Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V – Palbociclib

of 18 May 2017

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 proof 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 relevant date for the first placing on the market of the active ingredient palbociclib in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 December 2016. 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, number 1 VerfO on 22 November 2016.

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 1 March 2017, 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 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 palbociclib.

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 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

In pre- or peri-menopausal women, the endocrine therapy should be combined with an LHRH agonist (LHRH = luteinizing hormone-releasing hormone).

2.1.2 Appropriate comparator therapy

a1) The appropriate comparator therapy for post-menopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer as initial endocrine therapy is:

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

a2) The appropriate comparator therapy for pre- and peri-menopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer as initial endocrine therapy is:

Tamoxifen in combination with an elimination of ovarian function.

b) The appropriate comparator therapy for women with HR-positive and HER2-negative advanced or metastatic breast cancer who have received prior endocrine therapy is:

b1) For post-menopausal women who have experienced progression after endocrine therapy, a further endocrine therapy depending on the previous therapy with:

- Tamoxifen

or

- Anastrozole

or

- Fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment

or

- Letrozole; only for patients with relapse or progress after anti-oestrogen treatment

[1] General Methods, Version 4.2 dated 22 April 2015. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

or

- Exemestane; only for patients with progress after anti-oestrogen treatment

or

Everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

b2) For pre- and peri-menopausal women who have experienced progression after endocrine therapy:

Endocrine therapy according to the doctor's instructions, taking into account the respective marketing authorisation.

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 palbociclib, medicinal products with the following active ingredients are approved for the present therapeutic indication: anastrozole, everolimus, exemestane, fulvestrant, goserelin, letrozole, leuprorelin, medroxyprogesterone acetate, megestrol acetate, tamoxifen, and toremifene.

Medicinal products with explicit marketing authorisation for hormone receptor-negative and HER2/newly-positive mammary carcinomas were not considered.

For the present therapeutic indication, it is assumed that an endocrine therapy is indicated for the patients and that there is no indication for chemotherapy.

On 2. As non-medicinal treatments, surgical resection and/or radiotherapy are generally considered for the treatment of mammary carcinoma. In the context of endocrine therapy, an 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 medicinal therapies in the present therapeutic indication:

Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V:

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 for initial endocrine therapy in advanced or metastatic stages in post-menopausal women. As an alternative in the case of aromatase inhibitor intolerance, tamoxifen, which is also approved, is an appropriate therapy.

For the initial endocrine-based therapy of pre- and peri-menopausal patients included in this therapeutic indication (sub-population a2), tamoxifen in combination with an elimination of the ovarian function is recommended. Here, ovarian suppression by LHRH analogues or oophorectomy may be considered.

In the therapy situation of disease progression in post-menopausal patients after endocrine pre-treatment, the guidelines unanimously recommend further endocrine therapy using an alternative active ingredient unless there is an indication for chemotherapy. With regard to the significance of gestagens, the corresponding statements in the guidelines are less clear than for the other therapy options mentioned. In addition, their use is described as a rather subordinate option in the treatment cascade, which is why the G-BA does not regard the gestagens as a regular treatment option for the present therapy situation and therefore does not include them in the appropriate comparator therapy. The restrictions to certain patient populations in the case of fulvestrant, letrozole, exemestane, and everolimus in combination with exemestane reflect the respective authorisation status.

For the sub-population pre- and peri-menopausal patients with progression after endocrine therapy (sub-population b2), there is a limited number of approved treatment options. In accordance with the marketing authorisation, tamoxifen, medroxyprogesterone acetate, megestrol acetate, and GnRH analogues as well as the aromatase inhibitors exemestane and letrozole (in connection with an induced post-menopause) are possible candidates. In this situation, however, tamoxifen will have been predominantly used as an initial therapy. As an alternative, an aromatase inhibitor may be considered (subject to marketing authorisation). The evidence available for the relevant progestins is not considered sufficient for a concrete recommendation.

It is assumed that ovarian suppression is continued with a GnRH analogue.

According to the guidelines, further endocrine therapy is unanimously recommended after initial endocrine-based therapy unless there is an indication for chemotherapy.

The endocrine therapy should be carried out according to the doctor’s instructions in the respective treatment situation. The therapy should take information from the marketing authorisation into account, as well as the dosage instructions in the product information for the active ingredients, and any deviations should be justified separately.

For the 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. Further-

more, it is assumed that in pre- and peri-menopausal patients, ovarian function is suppressed by oophorectomy or a GnRH analogue.

Division according to menopause status (pre- or peri-menopausal and post-menopausal patients):

In the written statements in the present benefit assessment procedure, including the opinions of medical experts, the view is expressed that in pre-menopausal patients in whom ovarian function has been eliminated by means of ovariectomy or medicinal therapy with GnRH analogues the condition of a functional post-menopause is brought about, thereby calling into question the sub-division according to menopausal status.

