in this therapeutic situation. This applies in particular after adjuvant tamoxifen therapy and in the case of contraindications or intolerances to tamoxifen. However, in the written statements of medical experts in the present benefit assessment procedure, the aromatase inhibitors were not given a relevant significance in the reality of care. In addition to tamoxifen, the aromatase inhibitor letrozole can also be considered as an appropriate comparator therapy in view of the marketing authorisation status.

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 physician's instructions in the respective treatment situation.

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

[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.

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. The active ingredient ribociclib in combination with an aromatase inhibitor is currently the subject of a benefit assessment procedure in parallel with the present assessment.
Also for abemaciclib in combination with an aromatase inhibitor or with fulvestrant, 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 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 past benefit assessment procedures in this indication 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.

<u>Change of the appropriate comparator therapy:</u>

Sub-population a2)

For 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, the appropriate comparator therapy was originally formulated as follows:

tamoxifen in combination with an elimination of the ovarian function".

This resolution adds letrozole, an aromatase inhibitor, to this appropriate comparator therapy and takes the following form:

"

- tamoxifen in combination with an elimination of the ovarian function,

- possibly letrozole in combination with an elimination of ovarian function in women previously treated with anti-oestrogens

".

In the written statements of medical experts in the present benefit assessment procedure, reference was made to the relevant therapeutic significance of aromatase inhibitors in the reality of care. Aromatase inhibitors can be used in combination with the suppression of ovarian function, especially after adjuvant tamoxifen therapy and in the case of contraindications or intolerances to tamoxifen.

The change in the appropriate comparator therapy does not require a renewed benefit assessment. On one hand, this is because the G-BA takes account of the objections received in the written statement procedure by changing the appropriate comparator therapy. On the other hand, the study on ribociclib in combination with fulvestrant in the present therapeutic indication (MONALEESA-3 study) presented in the dossier by the pharmaceutical company does not provide any evidence for the additional benefit in the present sub-population because only post-menopausal patients were included in this study.

2.1.3 Extent and probability of the additional benefit

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

Description of the MONALEESA-3 study

The pharmaceutical company submitted results from the randomised, double-blind MONALEESA-3 Phase III study to demonstrate the additional benefit of ribociclib in combination with fulvestrant.

This multinational study (N = 726) included post-menopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who had received at most one line of endocrine therapy to treat locally advanced or metastatic disease. The medicinal product combination ribociclib + fulvestrant (N = 484) was compared with placebo + fulvestrant (N = 242).

With regard to previous therapy, patients who were *de novo* in the metastatic stage or who had relapsed during or after completion of (neo-)adjuvant endocrine therapy and who had not yet received therapy in the locally advanced or metastatic stage were included. In these patients, relapse could have occurred either during, within, or later than 12 months after completion of (neo-)adjuvant endocrine therapy. In addition, patients with progression after at most one line of endocrine therapy in the locally advanced or metastatic stage who had relapsed later than 12 months after completion of (neo-)adjuvant endocrine therapy or who had not previously received (neo-)adjuvant endocrine therapy were included.

In the in MONALEESA-3 study, stratification factors were presence of lung and/or liver metastases (yes vs no) and prior endocrine therapy (no therapy in advanced situation vs maximum one line of therapy in advanced situation). With regard to the latter stratification factor, patients with a relapse during or ≤ 12 months after completion of (neo-)adjuvant endocrine therapy and without previous endocrine therapy in the locally advanced or metastatic stage were included by the pharmaceutical company in the patient group with prior endocrine therapy in the advanced situation (sub-population b).

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 MONALEESA-3.

The risk of bias at the study level is classified as low. At the endpoint level, the results on health status, symptomatology and health-related quality of life are potentially highly biased because it can be assumed that there is potentially informative censoring with different median observation durations in the study arms, which are largely controlled by disease

progression and because the respective survey instruments were filled in at the end of the therapy break specified in the product information of ribociclib and explicitly inquire about the state of health in the previous (therapy-free) week.
A high risk of bias must be considered for the endpoints of side effects (except for discontinuation because of AE). Nevertheless, the endpoints of severe adverse events and diseases of the blood and lymphatic system for the effects observed are assumed to have a high certainty of outcome because of the magnitude of the effects and the early occurrence compared with the median observation time.

