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 Ribociclib (Reassessment after the Deadline (Breast Cancer, HR+, HER2-, Combination with Fulvestrant))

of 20 August 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 first submitted a dossier for the benefit assessment of the active ingredient ribociclib on 14 January 2019. The resolution of 4 July 2019 passed by the G-BA in this procedure was limited in time for the patient populations of a1) post-menopausal patients with initial endocrine therapy and b1) post-menopausal patients with progression after previous endocrine therapy. In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 7 VerfO or Chapter 5, Section 8, paragraph 1, number 5, the benefit assessment procedure for the medicinal product Kisqali shall start again on the day the deadline has expired. To this end, the pharmaceutical company submitted the final dossier to the G-BA on 29 February 2020 to prove the additional benefit of ribociclib 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, paragraph 1, No. 5 VerfO). 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 2 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 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 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 ribociclib.

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 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. The present benefit assessment procedure focuses on patient groups “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 “post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy”.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy 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-based therapy:

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

b1) Post-menopausal 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:

[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.

- 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".

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 ribociclib, 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 treatments, 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:

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

Ribociclib (combination with fulvestrant): 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

Ribociclib (combination with an aromatase inhibitor): Resolution of 16 March 2018

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 post-menopausal 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 post-menopausal 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 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 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 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.

Similarly, ribociclib in combination with an aromatase inhibitor as an initial endocrine-based 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 corresponding reassessment after the deadline is currently in the benefit assessment procedure in parallel to the present assessment.

For ribociclib in combination with an aromatase inhibitor as an initial endocrine therapy in pre-peri-menopausal women (a2) and after previous endocrine therapy in both post-

[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.

menopausal women (b1) and pre/peri-menopausal women (b2), no additional benefit was determined by the resolution of 4 July 2019.

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. The corresponding reassessment after the deadline for abemaciclib in combination with fulvestrant is currently in the benefit assessment procedure in parallel to the present assessment.

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.

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

2.1.3 Extent and probability of the additional benefit

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

To demonstrate an additional benefit of ribociclib 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 MONALEESA-3 study, which is already known from the previous benefit assessment of ribociclib in the present therapeutic indication.

This multinational study included post-menopausal patients with locally advanced or metastatic HR-positive HER2-negative breast cancer who had received at most one line of endocrine treatment to treat locally advanced or metastatic disease.

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 (Patient group a1). 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 previous endocrine therapy were included (Patient group b1).

In the in MONALEESA-3 study, stratification factors were presence of lung and/or liver metastases (yes vs no) and prior endocrine therapy.

Treatment was carried out continuously in cycles of 28 days until disease progression, unacceptable toxicity, or discontinuation of therapy for other reasons.

The tumour should not have been suitable for resection or radiotherapy with curative intent. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 at the start of study.

The primary endpoint of the study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, symptomatology, health status, health-related quality of life, and adverse events (AEs).
The MONALEESA-3 study is completed. There are evaluations on 2 data cut-offs:

- 1st data cut-off (3 November 2017): planned interim analysis after 364 PFS events
- 2nd data cut-off (3 June 2019): planned interim analysis after 263 deaths

For the present benefit assessment, the results of the most recent data cut-off are 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.

On the basis of this study, the pharmaceutical company once again assesses the additional benefit for all post-menopausal women, without distinguishing between the therapy lines as described in research questions A1 and B1. However, the pharmaceutical company presents the findings separately for research questions A1 and B1 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 ribociclib (in combination with fulvestrant) in the resolution of 4 July 2019. The current assessment is therefore based on the evaluations of each sub-population.

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 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.

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-based therapy:

Indication of a minor additional benefit

Justification:

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.

In the MONALEESA-3 study, the median survival time at the time of the 2nd data cut-off of 3 June 2019 was 40 months in the comparator arm. In the intervention arm (ribociclib + fulvestrant), the median survival time was not yet reached.

For overall survival, the MONALEESA-3 study showed a statistically significant difference in the benefit of ribociclib in combination with fulvestrant compared with fulvestrant for patients who had not yet received initial endocrine therapy in locally advanced or metastatic stage*.

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.

PFS was statistically significantly longer in the ribociclib treatment group compared with the control group.

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. 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.

However, in the MONALEESA-3 study, prolonged PFS under ribociclib was not associated with any benefit with respect to morbidity or quality of life.

