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 an Aromatase Inhibitor))

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 early benefit assessment of the active ingredient ribociclib (Kisqali®) on 4 September 2017. The resolution of 16 March 2018 passed by the G-BA in these proceedings was limited until 1 March 2019. At the request of the pharmaceutical company, this limitation was prolonged by a limitation to 1 March 2020 by a resolution of the G-BA of 21 February 2019.

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

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 29 February 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 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 an aromatase inhibitor. For the assessment of the additional benefit of ribociclib with fulvestrant, reference is made to the separate benefit assessment procedure for this combination therapy. The subject of this benefit assessment procedure is the patient group "post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial 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 therapy:

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

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.

[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.

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-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.

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. 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 the present indication.

National and international guidelines recommend aromatase inhibitors for initial endocrine therapy in advanced or metastatic stages in post-menopausal women. As an alternative in the case of aromatase 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[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 therapy. Fulvestrant is therefore also considered to be an appropriate therapy option for the present therapeutic indication.

For the CDK 4/6 inhibitor palbociclib in combination with an aromatase inhibitor as initial endocrine therapy, no additional benefit was found by the G-BA. The period of validity of the corresponding resolution of 18 May 2017 was limited. For palbociclib in combination with fulvestrant, no additional benefit was identified by resolution of 22 March 2019.

For ribociclib in combination with fulvestrant as an initial endocrine therapy and after previous endocrine therapy in both post-menopausal women and pre/peri-menopausal women, no additional benefit was determined by the resolution of 4 July 2019. The period of validity of the corresponding resolution of 4 July 2019 was limited as initial endocrine therapy (a1) and after previous endocrine therapy (b1) for post-menopausal women. 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-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.

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

[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.

2.1.3 Extent and probability of the additional benefit

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

Hint for a minor additional benefit

Justification:

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

The MONALEESA-2 pivotal study included 668 post-menopausal women with locally advanced or metastatic hormone receptor-positive and HER2-negative breast cancer; these were randomised to the two treatment arms. Randomisation into the two study arms was performed at a ratio of 1:1 with stratification according to liver and/or lung metastases (yes vs no). The patients had to have an ECOG-PS[4] < 2 at the start of study and were not allowed to receive systemic cancer therapy for the advanced or metastatic stage. Endocrine-based therapies in adjuvant settings were allowed.

The primary endpoint of the study was progression-free survival. Patient-relevant secondary endpoints were overall survival, symptomatology, health status, health-related quality of life, and adverse events. Only the overall survival is surveyed until the end of the study. Observation times for other endpoints are systematically shortened because they were recorded only up to progression (for adverse events, an additional 30 days after the end of treatment).

Treatment with the study medication was continued until disease progression, unacceptable toxicity, death, or discontinuation for other reasons. After discontinuation of the study medication, patients in both study arms were able to start follow-up treatment. A change of treatment to ribociclib in combination with an aromatase inhibitor was not permitted.

For the MONALEESA-2 study, analyses of three data cut-offs are available:

- Data cut-off (29 January 2016): planned interim analysis for progression-free survival, first interim analysis for overall survival
- Data cut-off (2 January 2017): planned second interim analysis for overall survival. There is also an addendum to this data cut-off with a data cut-off of 4 January 2017 in which results on morbidity, quality of life, and side effects were reported.
- Data cut-off (8 May 2019): planned third interim analysis for overall survival after 300 deaths.

The final analysis of the MONALEESA-2 study is planned after 400 deaths have occurred.

For all patient-relevant endpoints, evaluations are for the three planned data cut-offs are available. The data of the last data cut-off are used for the benefit assessment.

[4] Eastern Cooperative Oncology Group Performance Status

Extent and probability of the additional benefit

Mortality

Overall survival was defined as the period between the date of randomisation and the date of death regardless of the underlying cause. If no event occurred, censoring was performed at the last time the patient was demonstrably alive (time of last contact). Overall survival was a secondary endpoint of the MONALEESA-2 study.