The ongoing MONALEESA-3 study was started in June 2015 and is being conducted multicentrally in 175 study centres in Asia, Australia, Europe, and North and South America.
For the benefit assessment, the data cut-off of 3 November 2017 was used.

On the relevant sub-populations of the MONALEESA-3 study for the assessment of the additional benefit in sub-populations a1 and b1

The MONALEESA-3 study included post-menopausal 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.

The results of the study were presented by the pharmaceutical company in the dossier for the benefit assessment as part of a summarised evaluation of the overall population of the study regardless of whether the patients in the locally advanced or metastatic stage had already received previous endocrine therapy. 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 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 (see also Section 2.1.2 on appropriate comparator therapy).

The written statements in the present benefit assessment procedure, including the opinions of medical experts as well as the comments in the dossier of the pharmaceutical company take the view that the results of the entire study population of the MONALEESA-3 study should be used for the benefit assessment. Both for patients without previous endocrine therapy in the advanced or metastatic stage and for those who have already received endocrine therapy in this stage, fulvestrant has been established as an appropriate comparator therapy. Furthermore, there would be no effect modification by the sub-group characteristic of “prior endocrine therapy”. Thus, the subdivision in dependence of a previous endocrine therapy in the advanced or metastatic stage is questioned.

In principle, the G-BA can understand this reasoning. However, for the reasons already mentioned, it still considers it appropriate to consider data from the MONALEESA-3 study separately according to the sub-populations defined. In this respect, 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 previous endocrine therapy.

In the dossier, the pharmaceutical company presented sub-group analyses in which patients without (sub-population a) and with (sub-population b) previous endocrine therapy in the locally advanced or metastatic stage were examined. Patients with an early relapse during or ≤ 12 months after completion of (neo-)adjuvant endocrine therapy and without previous endocrine therapy in the locally advanced or metastatic stage were included in the patient group with previous endocrine therapy in the advanced situation (sub-population b1), although the patients at this stage had *de facto* not yet received endocrine therapy.
With 208 patients, this patient group represented approx. 29% of the total study population (N = 726) and also outweighed the proportion of patients who had actually undergone

endocrine therapy in the advanced or metastatic stage (N=137). The latter patients were included in the study if they had shown a long disease-free interval (> 12 months) after successful adjuvant endocrine therapy and thus a late relapse or if they were already *de novo* in a locally advanced or metastatic stage.

The G-BA does not consider it appropriate to consider patients with early relapse and without initial endocrine therapy in the advanced or metastatic stage within sub-population b1. In this regard, the written statements of medical experts in the present benefit assessment procedure emphasised that, in relation to the disease-free interval after adjuvant endocrine therapy, the threshold value of 12 months is to be regarded as an arbitrary demarcation for which a stringent implementation cannot be assumed, even in clinical everyday life.
From the point of view of the G-BA, in the present indication, it is therefore appropriate to consider patients without previous endocrine therapy in the advanced or metastatic stage in sub-population a1 in consistency with previous assessment procedures. This applies regardless of whether, in the case of a prior endocrine therapy in the (neo-)adjuvant stage, a relapse has occurred earlier or later than 12 months after completion of this therapy. In contrast to patients in the b1 sub-population with late relapse and who have been additionally treated with endocrine therapy in the advanced or metastatic stage, these patients share the characteristic that they have not yet received endocrine therapy in this stage.

Within the framework of the written comments procedure on the present benefit assessment, the pharmaceutical company submitted additional analyses in this regard. In these, the relevant patient group with early relapse during or ≤ 12 months after completion of a (neo-)adjuvant endocrine therapy was assigned to sub-population a1 (without previous endocrine therapy in the advanced situation).

Summary: For these reasons, the present assessment differentiates the results of the MONALEESA-3 study in accordance with the respective sub-populations according to the established appropriate comparator therapy. The appropriate evaluations were presented in the written statement of the pharmaceutical company and evaluated by IQWiG in the addendum to the dossier evaluation. These evaluations are used for the present assessment.

Implementation of the appropriate comparator therapy in the MONALEESA-3 study:

In the MONALEESA-3 study, monotherapy with fulvestrant was prescribed for the control group as per study protocol. The MONALEESA-3 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 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.
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.

Extent and probability of the additional benefit

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:

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 ribociclib in combination with fulvestrant compared with fulvestrant is not proven.