In principle, the G-BA can understand this argumentation but still considers the subdivision to be justified for the following reasons: on one hand, pre-menopausal patients differ physiologically from post-menopausal patients; on the other hand, there is a significant pathophysiological difference with regard to the hormone-dependent tumour biology present here.
In the guidelines for endocrine therapy in advanced metastatic breast cancer, a clear and unanimous distinction is made between pre-menopausal and post-menopausal patients, each with distinct therapy recommendations.
In addition, for most of the medicinal products used in endocrine therapy in the respective approved therapeutic indications, the menopausal status of the patients is specifically taken into account, and restrictions are made in this regard.

The 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 palbociclib in combination with an aromatase inhibitor is assessed as follows:

a1) Post-menopausal patients in first-line treatment:

For post-menopausal patients in first-line treatment, an additional benefit compared with letrozole is not proven.

Justification:

The pharmaceutical company has presented the results of the PALOMA-2 (A5481008) study and the PALOMA-1 (A5481003) supportive study to demonstrate an additional benefit of palbociclib in combination with an aromatase inhibitor as initial therapy in post-menopausal patients.

The PALOMA-2 (N = 666) study is a randomised, double-blind phase III study comparing the active ingredient combinations palbociclib + letrozole (N=444) with placebo + letrozole (N = 222). This multi-centre, multinational study included post-menopausal patients with HR-positive, HER2-negative locally recurrent or metastatic breast cancer without prior systemic therapy for the advanced stage. The start of study was in February 2013; the expected end of study is November 2018. For the benefit assessment, the data cut-off of 26 February 2016 was presented.

The PALOMA-1 study consists of a single-arm, non-randomised Phase I sub-study and a randomised Phase II sub-study in which a patient population comparable to PALOMA-2 without previous endocrine therapy was included. The Phase II (N = 165) sub-study presented by the pharmaceutical company was a multi-centre, randomised, and open-label study and compared the active ingredient combination palbociclib + letrozole (N = 84) with letrozole monotherapy (N = 81). The duration of the PALOMA-1 study is from September 2008 to July 2018. For the benefit assessment, the data cut-off of 29 November 2013 was presented.

In both studies, a change of treatment from the reference arm to the intervention arm after discontinuation of the study medication was not allowed.

The PALOMA-2 study leads the way in interpreting the results and deriving the additional benefit of palbociclib in combination with letrozole. In addition to a smaller sample size, the PALOMA-1 study has a limited significance. Because of its open study design and methodological limitations, PALOMA-1 must be regarded as potentially highly biased both at the study and endpoint level. Against the background that the assessment of progression by the investigators, which differed significantly from the blinded, independent evaluation, was decisive for the decision to remain on the study medication, an increased risk of bias can be derived for all endpoints. Because of the open study design and the high proportion of potentially informative censorship, the results of the adverse events category must be considered as potentially highly biased.

Against this background, the results of the PALOMA-1 study are used only supportively.

Extent and probability of the additional benefit

Mortality

Overall survival

For overall survival, the PALOMA-2 study showed no statistically significant difference between the study arms. The pharmaceutical company did not provide any overall survival data in the dossier because, according to the pharmaceutical company, the sponsor of the study was blinded to corresponding interim analyses on overall survival. However, according to the review of the IQWiG, the study report did provide valid information on how many patients had died in the respective treatment arm up to the data cut-off.
IQWiG used this information to determine the relative risk (RR) with respect to overall survival. With approximately the same observation time in both treatment arms, the relative risk was used as an approximation for the present assessment (relative risk (RR)): 1.25 [95% confidence interval (CI): 0.89; 1.76]; p value 0.198).
Median survival had not yet been achieved because of the low number of events; final analyses on the endpoint overall survival are pending.
In the PALOMA-1 supplementary study, there was no significant difference between the treatment arms (PALOMA-1: 37.5 vs 33.3 months; HR: 0.81 [95% CI: 0.49; 1.35]; p = 0.421).

Median survival had not yet been achieved in the PALOMA-2 study because of the low number of events; final analyses on the endpoint overall survival are pending.

For the endpoint category mortality, there is no additional benefit from adding palbociclib to therapy with letrozole based on the results available.

Morbidity

Progression-free survival (PFS)

In the PALOMA-2 study, progression-free survival was the primary endpoint and was defined as the time between randomisation and disease progression (determined by the investigator using RECIST criteria) or death by any cause.

PFS in the palbociclib treatment group was statistically significantly longer by a median of 10.3 months compared with the control group (24.8 vs 14.5 months median; HR: 0.58 [95% CI: 0.46; 0.72]; p < 0.0001). In the supplementary PALOMA-1 study, the PFS was also significantly prolonged: 20.2 vs 10.2 months (median); HR: 0.49 [95% CI: 0.32; 0.75]; p = 0.001.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the PALOMA-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. Data on morbidity and health-related quality of life are potentially relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life. The data from the PALOMA-2 study do not show a statistically significant result for the endpoints

morbidity and health-related quality of life. Accordingly, extended PFS under palbociclib was not associated with an advantage with regard to morbidity or quality of life. One limitation is that the corresponding endpoints were evaluated only up to progression and therefore allow statements to be made only up to the time of progression. For the PALOMA-2 study, the pharmaceutical company presented an additional analysis of the health-related quality of life after progression in the written statement. However, according the pharmaceutical company, is not significant because of the limited amount of data. Apart from that, it is an isolated analysis of data exclusively by progression. However, in order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required.