For the overall survival endpoint, there is a statistically significant difference in favour of ribociclib in combination with letrozole compared with letrozole.

Morbidity

Progression-free survival (PFS)

Progression-free survival was defined as the period between the date of randomisation and the date of the first documented progression according to the Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) or the date of death regardless of cause. Clinical deterioration without objective radiological evidence was not considered documented disease progression. If no event occurred, censoring took place at the time of the last adequate tumour evaluation. In addition, a censoring was carried out at the beginning of a follow-up therapy. PFS was the primary endpoint in the MONALEESA-2 study.

For progression-free survival, there was a statistically significant difference between the treatment groups in favour of ribociclib.

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

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

However, in the MONALEESA-2 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, in particular myelosuppressive but also other 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.

Symptomatology

In the MONALEESA-2 study, the symptomatology was measured using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23. In each case, the time until permanent deterioration by ≥ 10 points is considered.

For the symptom scale dyspnoea of EORTC QLQ-C30, an effect modification by the characteristic age is shown. For patients ≥ 65 years, there is a statistically significant effect to the disadvantage of ribociclib plus letrozole compared with letrozole For patients < 65 years, there was no statistically significant difference between the treatment groups.

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

Health status

In the MONALEESA-2 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 letrozole.

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

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

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.

Health-related quality of life

The health-related quality of life was surveyed via the global health status and functional scales of the EORTC QLQ-C30 and the functional scales of the EORTC QLQ-BR23. In each case, the time until permanent deterioration by ≥ 10 points is considered.

For the endpoint “future perspective”, there was a statistically significant difference in favour of ribociclib + letrozole. There are no usable evaluations for the endpoint “sexual enjoyment”. For all further endpoints presented, there was no statistically significant difference between the treatment groups.

In the endpoint category health-related quality of life, a moderate benefit can be observed in only one domain.

Side effects

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

Serious adverse events (SAE)

With regards to serious adverse events, there is a statistically significant difference to the disadvantage of ribociclib + letrozole compared with placebo + letrozole.

Severe AE (CTCAE grade 3 or 4)

For the endpoint severe AE (CTCAE grade 3 or 4), there is a statistically significant difference in the disadvantage of ribociclib + letrozole compared with placebo + letrozole.

Discontinuation because of AE

A statistically significant effect to the detriment of ribociclib plus letrozole compared with letrozole was observed for this endpoint. 19.8% of patients in the intervention arm and 4.5% of patients in the control arm discontinued all or part of the study medication.

Specific AE

In detail, the specific adverse events show statistically significant disadvantages of the combination of ribociclib plus letrozole compared with letrozole with regard to the endpoints “blood and lymphatic system disorders” (CTCAE grade 3 or 4), “gastrointestinal disorders” (CTCAE grade 3 or 4), “infections and infestations” (CTCAE grade 3 or 4), and “examinations”, (CTCAE grade 3 or 4).
The neutropoenia (CTCAE grade 3 or 4) contained in the endpoint “Blood and lymphatic system disorders” is the determining event here.

Overall assessment/conclusion

For the assessment of the additional benefit of ribociclib in combination with letrozole, results from the MONALEESA-2 study in comparison to letrozole on mortality (overall survival), morbidity (symptomatology and health status), quality of life, and side effects are available.

For overall survival, the MONALEESA-2 study shows an advantage of ribociclib + letrozole compared with letrozole.

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

For the health-related quality of life, neither advantages nor disadvantages can be deduced overall for treatment with ribociclib in combination with letrozole compared with letrozole.

Overall, the results on side effects show statistically significant and meaningful disadvantages for ribociclib in combination with letrozole compared with letrozole 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 an aromatase inhibitor, 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, the G-BA concluded that ribociclib in combination with letrozole in the treatment of post-menopausal patients with HR+ and HER2- advanced or metastatic breast cancer who have not yet received initial endocrine therapy has a minor additional benefit compared with letrozole monotherapy because of the prolongation of lifespan.

