Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Palbociclib (reassessment after the deadline: breast cancer, HR+, HER2-, combination with aromatase inhibitor)

of 15 December 2022

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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient palbociclib (Ibrance) on 1 December 2016. For the resolution of 18 May 2017 made by the G-BA in this procedure, a limitation until 1 March 2019 was pronounced for the patient population a1) (postmenopausal patients in first-line therapy). At the pharmaceutical company's request, this limitation was extended until 1 January 2021 by the resolution of the G-BA of 20 September 2018. By resolution of the G-BA of 15 October 2020, the limitation was extended again until 1 July 2022.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Ibrance recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 June 2022.

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 4 October 2022, 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 palbociclib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of palbociclib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to 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 Palbociclib (Ibrance) in accordance with the product information

IBRANCE is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor
- in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1 of the product information)

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Therapeutic indication of the resolution (resolution of 15 December 2022):

Ibrance in combination with an aromatase inhibitor is indicated for the first-line treatment of postmenopausal patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) <u>First-line treatment of postmenopausal patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer</u>

Appropriate comparator therapy for palbociclib in combination with an aromatase inhibitor:

– Anastrozole

or

– Letrozole

or

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

– Fulvestrant

or

– Tamoxifen, if necessary, if aromatase inhibitors are unsuitable

or

– Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

or

– Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

or

– Ribociclib in combination with fulvestrant

or

– Abemaciclib in combination with fulvestrant

or

– Palbociclib in combination with fulvestrant

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 in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the (G-BA 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 principle, medicinal products with the following active ingredients are approved in the therapeutic indication:

the antiestrogens tamoxifen, toremifene, fulvestrant; the non-steroidal aromatase inhibitors anastrozole and letrozole; the steroidal aromatase inhibitor exemestane; the progestogens megestrol acetate and medroxyprogesterone acetate; the protein kinase inhibitors everolimus, palbociclib, ribociclib and abemaciclib; and the PIK3 inhibitor alpelisib.

On 2. Both surgical resection and/or radiotherapy as well as ovariectomy for the cessation of ovarian function are generally considered as non-medicinal therapies for the treatment of breast carcinoma.

In the present therapeutic indication, it is assumed that radiotherapy and/or (secondary) resection with a curative objective is not indicated. The (secondary) resection and/or radiotherapy were therefore not included in the appropriate comparator therapy.

On 3. Resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are:

- Abemaciclib (in combination with fulvestrant): Resolutions of 2 May 2019, 3 September 2020 and 19 May 2022
- Abemaciclib (in combination with aromatase inhibitors): Resolution of 2 May 2019
- Palbociclib: Resolutions of 18 May 2017 and 22 March 2019
- Ribociclib (in combination with fulvestrant): Resolutions of 4 July 2019 and 20 August 2020
- Ribociclib (in combination with aromatase inhibitors): Resolutions of 04 July 2019 and 20 August 2020
- Alpelisib (in combination with fulvestrant): Resolution of 18 February 2021

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately.

For the present therapeutic indication, it is assumed that (possibly further) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative objectives.

In national and international guidelines, aromatase inhibitors are recommended for initial endocrine therapy in the advanced or metastatic stage in postmenopausal women. Specifically, among the aromatase inhibitors, the two non-steroidal aromatase inhibitors anastrozole and letrozole are approved in the therapeutic indication and are therefore included in the appropriate comparator therapy. As an alternative in cases of aromatase inhibitor intolerance, tamoxifen, which is also approved, is an appropriate therapy.

In addition, the antiestrogen fulvestrant is another recommended treatment option for initial endocrine therapy.

On the CDK4/6 inhibitors (ribociclib, abemaciclib, palbociclib) in the appropriate comparator therapy

The CDK4/6 inhibitors (ribociclib, abemaciclib, palbociclib) in combination with a non-steroidal aromatase inhibitor or fulvestrant are also approved treatment options for postmenopausal women for initial endocrine therapy.

The results of the benefit assessment procedures to date for the CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) for postmenopausal women with initial endocrine therapy in the therapeutic indication can be summarised as follows:

For postmenopausal women with initial endocrine therapy, a hint for a minor additional benefit was shown for ribociclib in combination with letrozole compared with letrozole and an indication of a minor additional benefit was shown for ribociclib in combination with fulvestrant compared with fulvestrant.