The extent to which the extended PFS under palbociclib also translates into extended survival cannot be assessed at present – the final analysis of the overall survival endpoint is still pending.

With regard to the question of whether PFS can be regarded as a surrogate for overall survival, the analyses submitted by the pharmaceutical company in the dossier as well as in the written statement do not provide sufficient proof that 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 palbociclib – radiologically determined disease progression according to the RECIST criteria – is associated with an improvement in morbidity or health-related quality of life. Furthermore, the data available do not suggest that prolonged progression-free time is associated with a prolongation of survival.

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

Time to first subsequent (intravenous) chemotherapy

The endpoint “time to first subsequent (intravenous) chemotherapy” is defined as the period from randomisation to the start of first subsequent (intravenous) chemotherapy.

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 side effects (in particular myelosuppressive but also other relevant side effects) as well as intravenous application, may be relevant.

For the PALOMA-2 study, there are serious uncertainties regarding the significance of the results for the endpoint time to first subsequent chemotherapy. On one hand, mortality and morbidity were not taken into account in the corresponding evaluation. For example, the methodological assessment of the IQWiG of the endpoint time to first subsequent intravenous chemotherapy showed that in the intervention arm with palbociclib plus letrozole, a larger proportion of patients without subsequent intravenous chemotherapy died than did in the control arm. As a result, including death, there is no significant difference in event rates for the time to first subsequent intravenous chemotherapy between the treatment arms.

Furthermore, the endpoint was defined *post hoc* in the benefit dossier for palbociclib. The pharmaceutical company does not describe significant information about the circumstances of the treatment decision for or against chemotherapy. It can also be assumed that after treatment with palbociclib in combination with letrozole or with letrozole in the control group,

the patients received further endocrine therapies according to the guidelines before chemotherapy was started for the first time. There is a complete lack of appropriate information on these post-progression therapies.

In the present benefit assessment, there are thus serious uncertainties in the interpretation of the results for the endpoint time to first subsequent (intravenous) chemotherapy.

Health status (EQ-5D visual analogue scale)

In the PALOMA-2 study, data on general health status were collected using the visual analogue scale of the EQ-5D. The mean values of the change between the start of study and end of treatment did not differ significantly between the study arms.
For the endpoint health status (EQ-5D-VAS), an additional benefit of palbociclib in combination with letrozole is therefore not proven.

Quality of life

Time to deterioration of quality of life (FACT-B[2])

In the PALOMA-2 study, data on health-related quality of life were collected using the disease-specific FACT-B patient questionnaire. The FACT-B questionnaire consists of the cross-tumour disease questionnaire (FACT-G[3]) and a breast cancer specific sub-scale (BCS[4]).

The assessment of the additional benefit is based on the results of the evaluation of the time to deterioration in health-related quality of life. In addition to evaluations for the total scale (FACT-B), separate evaluations are available for FACT-G, its four sub-scales, the disease-specific sub-scale (BCS), and the TOI[5]. There is no statistically significant difference between the treatment arms for either the total scale of FACT-B or the other (sub-) scales considered.
When assessing the results on health-related quality of life, the high risk of bias must be taken into account. This results, in particular, from the high proportion of potentially informative censoring because no measurements were received after the end of treatment, and a different observation period was derived from the median treatment time in both study arms (20 vs 14 months).

For palbociclib in combination with letrozole in the endpoint category quality of life, an additional benefit is not proven.

Side effects

Adverse events (AE)

For almost all patients in both study arms of the PALOMA-2 study, one adverse event was recorded (intervention arm: 98.9%, comparator arm: 95.5%). In the supplementary PALOMA-

[2] Functional Assessment of Cancer Therapy – Breast
[3] Functional Assessment of Cancer Therapy – General
[4] Breast Cancer Sub-scale
[5] Trial Outcome Index

1 study, 100.0% of patients in the intervention arm and 84.4% in the comparator arm were affected by AE.

Serious adverse events (SAE)

For the serious adverse events there is a statistically significant treatment effect to the detriment of palbociclib (PALOMA-2: HR: 1.63 [95% CI: 1.06; 2.49]; p = 0.023).
When assessing the results for the endpoint SAE, a high risk of bias because of potentially informative censoring at different observation times must be taken into account.
The results on SAE from the supportive PALOMA-1 study can therefore not be interpreted.