One limitation is that the corresponding endpoints were only collected up to progression and therefore allow statements to be made only up to the time of 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 analyses and publications submitted by the pharmaceutical company in the dossier do not provide sufficient evidence that the PFS is a valid surrogate endpoint for overall survival in the present indication.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under ribociclib 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 as well as intravenous treatment, may be relevant.

Possible benefits of ribociclib resulting from a prolonged period of time prior to follow-up therapy should also be reflected in other patient-relevant endpoints such an extension of the time until symptoms of the disease appear, stressful side effects of follow-up therapy, or deterioration of quality of life. In order to provide such evidence, it would have been necessary to collect data beyond the discontinuation of treatment with the study medication.

The findings for the "time to initial subsequent chemotherapy" endpoint are therefore not included in this assessment.

Health status

In the MONALEESA-3 study, the visual analogue scale (VAS) of the EQ-5D was used to collect data on general health status. Responder analyses were available for the time until permanent deterioration by a minimal important difference (MID) of 7 and 10 points.

In the dossier assessment of the IQWiG, the analyses of mean differences were used. The responder analyses were also presented in the annex to the dossier assessment. There are no comments on the decision-making process regarding the inclusion of continuous analyses or responder analyses.

In the recent past, the IQWiG has not used 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 prove the validity of the 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.

Instead of responder analyses, the IQWiG used analyses of mean differences. The mean differences do not show a statistically significant difference in favour of ribociclib in combination with fulvestrant.

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 nevertheless decided to draw on responder analyses in the current assessment to determine the effects on health status.

In the responder analyses there is no statistically significant difference between the two treatment arms for the endpoint health status for both an MID of 7 points and an MID of 10 points.

There is therefore no advantage or disadvantage in terms of health status.

Pain (BPI-SF)

The MMRM analysis is used to consider the change from baseline (pre-specified in the MONALEESA-3 study) for the various operationalisations. Pain intensity using BPI-SF items 3–6 represents an equally weighted average of different pain levels. Of these, the worst pain felt by the patients (item 3) has a special significance and is therefore presented separately.

The results on average pain intensity (BPI-SF items 3-6) are only presented additionally. Impairment because of pain (IBPI-SF items 9 a-g) is also included in the assessment.
There are no statistically significant differences between the treatment arms for the endpoints pain evaluated using the worst pain (BPI-SF item 3) and impairment because of pain (BPI-SF items 9 a-g).

Symptomatology

In the MONALEESA-3 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30. In each case, the time until permanent deterioration by ≥ 10 points is considered.

For none of the symptom scales of EORTC QLQ-C30 is there a statistically significant difference between the treatment groups.

Health-related quality of life

To survey the health-related quality of life, the MONALEESA-3 study recorded the global health status and the functional scales of the disease-specific questionnaire EORTC QLQ-C30. In each case, the time until permanent deterioration by ≥ 10 points is considered.
There is no statistically significant difference between the treatment groups for any of the 5 functional scales nor for the global health status.

Side effects

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

Adverse events

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.

Severe AE (CTCAE grade 3 or 4)

In terms of time to the occurrence of severe adverse events with CTCAE grade 3 or 4, there was a statistically significant treatment effect to the detriment of ribociclib in combination with fulvestrant.

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.

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 or 4). The neutropoenia contained therein (CTCAE grade 3 or 4) represent the leading event.

Overall assessment/conclusion

To assess the additional benefit of ribociclib in combination with fulvestrant compared with fulvestrant in sub-population a1, results on mortality (overall survival), morbidity (symptomatology, health status, and pain), quality of life, and side effects from the MONALEESA-3 study are available.

With regards to overall survival, the MONA-LEESA-3 study reveals a benefit for ribociclib in combination with fulvestrant compared with fulvestrant.

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

Overall, the results on side effects show statistically significant and disadvantages for ribociclib in combination with fulvestrant compared with fulvestrant with regard to the endpoints serious AE, severe AE (CTCAE grade 3 to 4), therapy discontinuation because of AE, and, in detail, the specific AE mentioned.

The overall side effect profile of ribociclib differs significantly from that of endocrine therapy. In studies of patients who received ribociclib in combination with fulvestrant, the side effects often led to a delay or interruption in taking the medication. In clinical studies, asymptomatic haematological laboratory parameters with short-term adjustment of the dose of ribociclib are more closely controlled than in healthcare practice. The side effects may therefore be underestimated based on study results.