Mortality

In the MONALEESA-3 study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death. In MONALEESA-3, overall survival was a secondary endpoint.
For overall survival, MONALEESA-3 showed no statistically significant difference between treatment groups for patients who had not yet received initial endocrine therapy in locally advanced or metastatic stages (HR: 0.66; [95% CI: 0.43; 1.02]; p-value = 0.061). Median survival has not yet been achieved because of the low number of events.

Based on the total population of the MONALEESA-3 study (patients without and with prior endocrine therapy in locally advanced or metastatic stage), there was a statistically significant difference to the benefit of ribociclib + fulvestrant for overall survival (HR: 0.67; [95% CI: 0.47; 0.96]; p-value = 0.030). In dossier evaluation of the IQWiG or its addendum to the benefit assessment, it is stated that in the present data situation, the results of the entire population could be transferred to the sub-population when interpreting the results.

This transfer of the results of the entire population to the sub-population of patients who had not yet received initial endocrine therapy in the locally advanced or metastatic stage is associated with considerable uncertainties because of methodological and clinical aspects.

In the present indication, the G-BA considers it necessary to differentiate between patients who have not previously received initial endocrine therapy in the locally advanced or metastatic stage and those who have already been treated with a previous endocrine therapy in this stage. These patient groups differ not only in their previous therapy but also in their prognosis and burden of disease. This results in an initial separate basis of evaluation for the corresponding sub-population.

Even if the consideration of results of the entire population can in principle be considered in the data situation at hand, the differences between the treatment arms in favour of ribociclib plus fulvestrant, which would be based exclusively on a transfer of overall survival results to the sub-populations to be evaluated, are subject to considerable uncertainties. Another important factor here is that the statistically significant advantage in the total population is based on a relatively small number of events. The approval authority also classifies the overall survival data as provisional.

Morbidity

Progression-free survival (PFS)

In the MONALEESA-3 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 ribociclib treatment group there was a statistically significant increase in median PFS of 7.7 months compared with the control group (median of 20.6 vs 12.9 months; HR: 0.61; [95% CI: 0.48; 0.77]; p value < 0.001).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the MONALEESA-3 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. Data on morbidity and health-related quality of life are potentially relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life.

The data available from the MONALEESA-3 study showed no differences between treatment groups in the endpoint categories morbidity and health-related quality of life. Accordingly, prolonged PFS under ribociclib was not associated with an advantage in terms of morbidity or quality of life. It should be noted that the corresponding endpoints were evaluated for the last time 30 days after the end of treatment or at the time of disease progression and therefore only allow statements to be made up to this point in time. In the MONALEESA-3 study, the end of treatment was largely controlled by disease progression. 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.

The extent to which the prolongation of PFS under ribociclib also translates into prolonged survival cannot currently be conclusively assessed.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under ribociclib – radiologically determined disease progression according to the RECIST criteria – is associated with an improvement in morbidity or health-related quality of life.

The results on the progression-free survival endpoint are not therefore 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 MONALEESA-3 was defined *post hoc* in the benefit dossier for ribociclib.

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 responder analyses for the time until deterioration by ≥ 7 points and by ≥ 10 points of the VAS score compared with baseline in the dossier for the benefit assessment for the sub-population under consideration. These responder analyses were not pre-specified in the MONALEESA-3 study.

These responder analyses were not used in the dossier evaluation of the IQWiG or its addendum on the benefit assessment because the study underlying the derivation of the MID (Pickard *et al.*, 2007[4]) of the IQWiG was classified as unsuitable to validate the MID. This is justified on one hand 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. The anchors ECOG-PS and FACT-G total score of the IQWiG used in the study are also not considered suitable for deriving the MID.

In view of the fact that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean value differences and taking into account that the validation study in question has already been used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology.

These show no statistically significant difference between the treatment arms for the time until permanent deterioration.

An additional benefit of ribociclib in combination with fulvestrant for the endpoint health status (EQ-5D-VAS) is not proven.

Symptomatology

In the MONALEESA-3 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30.

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

None of the endpoints presented showed a statistically significant difference between treatment groups.

[4] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual. Life Outcomes* 2007; 5: 70.