Severe AE (CTCAE grade 3/4)

With regard to the time to the occurrence of severe adverse events with CTCAE grade 3 or 4, there is a significant treatment effect to the detriment of palbociclib plus letrozole (PALOMA-2: HR: 5.50 [95% CI: 4.14; 7.31]; p < 0.001). In the intervention arm, severe AE occurred after 1.0 months (median; comparative arm: not reached).
A statistically significant effect to the detriment of palbociclib was also found in the separate evaluation of severe AE, excluding laboratory parameters (HR: 1.47 [95% CI: 1.08; 1.99]; p = 0.013). According to IQWiG, however, no explicit information was available from the pharmaceutical company as to which specific laboratory values were excluded in the calculation of the corresponding effect estimate (for severe AE (CTCAE grade 3 or 4), without laboratory values).
The results of the PALOMA-1 supplementary study also show a significant treatment effect to the detriment of palbociclib plus letrozole (PALOMA-1: HR: 5.47 [95% CI: 3.15; 9.51]; p < 0.001). Patients treated with palbociclib plus letrozole experience severe AE after 1.4 months (median) (in the comparator arm: not achieved). Excluding laboratory values, this effect was not statistically significant (HR: 1.72 [95% CI: 0.94; 3.15]; p = 0.078).

Discontinuation because of AE

In the PALOMA-2 study, the median time to therapy discontinuation because of an adverse event did not differ between the treatment arms in a statistically significant way – neither with regard to the discontinuation of palbociclib or placebo nor the discontinuation of all active ingredient components. In the PALOMA-1 supportive study, there were also no statistically significant differences between the treatment arms regarding the discontinuation of all active ingredient components. In the PALOMA-1 study, no patient had discontinued only one of the two active ingredient components.

With regard to the assessment of the results in the endpoint category adverse events, it must be considered for that the data submitted in the dossier on adverse events as a whole and on severe adverse events (CTCAE grade 3 or 4), both the analyses at the SOC (system organ classes) and PT (*preferred terms*) level were insufficiently presented. Survival time analyses of specific adverse events are completely missing. These deficits were also not remedied by the pharmaceutical company in the course of the written statement procedure.

In the studies, the side effects led to high rates of temporary discontinuation of medication in the palbociclib arm (see EPAR on Ibrance[6]). The transferability and significance of this study effect to medical practice is subject to uncertainty because in clinical studies, asymptomatic

[6] European Medicines Agency. Assessment report: IBRANCE. 15 September 2016, pages 118 and 123

haematological laboratory parameters with short-term adjustment of the dose of ribociclib are more closely controlled than in medical practice. The EMA lists in particular the myelosuppressive side effects of palbociclib in the Risk Management Plan[7].

The side effect profile of palbociclib is qualitatively comparable to the side effect profile of cytotoxic chemotherapy (especially myelosuppression but also alopecia and fatigue) and differs significantly from the side effect profile of endocrine therapy in the comparator arms of the studies.

In view of the survival analyses presented in the endpoint category adverse events, it can be assumed that data collection in this category took place for a longer period than only up to 28 days after the end of treatment. Against this background, it cannot be ruled out that adverse events that occurred during treatment with follow-up therapies (which could include chemotherapy) were recorded.

In the overall consideration of the endpoints on side effects, there were no advantages but significant disadvantages because of an increase in serious AE and severe AE (CTCAE grade 3 or 4) when treated with palbociclib and letrozole compared with the appropriate comparator therapy letrozole.

[7] European Medicines Agency. Assessment report: IBRANCE. 15 September 2016, page 131

Overall assessment

For the assessment of the extent of the additional benefit of palbociclib in combination with letrozole, results from the PALOMA-2 study in comparison to letrozole on mortality (overall survival), morbidity, quality of life, and side effects are available. The results of the PALOMA-1 study on mortality and side effects were also used supportively.

With regard to the endpoint category mortality, the data on the overall survival endpoint are preliminary, and therefore no assessment of effectiveness can as yet be drawn for the overall survival endpoint category. Final analyses on the endpoint of overall survival are pending. Based on the data available, an additional benefit of palbociclib in combination with letrozole is not proven for overall survival.
The results for the endpoint category morbidity (health status endpoint) show no statistically significant difference between palbociclib plus letrozole and letrozole.

Because of the serious uncertainties described in interpreting the results available at the endpoint time to first subsequent (intravenous) chemotherapy, these are not considered valid and are therefore not included in the present benefit assessment.

A comparison of the effects of the treatments on health-related quality of life also shows no statistically significant difference. However, because the corresponding evaluations included only data up to the end of treatment and thus did not record potential effects as a result of progression, their significance is considered limited.

In terms of side effects, serious adverse events (SAE) and severe adverse events (CTCAE grade 3 or 4) are a significant disadvantage for palbociclib plus letrozole compared with letrozole in terms of the endpoints, in particular the marked myelosuppression caused by palbociclib. The overall side effect profile of palbociclib differs significantly from the side effect profile of endocrine therapy in the comparator arms of the studies.

In the studies, the side effects often led to a temporary discontinuation of the medication in the palbociclib arm. In clinical studies asymptomatic haematological laboratory parameters with short-term adjustment of the dose of palbociclib are more closely controlled than in health care practice. The side effects are therefore underestimated based on study results, and the transferability and significance of this study effect to medical practice is subject to uncertainty.