In a balancing decision of the advantage in overall survival and the significant disadvantages in side effects, the G-BA concluded that for ribociclib in combination with fulvestrant for the treatment of post-menopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have not yet received initial endocrine therapy, there is a minor additional benefit compared with fulvestrant.

Reliability of data (probability of additional benefit)

In the randomised, double-blind Phase III MONALEESA-3 study, ribociclib in combination with fulvestrant was compared with the appropriate comparator therapy fulvestrant.
Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

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

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

The risk of bias for the endpoints symptomatology and health-related quality of life is rated as high. However, a downgrading of the reliability of data for the overall assessment is not justified.

The reliability of data supporting the finding of an additional benefit must therefore be classified as an “indication”.

b1) Post-menopausal 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 MONALEESAS-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, in the MONALEESA-3 study, there were no statistically significant difference between treatment groups for patients with prior endocrine therapy in locally advanced or metastatic stages. In the MONALEESA-3 study, the median survival time at the time of the 2nd data cut-off of 3 June 2019 was 35.4 months in the comparator arm. In the intervention arm (ribociclib + fulvestrant), the median survival time was not yet reached.

In the dossier assessment of the IQWiG, the results of the total population of the MONALEESA-3 study are additionally considered in the overall assessment performed by IQWiG in the specific data constellation available here for the endpoint overall survival.

For the total population of the MONALEESA-3 study, a statistically significant effect in favour of ribociclib + fulvestrant was shown for the endpoint overall survival.

In this respect, IQWiG states that 78% of the deaths planned for the final analysis have been reached (275 out of 351). Sub-population b1 comprises only 19% of the study population. However, there is consistency in the direction of effect and location of the point estimates between sub-populations a1 and b1 as well as the total population. A similar situation was already evident in the earlier data cut-off of the initial assessment (at that time based on a significantly lower number of deaths).

Based on these methodological aspects and in view of the available meaningful data on overall survival, the G-BA considers this special data constellation to be a sufficient basis for additionally considering the results of the total population of the MONALEESA-3 study in the overall assessment of the additional benefit for the overall survival endpoint by way of exception. In contrast to the initial assessment of ribociclib in the present therapeutic indication in which the results of the entire population were not taken into account on the data basis at the time, the present reassessment after the expiry of the limitation much more significant data on overall survival.

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 post-menopausal women in advanced or metastatic stage with prior endocrine therapy, the PFS in the ribociclib treatment group was statistically significantly longer than in the control group.

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. 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.

One limitation here is that the corresponding endpoints were only collected up to progression and therefore allow statements to be made only up to the time of 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 analyses and publications submitted by the pharmaceutical company in the dossier do not provide sufficient evidence that the PFS is a valid surrogate endpoint for overall survival in the present indication.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under ribociclib 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

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

Health status

In the MONALEESA-3 study, the visual analogue scale (VAS) of the EQ-5D was used to collect data on general health status. Responder analyses were available for the time until permanent deterioration by a minimal important difference (MID) of 7 and 10 points.

In the dossier assessment of the IQWiG, the analyses of mean differences were used. The responder analyses were also presented in the annex to the dossier assessment. There are no comments on the decision-making process regarding the inclusion of continuous analyses or responder analyses.

In the recent past, the IQWiG has not used 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 prove the validity of the 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.

Instead of responder analyses, the IQWiG used analyses of mean differences.

For sub-population b1, no results were available on the analysis of mean differences.

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 nevertheless decided to draw on responder analyses in the current assessment to determine the effects on health status.

In the responder analyses there is no statistically significant difference between the two treatment arms for the endpoint health status for both an MID of 7 points and an MID of 10 points.

There is therefore no advantage or disadvantage in terms of health status.

Pain (BPI-SF)

The MMRM analysis is used to consider the change from baseline (pre-specified in the MONALEESA-3 study) for the various operationalisations. Pain intensity using BPI-SF items 3–6 represents an equally weighted average of different pain levels. Of these, the worst pain felt by the patients (item 3) has a special significance and is therefore presented separately. The results on average pain intensity (BPI-SF items 3-6) are only presented additionally. Impairment because of pain (IBPI-SF items 9 a-g) is also included in the assessment.

There are no statistically significant differences between the treatment arms for the endpoints pain evaluated using the worst pain (BPI-SF item 3) and impairment because of pain (BPI-SF items 9 a-g).

Symptomatology

In the MONALEESA-3 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30. The present assessment is based on an evaluation of the time until permanent deterioration of the symptomatology.
None of the endpoints presented showed a statistically significant difference between treatment groups.