In the benefit assessments of palbociclib in combination with a non-steroidal aromatase inhibitor or fulvestrant as well as in the benefit assessments of abemaciclib in combination with an aromatase inhibitor or fulvestrant, no additional benefit has been demonstrated so far in postmenopausal women with initial endocrine therapy.

According to the updated recommendations of the German S3 guideline of the AWMF (Association of the Scientific-Medical Societies)[2], endocrine-based therapy in postmenopausal patients with a CDK4/6 inhibitor should be carried out either in combination with an aromatase inhibitor or with fulvestrant, both in the initial endocrine therapy and after endocrine therapy has already taken place, if CDK4/6 inhibitors have not been used before.

In the S3 guideline, all three currently approved CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) are equally recommended or no specific preference is stated. In contrast, the results of the respective benefit assessments differed with regard to the additional benefit.

In the overall review of the evidence, the three CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) in the respective approved combinations are also considered equally suitable appropriate comparator therapies. Palbociclib in combination with an aromatase inhibitor is the medicinal product under assessment.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

[2] Interdisciplinary S3 guideline for early detection, diagnosis, therapy and follow-up of breast cancer of the AWMF (Association of the Scientific-Medical Societies); Version 4.4

2.1.3 Extent and probability of the additional benefit

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

a1) Postmenopausal patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer in first-line therapy

An additional benefit is not proven.

Justification:

The randomised controlled studies PALOMA-1, PALOMA-2 and PALOMA-4 are relevant for the benefit assessment of palbociclib in combination with an aromatase inhibitor. The PALOMA-1 and PALOMA-2 studies are already known from the previous benefit assessment of palbociclib in combination with an aromatase inhibitor in the present therapeutic indication. No results were available for the PALOMA-4 study at the time of the previous benefit assessment. In contrast, results from the PALOMA-1 and PALOMA-2 studies were available for the first planned data cut-off and both studies were still ongoing. The pharmaceutical company submits data on more recent data cut-offs with the more recent dossier for both studies.

PALOMA-1 study

The PALOMA-1 study consists of a single-arm, non-randomised, phase I sub-study and a randomised, phase II sub-study that included a patient population comparable to PALOMA-2 without prior endocrine therapy. The phase II sub-study (N = 165) was multicentre, randomised, open-label and compared the combination of active ingredients palbociclib and letrozole (N = 84) with letrozole monotherapy (N = 81).

In contrast to the previous benefit assessment in the present therapeutic indication, which was based on the 1st data cut-off from 29.11.2013, a more recent data cut-off from 30.12.2016 is available, which apparently represents the final data cut-off on overall survival towards the end of the study. The pharmaceutical company does not use the PALOMA-1 study for the benefit assessment and not for the derivation of the additional benefit, but presents the results on the new data cut-off in the Annex to Module 4 G of the dossier. The pharmaceutical company justifies this procedure by stating that it concluded from the justification of the initial assessment that the PALOMA-1 study is unsuitable for the benefit assessment and for deriving the additional benefit because in the initial assessment the PALOMA-1 study was only used in a supportive manner due to methodological defects and a high risk of bias.

In principle, all scientific evidence for the assessment of the additional benefit that is available at the time of the new benefit assessment must be submitted in the dossier for the new benefit assessment after the deadline. Thus, the PALOMA-1 study is fundamentally relevant for the benefit assessment.

However, as already described in the justification for the initial assessment, there is a high risk of bias in the results of the PALOMA-1 study. In addition, with the PALOMA-2 and PALOMA-4 studies, two studies are available, each with a larger sample size than in the PALOMA-1 study. Against this background, it is not assumed in the present data situation that the assessment result based on the PALOMA-2 and PALOMA-4 studies is called into question by the results of the PALOMA-1 study.