In a balancing decision, the G-BA concludes that for Palbociclib in combination with letrozole for the treatment of post-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer, an additional benefit compared with letrozole is not proven. Even if a positive effect is assumed because of a delay in the (intravenous) chemotherapy that is subsequently used for the first time in the case of sufficient significance of the results, this would have to be compared with the pronounced side effects. The extent to which the negative side effects and the prolonged progression-free survival have an effect on overall survival cannot yet be assessed.

a2) Pre-/peri-menopausal patients in first-line treatment:

For pre-/peri-menopausal patients in first-line treatment, an additional benefit of palbociclib compared with the appropriate comparator therapy is not proven.

Justification:

For pre-/peri-menopausal patients in first-line treatment, no data were provided to assess the additional benefit of palbociclib compared with the appropriate comparator therapy. In the studies presented on first-line treatment (PALOMA-1 and PALOMA-2), only post-menopausal patients were examined.

b1) Post-menopausal patients with progression after previous endocrine therapy:

and

b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy:

For post-menopausal and pre-/peri-menopausal patients with progression after previous endocrine therapy, an additional benefit compared with the appropriate comparator therapy is not proven.

Justification:

To demonstrate an additional benefit of palbociclib in combination with fulvestrant after previous endocrine therapy, the pharmaceutical company presented the results of the randomised, double-blind Phase III PALOMA-3 study (A5481023).

This multi-centre, multinational study (N=521) included pre- and post-menopausal patients with HR-positive, HER2-negative metastatic breast cancer with progression after previous endocrine therapy. The medicinal product combination palbociclib + fulvestrant (N = 347) was compared with placebo + fulvestrant (N = 174). Pre-/peri-menopausal patients additionally received goserelin to suppress ovarian function.

According to the inclusion criteria, patients with progression were studied during or within 12 months of adjuvant therapy or during or within one month of the end of advanced therapy. Post-menopausal patients had to have received an aromatase inhibitor (either as an adjuvant or advanced stage therapy) as a previous therapy. Pre-/peri-menopausal patients had to have received tamoxifen as either an adjuvant therapy or an endocrine therapy as an advanced stage therapy). In addition to endocrine therapy, a previous line of chemotherapy was approved for advanced stages.

The study started in September 2013 and is scheduled to end in January 2018.

For the benefit assessment, the 1st data cut-off of 5 December 2014 was presented; this is the basis for the analyses in the study report. Only for this data cut-off are results available for all patient-relevant endpoints (overall survival, morbidity, health-related quality of life, and adverse events). In addition, analyses for the endpoint PFS and relative frequencies of deaths were presented for the 2nd (16 March 2015) and 4th data cut-off (23 October 2015). For adverse events, additional analyses were presented for the 3rd data cut-off (31 July 2015). In addition to Kaplan-Meier analyses of overall survival, results on symptoms, health-related quality, of life and adverse events are missing from the most recent data cut-off.

An exemplary comparison of the data basis between the 1st and 3rd data cut-off in the endpoint category adverse events showed that patient-relevant events also occurred to a

significant extent after the 1st data cut-off. It can therefore be concluded that evaluations based only on the 1st data cut-off may be insufficient for assessing the PALOMA-3 study. In order to adequately assess the PALOMA-3 study, results for all patient-relevant endpoints from the most recent data cut-off would be required. Regardless of the resulting uncertainty, the results for the 1st data cut-off are considered.

Implementation of the appropriate comparator therapy:

In the PALOMA-3 study, monotherapy with fulvestrant was prescribed for the control group as per study protocol. However, the G-BA determined fulvestrant as an appropriate comparator therapy for post-menopausal patients with relapse or progress after anti-oestrogen treatment (in this context: tamoxifen or toremifen) only to a limited extent according to the marketing authorisation. In the PALOMA-3 study, post-menopausal patients were included only if they had received an aromatase inhibitor as previous therapy (either adjuvant or as first-line treatment for advanced breast cancer). Only some of the patients in the study had received previous anti-oestrogen treatment.
The marketing authorisation of fulvestrant provides for its use only after previous anti-oestrogen therapy, which may be adjuvant or for advanced stages. However, the guidelines explicitly recommend fulvestrant as a treatment option for post-menopausal women after pre-treatment with aromatase inhibitors in addition to other active ingredients (e.g. tamoxifen). This significance of fulvestrant in the reality of care in the therapy situation after pretreatment with aromatase inhibitors was also emphasised in the corresponding written statements of medical societies in the present procedure, according to which fulvestrant is a therapy option regularly applied in the present treatment situation alongside other endocrine therapies.

For pre-/peri-menopausal patients with progression after endocrine therapy, the G-BA determined an “endocrine therapy according to the doctor’s instructions, taking into account the respective marketing authorisation” to be the appropriate comparator therapy. In PALOMA-3, all pre-/peri-menopausal patients were also treated with fulvestrant (plus goserelin for ovarian suppression). However, fulvestrant is approved for post-menopausal patients only. The investigator also did not have a choice of several therapy options that could be considered in the therapeutic indication in question. With regard to the present treatment situation, there is no information available as to how fulvestrant should be assessed as the appropriate endocrine therapy according to the doctor’s instructions for all patients.