Health-related quality of life

To survey the health-related quality of life, the MONALEESA-3 study used the global health status and the functional scales of the disease-specific questionnaire EORTC QLQ-C30. The present assessment is based on the evaluation of the time until permanent deterioration of the quality of life by ≥ 10 points.

For the symptom scale emotional function there is a statistically significant difference to the benefit of ribociclib in combination with fulvestrant.

The endpoint emotional function shows a statistically significant effect modification for the characteristic age (< 65 years, ≥ 65 years). In this endpoint, the results indicate a more favourable effect for older patients ≥ 65 years.

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 94.9% in the comparator arm experienced an adverse event.

Serious adverse events

For the SAEs endpoint, there was no statistically significant difference between the treatment groups.

Severe AEs (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 effect to the detriment of ribociclib in combination with fulvestrant.

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.

Specific AE

In detail, for the specific adverse events, there are statistically significant disadvantages of the combination of ribociclib plus fulvestrant compared with fulvestrant with regard to the endpoint "Blood and lymphatic system disorders" (CTCAE grade 3 or 4). The neutropoenia contained therein (CTCAE grade 3 or 4) represent the leading event.

Overall assessment/conclusion

To assess the additional benefit of ribociclib in combination with fulvestrant compared with fulvestrant in sub-population b1, results on mortality (overall survival), morbidity (symptomatology, pain, and health status), quality of life, and side effects from the MONALEESA-3 study are available.

For overall survival, the evaluations for sub-population b1 show no statistically significant difference between the treatment groups. Taking into account the methodological aspects mentioned above and in view of the available meaningful data on overall survival, the G-BA considers this special data constellation to be a sufficient basis for additionally considering the results of the total population of the MONALEESA-3 study in the overall assessment of the additional benefit for the overall survival endpoint by way of exception. These show an advantage of ribociclib in combination with fulvestrant compared with fulvestrant for the endpoint overall survival (total population).

In the morbidity category, there is no statistically significant difference between the treatment groups for the endpoints symptomatology and health status.

For the endpoint emotional function in the endpoint category quality of life, there is a benefit of ribociclib in combination with fulvestrant compared with fulvestrant.

Overall, the results on side effects show statistically significant and disadvantages for ribociclib in combination with fulvestrant compared with fulvestrant with regard to the endpoints severe AE (CTCAE grade 3 to 4), therapy discontinuation because of AE, and, in detail, the specific AE mentioned.

The overall side effect profile of ribociclib differs significantly from that of endocrine therapy. In studies of patients who received ribociclib in combination with fulvestrant, the side effects often led to a delay or interruption in taking the medication. In clinical studies, asymptomatic haematological laboratory parameters with short-term adjustment of the dose of ribociclib are more closely controlled than in healthcare practice. The side effects may therefore be underestimated based on study results.

In a balancing decision of the benefit in overall survival from the total population, the benefit in terms of the "emotional function" scale in the endpoint category quality of life and the significant disadvantages in terms of side effects, the G-BA concluded that for ribociclib in combination with fulvestrant for the treatment of post-menopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have not yet received initial endocrine therapy, there is a minor additional benefit compared with fulvestrant.

Reliability of data (probability of additional benefit)

In the randomised, double-blind Phase III MONALEESA-3 study, ribociclib in combination with fulvestrant was compared with the appropriate comparator therapy fulvestrant.

Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

For the present assessment, the evaluations of sub-population b1 (post-menopausal women with previous endocrine therapy) are used in addition to the overall survival endpoint. For the endpoint overall survival, the results of the total population are used for the reasons described above.

The risk of bias for the results for the endpoint overall survival in the total population is classified as low.

However, taking into account the results on overall survival of the total population for the assessment of the additional benefit in sub-population b1 is associated with relevant uncertainties. Therefore, for the additional benefit identified, the reliability of data is classified as a “hint”.

2.1.4 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient ribociclib because of the expiry of the limitation of the resolution of 4 July 2019. The assessment refers exclusively to the use of ribociclib in combination with fulvestrant for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in 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

b1) Post-menopausal women who have received hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with 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 suitable.

For this patient group, the pharmaceutical company presents results from a randomised controlled MONALEESA-3 study in which ribociclib plus fulvestrant is compared 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 treatment 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 June 2019.

In the endpoint category mortality, a benefit of ribociclib in combination with fulvestrant compared with fulvestrant was shown for the endpoint overall survival.