Pain (BPI-SF)

Pain was measured using the BPI-SF (Brief Pain Inventory - Short Form) questionnaire.
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.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for the time to permanent deterioration with regard to the endpoint "strongest pain" (defined *post hoc* as the increase of the score by at least 2 points compared with baseline without subsequent improvement to a score below this level). In the study protocol, however, two further evaluations of the BPI-SF were pre-specified ("pain intensity" and "impairment because of pain"). These were not presented in the dossier. Furthermore, a deviating response criterion was pre-specified in the study protocol.

Because of the incomplete data basis on BPI-SF, this endpoint is not used for this assessment.

Quality of life

In the MONALEESA-3 study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life.

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

None of the endpoints presented showed a statistically significant difference between treatment groups.

Side effects

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

Adverse events (AE)

In the MONALEESA-3 study, in patients who had not yet received initial endocrine therapy in the locally advanced or metastatic stage, 98.9% in the intervention arm and 96.0% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

For the serious adverse events, a statistically significant effect to the detriment of ribociclib in combination with fulvestrant was observed (HR: 1.61; [95% CI: 1.09; 2.38]; p-value = 0.015).

Severe adverse events (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 ribociclib in combination with fulvestrant (HR: 4.49; [95% CI: 3.39; 5.95]; p value < 0.001).

Discontinuation because of AE

In MONALEESA-3, therapy discontinuation was defined as the termination of therapy with ribociclib or placebo. In the study, it was not allowed to discontinue treatment with fulvestrant only. For the median time to therapy discontinuation because of AE, a statistically significant effect was observed to the detriment of ribociclib in combination with fulvestrant (HR: 2.33; [95% CI: 1.27; 4.26]; p-value = 0.005).

Specific AE

In detail, the combination of ribociclib plus fulvestrant showed a statistically significant disadvantage compared with fulvestrant with regard to the endpoint "Blood and lymphatic system disorders (CTCAE grade ≥ 3) (HR: 40.72; [95% CI: 13.00; 127.56]; p value < 0.001). The neutropaenia contained therein (CTCAE grade ≥ 3) represent the leading event.

The side-effect profile of ribociclib is qualitatively comparable to the side-effect profile of cytotoxic chemotherapy, especially with regard to myelosuppression, and differs significantly from the side-effect profile of endocrine therapy.

Overall assessment

For the assessment of the additional benefit of ribociclib in combination with fulvestrant, results from the MONALEESA-3 study in comparison to fulvestrant on mortality (overall survival), morbidity (symptomatology and health status), quality of life, and side effects are available.

In the endpoint category mortality, for the endpoint overall survival in sub-population a1, there is no statistically significant difference between the treatment groups.

A transfer of the result of the entire population, which shows a statistically significant difference in favour of ribociclib in combination with fulvestrant, is associated with considerable uncertainties based on methodological and clinical aspects. The results in terms of mortality for the sub-population considered here cannot be interpreted with certainty. Current analyses on the endpoint of overall survival are pending.

The results for the endpoint categories morbidity and health-related quality of life show no statistically significant differences between treatment arms.

For the side effects in terms of the endpoints serious adverse events (SAE), severe adverse events (CTCAE grade 3 or 4), treatment discontinuations because of adverse events, and, in detail, the specific AE blood and lymphatic system disorders (CTCAE grade 3 or 4), there are statistically significant considerable disadvantages for ribociclib in combination with fulvestrant compared with fulvestrant, especially with regard to the pronounced myelosuppression caused by ribociclib. The overall side effect profile of ribociclib differs significantly from that of endocrine therapy.

In a balancing decision, the G-BA concludes that for ribociclib in combination with fulvestrant for the treatment of post-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy in this disease stage, an additional benefit compared with fulvestrant is not proven.
Even assuming a positive effect in overall survival because of a transfer of the results from the entire population of the MONLEESA-3 study to the relevant sub-population, if the results are sufficiently significant, in the present case, the pronounced side effects would have to be

compared. The extent to which the negative side effects and the prolonged progression-free survival have an effect on overall survival cannot yet be conclusively assessed.

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 ribociclib in combination with fulvestrant compared to the appropriate comparator therapy is not proven.

Justification:

For pre-/peri-menopausal patients who have not yet received initial endocrine therapy, no data were provided to assess the additional benefit of ribociclib in combination with fulvestrant compared with the appropriate comparator therapy. In the MONALEESA-3 study, only post-menopausal patients were examined.