Taking into account remaining uncertainties on the question of the extent to which fulvestrant or fulvestrant alone (without taking into account other endocrine therapies indicated in accordance with the guidelines in the present treatment situation) represents a sufficiently suitable comparator in the special therapy and medical treatment situation in the present therapeutic indication and taking into account the corresponding statements by medical experts in the present written statement procedure, the G-BA sees a medical reason that justifies including the data from the PALOMA-3 study in the decision-making process.

The G-BA points out that it will continue to adhere to the principles laid down in the provisions on benefit assessment according to Section 35a SGB V (Ordinance on the Benefit Assessment of Pharmaceuticals and Chapter 5 of the Rules of Procedure of the Federal Joint Committee), and thus also to the requirement laid down in Chapter 5, Section 6, paragraph 3, sentence 2, No. 1 VerfO that the comparator therapy is used in the clinical study used for benefit assessment in a manner compliant with marketing authorisation.

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.

Irrespective of the question as to whether the PALOMA 3 study can formally be used for the benefit assessment because of the intended use of fulvestrant, which is not approved for this therapeutic indication but is used to a relevant extent in health care, the G-BA included the PALOMA 3 study in its decision-making process and addresses the study results.

PALOMA-3 study: Palbociclib + fulvestrant vs placebo + fulvestrant[8]

Endpoint	**Intervention group** Palbociclib + fulvestrant		**Control group** Placebo + fulvestrant		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Hazard Ratio [95% CI] p value[a] Absolute difference
Mortality					
Overall survival[b]					
	347	n.a. [n.a.; n.a.] 19 (5.5)	174	n.a. [n.a.; n.a.] 9 (5.2)	1.02 [0.46; 2.25]; 0.970
Morbidity					
Progression-free survival					
	347	9.2 [7.5; n.a.] 102 (29.4)	174	3.8 [3.5; 5.5] 93 (53.4)	0.42 [0.32; 0.56] < 0.001 AD: + 5.4 months[c]
Time to first subsequent chemotherapy					
	347	n.a. [n.a.; n.a.] 53 (15.3)	174	n.a. [7.5; n.a.] 55 (31.6)	0.41 [0.28; 0.60] < 0.001
Time to first subsequent intravenous chemotherapy					
	347	n.a. [n.a.; n.a.] 26 (7.5)	174	n.a. [n.a.; n.a.] 28 (16.1)	0.43 [0.25; 0.74] 0.002

Endpoint	**Intervention group** Palbociclib + letrozole			**Control group** Placebo + letrozole			Intervention vs control
	N[d]	Values at the start of study MV (SD)	Change at the end of treatment MV [95% CI][e]	N[d]	Val-ues at the start of study MV (SD)	Change at the end of treatment MV [95% CI][e]	MD [95% CI] p value[e]
Health status (EQ-5D-VAS)							
	330	72.9 (17.2)	−1.8 [−3.3; −0.3]	164	70.3 (19.8)	−2.6 [−4.8; −0.4]	0.8 [−1.9; 3.5]; 0.552

(Continuation)

[8] Data from the IQWiG addendum to order 16-74 unless otherwise indicated.

Endpoint	**Intervention group** Palbociclib + fulvestrant		**Control group** Placebo + fulvestrant		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Hazard Ratio [95% CI] p value[a] Absolute difference
Morbidity					
Morbidity – Time to deterioration[f]					
Symptomatology (EORTC QLQ-C30, decrease by ≥10 points)					
Fatigue	335[g]	2.1 [1.9; 2.8] 205 (61.2)	166[g]	2.8 [1.9; 4.6] 90 (54.2)	1.15 [0.89; 1.47]; 0.208
Nausea and vomiting	335[g]	6.7 [4.6; n.a.] 144 (43.0)	166[g]	4.9 [2.8; n.a.] 72 (43.4)	0.89 [0.67; 1.19]; 0.464
Pain	335[g]	8.0 [5.6; n.a.] 131 (39.1)	166[g]	2.8 [2.3; 5.4] 83 (50.0)	0.63 [0.48; 0.84]; 0.002 AD: + 5.2 months[c]
Dyspnoea	335[g]	n.a. [8.5; n.a.] 107 (31.9)	166[g]	n.a. [4.0; n.a.] 61 (36.7)	0.74 [0.54; 1.01]; 0.060
Insomnia	335[g]	n.a. [6.6; n.a.] 125 (37.3)	166[g]	n.a. [4.7; n.a.] 56 (33.7)	0.99 [0.72; 1.35]; 0.971
Loss of appetite	335[g]	8.3 [6.7; n.a.] 118 (35.2)	166[g]	8.7 [5.7; 8.7] 54 (32.5)	0.97 [0.70; 1.34]; 0.849
Constipation	335[g]	8.0 [4.9; n.a.] 133 (39.7)	166[g]	12 [4.9; 12] 60 (36.1)	0.97 [0.72; 1.33]; 0.928
Diarrhoea	335[g]	12.3 [7.7; 12.3] 105 (31.3)	166[g]	10.2 [8.3; 10.2] 47 (28.3)	1.03 [0.73; 1.45]; 0.863
Symptomatology (EORTC QLQ-BR23, decrease by ≥10 points)					
Side effects of the systemic therapy	335[g]	6.4 [4.8; 7.2] 151 (45.1)	166[g]	6.6 [4.6; n.a.] 57 (34.3)	1.10 [0.80; 1.49]; 0.538
Breast symptoms	335[g]	n.a. [8.4; n.a.] 72 (21.5)	166[g]	n.a. [7.9; n.a.] 34 (20.5)	0.89 [0.59; 1.34]; 0.577
Arm symptoms	335[g]	6.5 [4.9; 8.2] 148 (44.2)	166[g]	4.6 [2.8; 6.5] 77 (46.4)	0.79 [0.59; 1.04]; 0.097
Suffering because of hair loss [h]	335[g]	n.a. [6.5; n.a.] 38 (11.3)	166[g]	n.a. [n.a.; n.a.] 9 (5.4)	2.43 [1.17; 5.07]; 0.014