PALOMA-2 study

For the proof of an additional benefit of palbociclib in combination with letrozole compared to letrozole, the pharmaceutical company has presented results of the randomised, double-blind, controlled phase II PALOMA-2 study. This multinational study included postmenopausal patients with locoregionally relapsed or metastatic HR-positive, HER2-negative breast cancer. The patients were not allowed to have received any prior systemic therapy for the advanced stage of the disease. Endocrine therapies in the (neo-)adjuvant therapy setting were allowed, whereby in the case of a prior (neo-)adjuvant treatment with aromatase inhibitors (e.g. anastrozole or letrozole) no relapse was allowed to have occurred during or within 12 months of this treatment.

A total of 666 patients were enrolled in the study and allocated in a 2:1 ratio to treatment with palbociclib + letrozole (N = 444) or placebo + letrozole (N = 222). Patients had to have an ECOG-PS ≤ 2 at the time of enrolment in the study.

The primary endpoint of the PALOMA-2 study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, health status, health-related quality of life, and adverse events.

The PALOMA-2 study, which is currently still ongoing, began in February 2013. The multicentre study is being conducted in 186 study sites in Asia, Australia, Europe and North America. So far, 3 data cut-offs are available. The first data cut-off from 26 February 2016 was intended for the final analysis of the PFS according to the study design and was used in the previous benefit assessment. The second data cut-off from 31 May 2017 was not planned according to the study design. The third data cut-off from 15 November 2021 was pre-specified for the final overall survival analysis according to study documents. In the current dossier, the pharmaceutical company presents evaluations of the second and third data cut-offs for the PALOMA-2 study, depending on the endpoint. The results of the third and most recent data cut-off from 15.11.2021 are relevant for the present benefit assessment.

PALOMA-4 study

The PALOMA-4 study is a double-blind, randomised and controlled phase III study comparing palbociclib in combination with letrozole to letrozole. The study was conducted exclusively with Asian female patients aged 18 to 70 years. Patients had to have an ECOG-PS ≤ 1 at study entry. The study included only postmenopausal women with HR-positive, HER2-negative locoregionally relapsed or metastatic breast cancer who had not previously received endocrine therapy based on advanced disease stage. In the case of previous (neo-)adjuvant treatment with aromatase inhibitors (e.g. anastrozole or letrozole), no relapse was allowed to have occurred during or within 12 months of this treatment.

A total of 340 patients were allocated in a 1:1 ratio to treatment with palbociclib + letrozole (N = 169) or placebo + letrozole (N = 171).

The primary endpoint of the PALOMA-4 study is progression-free survival (PFS). Patient-relevant secondary endpoints are overall survival, health status, health-related quality of life, and adverse events.

The study, which is currently still ongoing, began in March 2015. For the present assessment, the results of the first data cut-off from 31.08.2020 are relevant, which was intended for the final analysis of the PFS according to the study design. Another data cut-off is pre-specified for the final analysis of overall survival.

Meta-analysis:

In the dossier, the pharmaceutical company presents a fixed-effect meta-analysis based on individual patient data (IPD) of the PALOMA-2 and PALOMA-4 studies and uses their results to derive the additional benefit. The studies are largely comparable with regard to the study design, the inclusion and exclusion criteria as well as the characteristics of the patients enrolled.

There are differences between the studies, particularly with regard to ethnicity, age and previous chemotherapy in the (neo-)adjuvant treatment setting. However, the differences do not fundamentally call into question the feasibility of a meta-analysis, as the studies are considered sufficiently comparable for the research question investigated.

Results on health-related quality of life and morbidity:

IQWiG noted in the dossier assessment that the pharmaceutical company had not completely processed the results for all endpoints relevant to the benefit assessment in the dossier for the current third data cut-off of the PALOMA-2 study from 15.11.2021. Specifically, the pharmaceutical company only submits evaluations from the PALOMA-2 study on health-related quality of life and morbidity for the second data cut-off from 31 May 2017, but not for the current third data cut-off from 15.11.2021. The second data cut-off from 31 May 2017 was an unplanned data cut-off, while the current third data cut-off was pre-specified (final analysis for overall survival). The pharmaceutical company justified this procedure in the dossier by stating that at the time of the second data cut-off, the treatment had already been completed for the majority of patients in the intervention and comparator arms and that it could be assumed that the symptomatology and quality of life would essentially change during the therapy and less in the course of the follow-up. Thus, no new findings relevant to the assessment would be available from the later data cut-off.