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)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy, an additional benefit of ribociclib in combination with fulvestrant compared with fulvestrant is not proven.

Mortality

In the MONALEESA-3 study, overall survival was defined as the time between randomisation and death regardless of the underlying cause of death. In MONALEESA-3, overall survival was a secondary endpoint.
For overall survival, MONALEESA-3 showed no statistically significant difference between treatment groups for patients with prior endocrine therapy in locally advanced or metastatic stages (HR: 0.60; [95% CI: 0.30; 1.23]; p-value = 0.166). Median survival has not yet been achieved because of the low number of events.

Based on the total population of the MONALEESA-3 study (patients without and with prior endocrine therapy in locally advanced or metastatic stage), there was a statistically significant difference to the benefit of ribociclib + fulvestrant for overall survival (HR: 0.67; [95% CI: 0.47; 0.96]; p-value = 0.030). In dossier evaluation of the IQWiG or its addendum to the benefit assessment, it is stated that in the present data situation, the results of the entire population could be transferred to the sub-population when interpreting the results.

This transfer of the results of the entire population to the sub-population of patients with previous endocrine therapy in the locally advanced or metastatic stage is associated with considerable uncertainties because of methodological and clinical aspects.

In the present indication, the G-BA considers it necessary to differentiate between patients who have not previously received initial endocrine therapy in the locally advanced or metastatic stage and those who have already been treated with a previous endocrine therapy in this stage. These patient groups differ not only in their previous therapy but also in their

prognosis and burden of disease. This results in an initial separate basis of evaluation for the corresponding sub-population.

Even if the consideration of results of the entire population can in principle be considered in the data situation at hand, the differences between the treatment arms in favour of ribociclib plus fulvestrant, which would be based exclusively on a transfer of overall survival results to the sub-populations to be evaluated, are subject to considerable uncertainties. Another important factor here is that the statistically significant advantage in the total population is based on a relatively small number of events. The approval authority also classifies the overall survival data as provisional.

Morbidity

Progression-free survival (PFS)

In post-menopausal women in advanced or metastatic stage with prior endocrine therapy, PFS was statistically significantly extended by 7.4 months (median) in the ribociclib treatment group compared with the control group (median of 18.8 vs 11.4 months; HR: 0.52; [95% CI: 0.32; 0.86]; p-value = 0.009).

The results on the progression-free survival endpoint are not used in this assessment.

For further information on the endpoint PFS, please refer to the explanations under sub-population a1.

Time to first subsequent chemotherapy

For the endpoint time until the first subsequent chemotherapy, reference is made to the explanations under sub-population a1.

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 responder analyses for the time until deterioration by ≥ 7 points and by ≥ 10 points of the VAS score compared with baseline in the dossier for the benefit assessment for the sub-population under consideration. These responder analyses were not pre-specified in the MONALEESA-3 study.

These responder analyses were not used in the dossier evaluation of the IQWiG or its addendum on the benefit assessment because the study underlying the derivation of the MID (Pickard *et al.*, 2007[5]) of the IQWiG was classified as unsuitable to validate the MID. This is justified on one hand 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. The anchors ECOG-PS and FACT-G total score of the IQWiG used in the study are also not considered suitable for deriving the MID.

In view of the fact that responder analyses based on a MID have general advantages for a clinical evaluation of effects compared with an analysis of standardised mean value differences and taking into account that the validation study in question has already been

[5] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual. Life Outcomes* 2007; 5: 70.

used in earlier evaluations, the G-BA nevertheless uses the responder analyses in the present assessment to assess the effects on symptomatology.

These show no statistically significant difference between the treatment arms for the time until permanent deterioration.

An additional benefit of ribociclib in combination with fulvestrant for the endpoint health status (EQ-5D-VAS) is not proven.

Symptomatology

In the MONALEESA-3 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30.

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

None of the endpoints presented showed a statistically significant difference between treatment groups.

Pain (BPI-SF)

Pain was measured using the BPI-SF (Brief Pain Inventory - Short Form) questionnaire.
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.