The results for the endpoint categories morbidity and health-related quality of life show 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 of the benefit in overall survival and the significant disadvantages in terms of side effects, the G-BA concluded that for that for ribociclib in combination with fulvestrant for the treatment of post-menopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have not yet received initial endocrine therapy, there is an indication for a minor additional benefit compared with fulvestrant.

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
- 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 MONALEESA-3 study in which ribociclib plus fulvestrant is compared 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 treatment 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 June 2019.

For overall survival, the evaluations for sub-population b1 show no statistically significant difference between the treatment groups.

In the specific data constellation presented here and in view of the available meaningful data on overall survival, the G-BA sees a sufficient basis for additionally considering the results of the total population of the MONALEESA-3 study in the overall assessment of additional benefit for the overall survival endpoint by way of exception.

For the endpoint overall survival in the total population a benefit of ribociclib in combination with fulvestrant compared with fulvestrant is shown.

In the morbidity category, there is no statistically significant difference between the treatment groups for the endpoints symptomatology and health status.

For the endpoint emotional function in the endpoint category quality of life, there is a benefit of ribociclib in combination with fulvestrant compared with fulvestrant.

In the overall view, the results on side effects show statistically significant and significant disadvantages for ribociclib in combination with fulvestrant compared with fulvestrant with regard to the endpoints severe AE (CTCAE grade 3 to 4), therapy discontinuation because of AE and, in detail, for the specific AE blood and lymphatic system disorders.

In a balancing decision of the benefit in overall survival from the total population, the benefit in terms of the “emotional function” scale in the endpoint category quality of life and the significant disadvantages in terms of side effects, the G-BA concluded that for ribociclib in combination with fulvestrant for the treatment of post-menopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have not yet received initial endocrine therapy, there is a hint for a minor additional benefit compared with fulvestrant.

The reliability of data for the additional benefit is classified in the “hint” category because considering the results on overall survival of the total population for the assessment of the additional benefit in sub-population b1 involves relevant uncertainties.

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 Kisqali® (active ingredient: ribociclib) at the following publicly accessible link (last access: 2 June 2020):

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: 1 August 2020).

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.

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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/year	Treatment duration/ treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Ribociclib	On Day 1–21 of a 28-day cycle	13	21	273
plus fulvestrant				
Fulvestrant	continuous, Cycle 1: 1 × on Day 1, 15, and 29 From Cycle 2: 1 × monthly	14	1	14
Appropriate comparator therapy				
Patient population a1)				
Anastrozole	continuously, 1 × daily	365	1	365
Letrozole	continuously, 1 × daily	365	1	365
Exemestane	continuously, 1 × daily	365	1	365
Tamoxifen	continuously, 1 × daily	365	1	365
Patient population b1)				
Tamoxifen	continuously, 1 × daily	365	1	365
Anastrozole	continuously, 1 × daily	365	1	365
Fulvestrant	continuous, Cycle 1: 1 × on Day 1, 15, and 29 From Cycle 2: 1 × monthly	14	1	14
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

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					
Ribociclib	600 mg	600 mg	3 × 200 mg	273	819 × 200 mg
plus fulvestrant					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Fulvestrant	500 mg	500 mg	2 × 250 mg	14	28 × 250 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
Exemestane	25 mg	25 mg	1 × 25 mg	365	365 × 25 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	14	28 × 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
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

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					
Ribociclib	189 FCT	€ 7,086.87	€ 1.77	€ 411.92	€ 6,673.18
Fulvestrant	6 SFI	€ 2,024.98	€ 1.77	€ 98.88	€ 1,924.33

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
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	€ 4,449.98	€ 1.77	€ 220.66	€ 4,227.55
Abbreviations: FCT = film-coated tablets, SFI = solution for injection, TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 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 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 7 August 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 February 2020, 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 5 VerfO.

By letter dated 2 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 ribociclib.

[4] Fixed reimbursement rate

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 June 2020. The deadline for submitting written statements was 23 June 2020.

The oral hearing was held on 6 July 2020.

By letter dated 6 July 2020, 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 30 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 11 August 2020, and the proposed resolution was approved.

At its session on 20 August 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	7 August 2018	Determination of the appropriate comparator therapy
Working group Section 35a	1 July 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	6 July 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 July 2020 21 July 2020 4 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	11 August 2020	Concluding discussion of the draft resolution
Plenum	20 August 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 August 2020

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

Prof. Hecken