IQWiG states in the dossier assessment that an assumption that symptomatology and quality of life would change less in the course of the follow-up is not appropriate per se. In addition, in the PALOMA-2 study, the quality of life was partly assessed beyond the end of treatment. Furthermore, the pharmaceutical company's approach does not comply with the time limit requirements of the G-BA, according to which the final study results of the PALOMA-2 study on all endpoints relevant to the benefit assessment should be submitted in the dossier for the renewed benefit assessment after expiry of the time limit.

IQWiG states that the evaluations of health-related quality of life and morbidity from the PALOMA-2 study submitted by the pharmaceutical company in the dossier are therefore not usable for the benefit assessment and that the results submitted for the PALOMA-2 study are incomplete in terms of content. Although results for the endpoints health-related quality of life and morbidity from the PALOMA-4 study are available in the dossier for the current data cut-off of this study, these alone are not significant. Thus, according to IQWiG, no usable data are available on health-related quality of life and morbidity.

Furthermore, IQWiG states in the dossier assessment that the assessment result is not called into question by the missing evaluations of endpoints in the categories of morbidity and health-related quality of life for the most recent data cut-off. In the overall assessment, IQWiG states that there are only negative effects for palbociclib + letrozole compared with letrozole. In the overall statement on the additional benefit, IQWiG concludes that there is proof of a lower benefit of palbociclib + letrozole compared with letrozole.

In its written statement, the pharmaceutical company does not comment on this point of criticism made by IQWiG in the dossier assessment. In the oral hearing, when asked why the data on morbidity and health-related quality of life were not submitted for the current final

data cut-off in accordance with the time limit requirement, the pharmaceutical company repeated its argumentation that no additional knowledge could be gained from the current third data cut-off compared to the second data cut-off, but did not address IQWiG's points of criticism.

The G-BA fully agrees with IQWiG's criticism and, for its part, also states after completion of the written statement procedure that the evaluations submitted by the pharmaceutical company on health-related quality of life and morbidity from the PALOMA-2 study cannot be used for the benefit assessment and that the results submitted for the PALOMA-2 study are incomplete in terms of content.

Conclusion

Due to the fact that only incomplete evaluations of the quality of life and morbidity were submitted by the pharmaceutical company for the PALOMA-2 study, no assessable data on effects on quality of life and morbidity are available for the assessment. Significant data on quality of life and morbidity are generally given high priority in the benefit assessment, especially in advanced stages of the cancer. In the present assessment situation, it is in particular not possible to assess the extent to which the increase in significant side effects (CTCAE ≥ grade 3), a large percentage of which is determined by laboratory findings, corresponds to changes in quality of life compared to the control group.

For these reasons, the data basis presented for the benefit assessment in the present case is considered to be so severely incomplete that no sufficiently reliable and appropriate assessment can be made overall.

The G-BA states that, in accordance with Chapter 5, Section 18, paragraph 1 of the Rules of Procedure of the G-BA, the preparation of the documents in the dossier deviates from the requirements specified in Chapter 5, Section 9 of the Rules of Procedure of the G-BA to an extent that prevents a proper assessment of the additional benefit.

In accordance with the regulation in Chapter 5, Section 18 of the Rules of Procedure of the G-BA, the benefit assessment examines whether there is evidence of an additional benefit for the medicinal product compared to the appropriate comparator therapy. The validity and completeness of the information in the dossier are also checked. The dossier template in Annex II must be used for compiling the documents. The data according to Chapter 5, Section 9, paragraphs 1, 4 to 8 of the Rules of Procedure of the G-BA must be prepared and submitted in accordance with the requirements specified in Modules 1 to 5.