Reliability of data (probability of additional benefit)

In the randomised, double-blind Phase III MONALEESA-2 study, ribociclib in combination with letrozole was compared with the appropriate comparator therapy letrozole.

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 results available on overall survival are based on the third interim analysis after 300 deaths (data cut-off of 8 May 2019) of the MONALEESA-2 study.
Although these results on overall survival can be considered more meaningful than first benefit assessment because of more events and longer observation time (75% of the events of the planned final analysis have been reached), the data available for this benefit assessment are not yet the final analyses of the MONALEESA-2 study, which is planned after 400 deaths have occurred. In this respect, the broad 95% confidence interval for the hazard ratio of overall survival from the third interim analysis is also striking because it results in further uncertainty in the interpretation of the effect estimator.

Therefore, given the importance of the results on overall survival for the above weighing decision in the overall assessment of the additional benefit, the reliability of data for the established additional benefit 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 16 March 2018. The assessment refers exclusively to the use of ribociclib in combination with an aromatase inhibitor for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in the following patient population: a1) post-menopausal women who have not yet received initial endocrine therapy.

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-2 study comparing ribociclib plus letrozole with placebo plus letrozole. The MONALEESA-2 study included post-menopausal women with HR positive, HER2 negative metastatic breast cancer with initial endocrine therapy. Here the results of the MONALEESA-2 study from the data cut-off of 8 May 2019 are relevant.

For overall survival, the study showed an advantage of ribociclib plus letrozole compared with placebo and letrozole.

In the overall view, there were no advantages or disadvantages in the morbidity category.

For the health-related quality of life, neither advantages nor disadvantages can be deduced overall for treatment with ribociclib in combination with letrozole compared with letrozole.

In the side effects category, disadvantages of ribociclib plus letrozole were seen with respect to serious adverse events, severe adverse events, therapy discontinuation because of AE and, in detail, disadvantages in relation to specific adverse events.

In the overall view, there is a hint for a minor additional benefit for ribociclib plus letrozole compared with letrozole in the treatment of post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy.

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 aromatase inhibitor:				
Anastrozole	continuously, 1 × daily	365	1	365
Letrozole	continuously, 1 × daily	365	1	365
Exemestane	continuously, 1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ Year
Appropriate comparator therapy				
Patient population a1				
Anastrozole	continuously, 1 × daily	365	1	365
Letrozole	continuously, 1 × daily	365	1	365
Fulvestrant	Cycle 1: 1 × on Day 1, 15, and 29 From Cycle 2: 1 × monthly	14	1	14
Tamoxifen	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 aromatase inhibitor:					
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
Appropriate comparator therapy					
Patient population a1)					
Anastrozole	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Fulvestrant	500 mg	500 mg	2 × 250 mg	14	28 × 250 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Tamoxifen	20 mg	20 mg	1 × 20 mg	365	365 × 20 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
plus aromatase inhibitor:					
Anastrozole[5]	100 FCT	€ 55.83	€ 1.77	€ 3.66	€ 50.40
Letrozole[5]	120 FCT	€ 59.86	€ 1.77	€ 3.98	€ 54.11
Exemestane[5]	100 FCT	€ 124.05	€ 1.77	€ 9.19	€ 113.09
Appropriate comparator therapy					
Anastrozole[5]	100 FCT	€ 55.83	€ 1.77	€ 3.66	€ 50.40
Letrozole[5]	120 FCT	€ 59.86	€ 1.77	€ 3.98	€ 54.11
Fulvestrant	6 SFI	€ 2,024.98	€ 1.77	€ 98.88	€ 1,924.33
Tamoxifen[5]	100 FCT	€ 21.63	€ 1.77	€ 0.88	€ 18.98
Abbreviations: FCT = film-coated tablets; SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 August 2020

[5] Fixed reimbursement rate

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.

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 on 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 on 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 on 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