In the dossier for the benefit assessment, the pharmaceutical company submitted responder analyses for the time to permanent deterioration with regard to the endpoint “strongest pain” (defined *post hoc* as the increase of the score by at least 2 points compared with baseline without subsequent improvement to a score below this level). In the study protocol, however, two further evaluations of the BPI-SF were pre-specified (“pain intensity” and “impairment because of pain”). These were not presented in the dossier. Furthermore, a deviating response criterion was pre-specified in the study protocol.

Because of the incomplete data basis on BPI-SF, this endpoint is not used for this assessment.

Quality of life

In the MONALEESA-3 study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life.

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

None of the endpoints presented showed a statistically significant difference between treatment groups.

Side effects

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

Adverse events (AE)

In the MONALEESA-3 study, in patients with previous endocrine therapy in the locally advanced or metastatic stage, 100% in the intervention arm and 94.7% 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 treatment arms.

Severe adverse events (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 ribociclib in combination with fulvestrant (HR: 3.69; [95% CI: 1.95; 7.01]; p value < 0.001).

Discontinuation because of AE

In MONALEESA-3, therapy discontinuation was defined as the termination of therapy with ribociclib or placebo. In the study, it was not allowed to discontinue treatment with fulvestrant only. For the median time to therapy discontinuation because of AE, a statistically significant effect was observed to the detriment of ribociclib in combination with fulvestrant (HR: 4.58; [95% CI: 1.08; 19.48]; p-value = 0.024).

Specific AE

In detail, the combination of ribociclib plus fulvestrant showed a statistically significant disadvantage compared with fulvestrant with regard to the endpoint “Blood and lymphatic system disorders (CTCAE grade ≥ 3) (HR: 10.31; [95% CI: 2.49; 42.69]; p value < 0.001). The neutropaenia contained therein (CTCAE grade ≥ 3) represent the leading event.

The side-effect profile of ribociclib is qualitatively comparable to the side-effect profile of cytotoxic chemotherapy, especially with regard to myelosuppression, and differs significantly from the side-effect profile of endocrine therapy.

Overall assessment

For the assessment of the additional benefit of ribociclib in combination with fulvestrant, results from the MONALEESA-3 study in comparison to fulvestrant on mortality (overall survival), morbidity (symptomatology and health status), quality of life, and side effects are available.

In the endpoint category mortality, for the endpoint overall survival in sub-population b1, there is no statistically significant difference between the treatment groups.

A transfer of the result of the entire population, which shows a statistically significant difference in favour of ribociclib in combination with fulvestrant, is associated with considerable uncertainties based on methodological and clinical aspects. The results in terms of mortality for the sub-population considered here cannot be interpreted with certainty. Current analyses on the endpoint of overall survival are pending.

The results for the endpoint categories morbidity and health-related quality of life show no statistically significant differences between treatment arms.

For the side effects in terms of the endpoints severe adverse events (CTCAE grade 3 or 4), treatment discontinuations because adverse events, and, in detail, the specific AE blood and lymphatic system disorders (CTCAE grade 3 or 4), there are statistically significant, considerable disadvantages for ribociclib in combination with fulvestrant compared with fulvestrant, especially with regard to the pronounced myelosuppression caused by ribociclib. The overall side effect profile of ribociclib differs significantly from that of endocrine therapy.

In a balancing decision, the G-BA concludes that for ribociclib in combination with fulvestrant for the treatment of post-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer with previous endocrine therapy, an additional benefit compared with fulvestrant is not proven.
Even assuming a positive effect in overall survival because of a transfer of the results from the entire population of the MONLEESA-3 study to the relevant sub-population, if the results are sufficiently significant, in the present case, the pronounced side effects would have to be compared. The extent to which the negative side effects and the prolonged progression-free survival have an effect on overall survival cannot yet be conclusively assessed.

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)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy, an additional benefit of ribociclib in combination with fulvestrant compared with the appropriate comparator therapy is not proven.

Justification:

For pre-/peri-menopausal patients with previous endocrine therapy, no data were provided to assess the additional benefit of ribociclib in combination with fulvestrant compared with the appropriate comparator therapy. In the MONALEESA-3 study, only post-menopausal patients were examined.

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:

The limitation of the period of validity of the resolution on the benefit assessment of ribociclib (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.

The overall survival data from the MONALEESA-3 study available for this assessment are based on a small number of events at the time of this data cut-off. Further results from interim analyses and the final results from the current study are still pending.