The preparation of the pharmaceutical company's data presented here does not comply with the requirements laid down in Chapter 5, Section 9 Rules of Procedure and proves to be inadequate and incomplete, so that it remains an obstacle to a proper assessment of the additional benefit. Subsequently, the G-BA determines in accordance with Chapter 5, Section 18, paragraph 1, sentence 4 of the Rules of Procedure of the G-BA that an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient palbociclib due to the expiry of the limitation of the resolution of 18 May 2017. The assessment relates only to the use of palbociclib 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:

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

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

– Anastrozole

or

– Letrozole

or

– Fulvestrant

or

– Tamoxifen, if necessary, if aromatase inhibitors are unsuitable

or

– Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

or

– Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

or

– Ribociclib in combination with fulvestrant

or

– Abemaciclib in combination with fulvestrant

or

– Palbociclib in combination with fulvestrant

For the assessment of the additional benefit of palbociclib in combination with an aromatase inhibitor in the mentioned patient population, the pharmaceutical company presents results from the randomised, controlled, double-blind PALOMA-2 and PALOMA-4 studies or a meta-analysis based on individual patient data from these two studies. In both studies, palbociclib in combination with the aromatase inhibitor letrozole is compared with letrozole alone.

In accordance with the time limit of the previous benefit assessment, the final study results of the PALOMA-2 study on all endpoints relevant to the benefit assessment should be submitted in the dossier for the new benefit assessment after expiry of the time limit.

The pharmaceutical company did not provide the data on quality of life and morbidity. Specifically, from the PALOMA-2 study on quality of life and morbidity, the pharmaceutical company only submits evaluations of the unplanned second data cut-off from 31 May 2017, but not of the more recent third data cut-off from 15.11.2021, which was also pre-specified (final analysis on overall survival). The data on quality of life and morbidity from the PALOMA-4 study are not significant when considered alone.

Thus, the submitted evaluations on quality of life and morbidity from the PALOMA-2 study are not usable for the benefit assessment and the submitted study results for the PALOMA-2 study are incomplete in terms of content.

Significant data on quality of life and morbidity are generally given high priority in the benefit assessment, especially in advanced stages of the cancer. As a result of the lack of assessable data on effects on quality of life, it is in particular not possible to assess the extent to which the increase in significant severe side effects (CTCAE ≥ grade 3) caused by palbociclib, a high percentage of which is determined by laboratory findings, corresponds to changes in quality of life compared to the control group.

For these reasons, the G-BA states that the preparation of the pharmaceutical company's data presented here does not meet the requirements and proves to be so incomplete that it prevents a sufficiently reliable and appropriate assessment of the additional benefit. The G-BA concludes that an additional benefit is not proven.

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

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

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of abemaciclib (resolution of 19 May 2022).

The above range takes into account the existing uncertainties in the data basis and reflects the minimum and maximum values obtained in the 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 Ibrance (active ingredient: palbociclib) at the following publicly accessible link (last access: 22 September 2022):

https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_en.pdf

Treatment with palbociclib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, obstetrics and gynaecology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with locally advanced or metastatic breast cancer.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2022).

The annual treatment costs shown refer to the first year of treatment.

Treatment period:

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", time intervals between individual treatments and for 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				
Palbociclib	Continuously, 1 x on day 1 – 21 of a 28-day cycle	13.0	21	273
In combination with an aromatase inhibitor				
Anastrozole	Continuously, 1 x daily	365	1	365
Letrozole	Continuously, 1 x daily	365	1	365
Exemestane	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Non-steroidal aromatase inhibitors				
Anastrozole	Continuously, 1 x daily	365	1	365
or				
Letrozole	Continuously, 1 x daily	365	1	365
or				
Fulvestrant				
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12[3]	1 - 2	13
or				
Tamoxifen				
Tamoxifen	Continuously, 1 x daily	365	1	365
or				
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Ribociclib	Continuously, 1 x on day 1 – 21 of a 28-day cycle	13.0	21	273
Anastrozole	Continuously, 1 x daily	365	1	365
Letrozole	Continuously, 1 x daily	365	1	365
or				
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Abemaciclib	Continuously, 2 x daily	365	1	365
Anastrozole	Continuously, 1 x daily	365	1	365
Letrozole	Continuously, 1 x daily	365	1	365
or				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Ribociclib in combination with fulvestrant				
Ribociclib	Continuously, 1 x on day 1 – 21 of a 28-day cycle	13.0	21	273
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 from cycle 2 onwards: 1 x monthly	12[3]	1 - 3	14
or				
Abemaciclib in combination with fulvestrant				
Abemaciclib	Continuously, 2 x daily	365	1	365
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15; from cycle 2 onwards: 1 x monthly	12[3]	1 - 2	13
or				
Palbociclib in combination with fulvestrant				
Palbociclib	Continuously, 1 x on day 1 – 21 of a 28-day cycle	13.0	21	273
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 from cycle 2 onwards: 1 x monthly	12[3]	1 - 3	14