Endpoint	**Intervention group** Palbociclib + fulvestrant		**Control group** Placebo + fulvestrant		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Hazard Ratio [95% CI] p value[a] Absolute difference
Health-related quality of life – time to deterioration [c]					
EORTC QLQ-C30, decrease by ≥10 points					
Global health status	335 [g]	6.2 [4.7; n.a.] 145 (43.3)	166 [g]	3.8 [2.8; n.a.] 78 (47.0)	0.81 [0.61; 1.06]; 0.136
Role functioning	335 [g]	6.5 [4.9; n.a.] 145 (43.3)	166 [g]	4.9 [2.8; n.a.] 79 (47.6)	0.80 [0.61; 1.06]; 0.127
Physical function-ing	335 [g]	10.2 [10.2; n.a.] 103 (30.7)	166 [g]	n.a. [6.5; n.a.] 48 (28.9)	0.95 [0.67; 1.34]; 0.787
Emotional functioning	335 [g]	10.2 [8.0; n.a.] 101 (30.1)	166 [g]	6.5 [3.9; n.a.] 64 (38.6)	0.66 [0.48; 0.91]; 0.011 AD: +3.7 months[c]
Cognitive functioning	335 [g]	6.5 [3.7; 8.2] 151 (45.1)	166 [g]	4.6 [2.8; 6.8] 76 (45.8)	0.89 [0.67; 1.17]; 0.399
Social functioning	335 [g]	10.2 [5.3; n.a.] 135 (40.3)	166 [g]	n.a. [4.5; n.a.] 65 (39.2)	0.90 [0.67; 1.22]; 0.538
EORTC QLQ-BR23, decrease by ≥10 points					
Body image	335 [g]	8.3 [6.9; 12.6] 117 (34.9)	166 [g]	n.a. [5.7; n.a.] 52 (31.3)	0.97 [0.70; 1.35]; 0.840
Sexual functioning	335 [g]	10.1 [8.5; n.a.] 91 (27.2)	166 [g]	8.7 [8.7; 10.2] 38 (22.9)	1.12 [0.76; 1.63]; 0.562
Sexual enjoyment [i]	335 [g]	8.5 [6.9; n.a.] 45 (13.4)	166 [g]	n.a. [n.a.; n.a.] 15 (9.0)	1.78 [0.99; 3.21]; 0.0496
Future perspective	335 [g]	10.5 [8.5; 12.1] 96 (28.7)	166 [g]	8.6 [5.6; 8.6] 52 (31.3)	0.76 [0.54; 1.07]; 0.107
Side effects					
Adverse events (AE) (presented additionally)					
	345	no data available 337 (97.7)	172	no data available 153 (89.0)	-
Serious adverse events (SAE)					

Endpoint	**Intervention group** Palbociclib + fulvestrant		**Control group** Placebo + fulvestrant		Intervention vs control
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Hazard Ratio [95% CI] p value[a] Absolute difference
	345	n.a. [n.a.; n.a.] 33 (9.6)	172	n.a. [10.5; n.a.] 24 (14.0)	0.66 [0.39; 1.11]; 0.116
Severe AE (CTCAE grade 3 or 4)					
	345	1.0 [0.9; 1.9] 242 (70.1)	172	n.a. [n.a.; n.a.] 31 (18.0)	6.19 [4.25; 9.02]; < 0.001
Discontinuation because of AE					
Discontinuation of palbociclib or placebo	345	n.a. [n.a.; n.a.] 13 (3.8)	172	n.a. [n.a.; n.a.] 7 (4.1)	0.95 [0.38; 2.37]; 0.904
Discontinuation of fulvestrant	345	no data available [no data available] 11 (3.2)	172	no data available [no data available] 5 (2.9)	no data available [no data available]; no data available

(Continuation)