In view of the fact that clinical data on overall survival relevant for the benefit assessment of the drug 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 ribociclib in combination with fulvestrant is available. The limitation will permit the expected results from interim analyses from the MONALEESA-3 study to be promptly incorporated into the benefit assessment of the drug in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the resolution until 1 March 2020 to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after the deadline, the results of the interim analysis (after 263 deaths for all endpoints) expected in the third quarter of 2019, which will be used to demonstrate an additional benefit from the ongoing MONALEESA-3 study, will be presented in the dossier.

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 ribociclib 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 ribociclib 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 ribociclib 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 assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient ribociclib. The therapeutic indication assessed here is as follows: “Ribociclib is indicated for the treatment of women with a 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 an 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)".

The present assessment relates exclusively to the use of ribociclib 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 who have received hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with prior endocrine therapy

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

On sub-population a1)

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 results from a randomised controlled study (MONALEESA-3) comparing ribociclib plus fulvestrant with placebo plus fulvestrant. MONALEESA-3 included post-menopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer who had received at most one line of endocrine therapy at this stage of the disease. Here, the results of MONALEESA-3 are relevant for the sub-population of post-menopausal women without initial endocrine therapy from the data cut-off of 3 November 2017.

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

A transfer of the result of the entire population of the study, which shows a statistically significant difference in favour of ribociclib in combination with fulvestrant, is associated with considerable uncertainties based on methodological and clinical aspects. The results in terms of mortality for the sub-population considered here cannot be interpreted with certainty. Current analyses on the endpoint of overall survival are pending.

The results for the endpoint categories morbidity and health-related quality of life showed no statistically significant differences between treatment arms.

In the side effects category, there were disadvantages of ribociclib plus fulvestrant in terms of the endpoints serious adverse events, severe adverse events, therapy discontinuations because of adverse events, and, in detail, the specific AE blood and lymphatic system disorders.

In a balancing decision, the G-BA concluded that ribociclib in combination with fulvestrant does not have any additional benefit over fulvestrant.
Even assuming a positive effect in overall survival because of a transfer of the results from the entire population of the MONLEESA-3 study to the relevant sub-population, if the results are sufficiently significant, in the present case, the pronounced side effects would have to be compared.

On sub-population a2)

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

- tamoxifen in combination with an elimination of the ovarian function,
- possibly letrozole in combination with an elimination of ovarian function in women previously treated with anti-oestrogens,

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

The MONALEESA-3 study presented for the combination therapy of ribociclib with fulvestrant investigated exclusively post-menopausal patients.

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

On sub-population 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 results from a randomised controlled study (MONALEESA-3) comparing ribociclib plus fulvestrant with placebo plus fulvestrant. MONALEESA-3 included post-menopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer who had received at most one line of endocrine therapy at this stage of the disease. Here, the results of MONALEESA-3 are relevant for the sub-population of post-menopausal women with previous endocrine therapy from the data cut-off of 3 November 2017.

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

A transfer of the result of the entire population of the study, which shows a statistically significant difference in favour of ribociclib in combination with fulvestrant, is associated with considerable uncertainties based on methodological and clinical aspects. The results in terms of mortality for the sub-population considered here cannot be interpreted with certainty. Current analyses on the endpoint of overall survival are pending.

The results for the endpoint categories morbidity and health-related quality of life showed no statistically significant differences between treatment arms.

In the side effects category, there were disadvantages of ribociclib plus fulvestrant in terms of the endpoints severe adverse events, therapy discontinuations because of adverse events, and, in detail, in the specific AE blood and lymphatic system disorders.

In a balancing decision, the G-BA concluded that ribociclib in combination with fulvestrant does not have any additional benefit over fulvestrant.
Even assuming a positive effect in overall survival because of a transfer of the results from the entire population of the MONLEESA-3 study to the relevant sub-population, if the results are sufficiently significant, in the present case, the pronounced side effects would have to be compared.

On sub-population b2)

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 the patient group of pre-/peri-menopausal patients with previous endocrine therapy, no data were provided to assess the additional benefit of ribociclib in combination with fulvestrant compared with the appropriate comparator therapy.

The MONALEESA-3 study presented for the combination therapy of ribociclib with fulvestrant investigated exclusively post-menopausal patients.

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

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

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 Kisqali® (active ingredient: ribociclib) at the following publicly accessible link (last access: 23 May 2019):

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

Treatment with ribociclib 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 June 2019).