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

[3] Consistent with the presentation of the treatment mode for fulvestant in combination with ribociclib, as well as palbociclib, where fulvestrant is used, amongst others, on day 29 of the 1st cycle, fulvestrant is based on months (and not days), in contrast to the other active ingredients in this procedure.

The recommended dose for palbociclib is 125 mg. Palbociclib is used once daily as a tablet for 21 consecutive days, followed by 7 days without treatment. Each period of 28 days corresponds to one treatment cycle.

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					
Palbociclib	125 mg	125 mg	1 x 125 mg	273	273 x 125 mg
In combination with an aromatase inhibitor					
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
Exemestane	25 mg	25 mg	1 x 25 mg	365	365 x 25 mg
Appropriate comparator therapy					
Non-steroidal aromatase inhibitors					
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
or					
Fulvestrant					
Fulvestrant	500 mg	500 mg	2 x 250 mg	13	26 x 250 mg
or					
Tamoxifen					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
or					
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Ribociclib	600 mg	600 mg	3 x 200 mg	273	819 x 200 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
or					
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365	365 x 2.5 mg
or					
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 x 200 mg	273	819 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14	28 x 250 mg
or					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Abemaciclib in combination with fulvestrant					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365	730 x 150 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13	26 x 250 mg
or					
Palbociclib in combination with fulvestrant					
Palbociclib	125 mg	125 mg	1 x 125 mg	273	273 x 125 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14	28 x 250 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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging 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					
Palbociclib 125 mg	21 FCT	€ 2,461.87	€ 1.77	€ 137.31	€ 2,322.79
Anastrozole 1 mg[4]	100 FCT	€ 57.51	€ 1.77	€ 3.66	€ 52.08
Letrozole 2.5 mg[4]	120 FCT	€ 61.64	€ 1.77	€ 3.98	€ 55.89
Exemestane 25 mg[4]	100 FCT	€ 127.50	€ 1.77	€ 9.19	€ 116.54
Appropriate comparator therapy					
Abemaciclib 150 mg	168 FCT	€ 5,767.72	€ 1.77	€ 326.11	€ 5,439.84
Anastrozole 1 mg[4]	100 FCT	€ 57.51	€ 1.77	€ 3.66	€ 52.08
Exemestane 25 mg[4]	100 FCT	€ 127.50	€ 1.77	€ 9.19	€ 116.54
Fulvestrant 250 mg	2 SFI	€ 370.10	€ 1.77	€ 28.38	€ 339.95
Letrozole 2.5 mg[4]	120 FCT	€ 61.64	€ 1.77	€ 3.98	€ 55.89
Palbociclib 125 mg	21 FCT	€ 2,461.87	€ 1.77	€ 137.31	€ 2,322.79
Ribociclib 200 mg	189 FCT	€ 6,846.11	€ 1.77	€ 0.00	€ 6,844.34
Tamoxifen 20 mg[4]	100 TAB	€ 22.43	€ 1.77	€ 0.88	€ 19.78

[4] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; TAB = tablets					

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Costs for additionally required SHI services:

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

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

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

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Palbociclib

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 June 2022, the pharmaceutical company submitted a dossier for the benefit assessment of palbociclib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

By letter dated 1 July 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 palbociclib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 4 October 2022. The deadline for submitting written statements was 25 October 2022.

The oral hearing was held on 7 November 2022.

By letter dated 8 November 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 24 November 2022.

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 was discussed at the session of the subcommittee on 6 December 2022, and the proposed resolution was approved.

At its session on 15 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 October 2021	Determination of the appropriate comparator therapy
Working group Section 35a	1 November 2022	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	7 November 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 November 2022 29 November 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 December 2022	Concluding discussion of the draft resolution
Plenum	15 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 December 2022

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

Prof. Hecken