Ribociclib is taken once daily as a tablet for 21 consecutive days followed by 7 days without treatment. Each 28-day period corresponds to one treatment cycle.

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 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.

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/patient/year	Treatment duration/treatment (days)
Medicinal product to be assessed			
Ribociclib	continuous	1 × daily	273
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1, 15, and 29 Afterwards: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	First year of treatment: 1st month: 3 × monthly Afterwards: 1 × monthly Following year: 1 × monthly	First year of treatment: 14 Following year: 12
For sub-populations a2 and b2 additionally)			
Goserelin	continuous	every 28 days	13
Leuprorelin	continuous	1 × every 3 months	4
Appropriate comparator therapy			
Sub-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:	First year of treatment: 1st month: 2 × monthly From the 2nd month: 1 × monthly Following year: 1 × monthly	First year of treatment: 13 Following year: 12

	500 mg i.m.		
Tamoxifen	continuous, 1 × daily	1	365
Sub-population a2)			
Anti-oestrogens			
Tamoxifen	continuous	1 × daily	365
Letrozole	continuous	1 × daily	365
LHRH[6] analogue			
Goserelin	continuous	every 28 days	13
Leuprorelin	continuous	1 × every 3 months	4
Sub-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.	First year of treatment: 1st month: 2 × monthly From the 2nd month: 1 × monthly Following year: 1 × monthly	First year of treatment: 13 Following year: 12
Tamoxifen	continuous	1 × daily	365
Protein kinase inhibitors			
Everolimus	continuous	1 × daily	365
Sub-population b2)			
Aromatase inhibitor			
Exemestane	continuous	1 × daily	365

[6] Luteinising Hormone Releasing Hormone

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				
Ribociclib	200 mg	600 mg	189 Tablets	819 Tablets
Fulvestrant	250 mg	500 mg	6 prefilled syringes	First year of treatment: 28 prefilled syringes Following year: 24 prefilled syringes
For sub-populations a2 and b2 additionally)				
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				
Sub-population a1)				
Aromatase inhibitor				
Anastrozole	1 mg	1 mg	100 tablets	365 Tablets

Designation of the therapy	Potency	Cost per patient per treatment day	Quantity per package	Annual mean consumption according to potency
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
Sub-population a2)				
Anti-oestrogens				
Tamoxifen	20 mg	20 mg	100 Tablets	365 Tablets
Letrozole	2.5 mg	2.5 mg	120 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
Sub-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

Designation of the therapy	Potency	Cost per patient per treatment day	Quantity per package	Annual mean consumption according to potency
Protein kinase inhibitors				
Everolimus	10 mg	10 mg	90 Tablets	365 Tablets
Sub-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 syringes	13 prefilled 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
Ribociclib	200 mg, 189 film-coated tablets	€ 7,270.09	€ 1.77	€ 411.92	€ 6,856.40

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
Anastrozole	1 mg, 100 film-coated tablets	€ 77.93[7]	€ 1.77	€ 5.29	€ 70.87
Everolimus	10 mg, 90 tablets	€ 5,833.84	€ 1.77	€ 754.05	€ 5,078.02
Exemestane	25 mg, 100 tablets	€ 127.20[7]	€ 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[7]	€ 1.77	€ 5.71	€ 75.67
Leuprorelin	11.25 mg, 2 prefilled syringes	€ 948.89	€ 1.77	€ 51.93	€ 895.19
Medroxyprogesterone 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[7]	€ 1.77	€ 0.88	€ 19.48

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

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.

7 Fixed amount Level I

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 7 August 2018.

On 14 January 2019, the pharmaceutical company submitted a dossier for the benefit assessment of ribociclib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 14 January 2019 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 ribociclib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 April 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 April 2019. The deadline for submitting written statements was 6 May 2019.

The oral hearing was held on 27 May 2019.

By letter dated 27 May 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 17 June 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 June 2019, and the proposed resolution was approved.

At its session on 4 July 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 August 2018	Determination of the appropriate comparator therapy
Working group Section 35a	14 May 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	27 May 2019	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 June 2019 18 June 2019	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure

Subcommittee Medicinal product	24 June 2019	Concluding discussion of the proposed resolution
Plenum	4 July 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 4 July 2019

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

Prof Hecken