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
Frequent severe AE (CTCAE grade ≥ 3) (in the SOC and PT ≥ 1% in at least one study arm)				
SOC[j] PT[j]				
Total rate of AE with CTCAE grade ≥ 3	345	242 (70.1)	172	33 (19.2)
Blood and lymphatic system disorders	345	178 (51.6)	172	4 (2.3)
Neutropoenia	345	167 (48.4)	172	0 (0)
Leukopoenia	345	47 (13.6)	172	0 (0)
Anaemia	345	8 (2.3)	172	3 (1.7)
Thrombocytopoenia	345	5 (1.4)	172	0 (0)
Investigations	345	84 (24.3)	172	4 (2.3)
Reduced neutrophil number	345	53 (15.4)	172	1 (0.6)
Reduced leukocyte number	345	41 (11.9)	172	1 (0.6)
Increased alanine aminotransfer-ase	345	5 (1.4)	172	2 (1.2)
Increased aspartate aminotrans-ferase	345	4 (1.2)	172	0 (0)
General disorders and administration site conditions	345	16 (4.6)	172	2 (1.2)
Fatigue	345	7 (2.0)	172	2 (1.2)
Gastrointestinal disorders	345	10 (2.9)	172	5 (2.9)
Ascites	345	0 (0)	172	4 (2.3)
Metabolism and nutrition disorders	345	10 (2.9)	172	5 (2.9)
Infections and infestations	345	6 (1.7)	172	3 (1.7)
Musculoskeletal and connective tissue disorders	345	6 (1.7)	172	8 (4.7)

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
Back pain	345	3 (0.9)	172	4 (2.3)
Pain in one extremity	345	0 (0)	172	3 (1.7)
Bone pain	345	2 (0.6)	172	2 (1.2)
Pathological fracture	345	0 (0)	172	2 (1.2)
Respiratory, thoracic and mediastinal disorders	345	6 (1.7)	172	6 (3.5)
Injury, poisoning, and procedural complications	345	0 (0)	172	5 (2.9)
Nervous system disorders	345	5 (1.4)	172	4 (2.3)
Vascular disorders	345	5 (1.4)	172	1 (0.6)
Hypertension	345	4 (1.2)	172	1 (0.6)
Psychiatric disorders	345	3 (0.9)	172	2 (1.2)

a: Unless otherwise indicated: Effect and 95% CI: Cox proportional hazards model, stratified by documented sensitivity to previous hormone therapy (yes vs no) and presence of visceral metastases (yes vs no) p value: two-sided log-rank test
b: For the data cut-off of 16 March 2015, 36 (10.4%) patients in the palbociclib + fulvestrant arm and 21 (12.1%) in the fulvestrant arm had died, RR: 0.86 [0.52; 1.43], p = 0.617. For the data cut-off of 23 October 2015, 71 (20.5%) patients in the palbociclib + fulvestrant arm and 41 (23.6%) in the fulvestrant arm had died, RR: 0.87 [0.62; 1.22], p = 0.448.
c: Own calculation
d: Number of patients included in the evaluation to calculate the effect estimator. Number of patients for whom a measurement was available at the end of treatment: Palbociclib + fulvestrant N = 81 and fulvestrant N = 74.
e: Changes, effect, 95% CI, and p value: Mixed model with repeated measurements (MMRM) with the factors treatment, time, the interaction term treatment*time, and the baseline value as a covariate.
f: Symptom scales: Increase of the score by at least 10 points compared with baseline, functional scales: Decrease of the score by at least 10 points compared with baseline.
g: Number of patients who have a value at the start of study and at least one value after the start of study before the end of the study medication (PRO Analysis Set).
h: The question was addressed only to patients with hair loss.
i: The question was addressed only to patients who were sexually active.
j: MedDRA version 17.1; SOC and PT designations taken from MedDRA without adaptation

CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European

Endpoint	**Intervention group** Palbociclib + letrozole		**Control group** Placebo + letrozole	
	N	Patients with event n (%)	N	Patients with event n (%)
Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast cancer module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life - 5 Dimensions; HR = hazard ratio; i.v.: intravenous; CI = confidence interval; n: Number of patients with (at least one) event; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; MMRM: mixed model with repeated measurements; MV: mean value; N: number of patients evaluated; n.a.: not achieved; PFS: progression-free survival; PT: preferred term; RCT: randomised controlled study; SD: standard deviation; SOC: system organ class; SAE: serious adverse event; AE: adverse event; vs: versus				

Extent and probability of the additional benefit

Mortality

Overall survival

In the PALOMA-3 study, there was no statistically significant difference between treatment with palbociclib plus fulvestrant compared with fulvestrant in the total study population (HR): 1.02 [95% CI: 0.46; 2.25]; p value = 0.970).

Median survival had not yet been achieved because of the low number of events; final analyses on the endpoint overall survival are pending.

For the endpoint category mortality, there is no additional benefit for the combination therapy of palbociclib and fulvestrant compared with fulvestrant based on the results available.

Morbidity

Progression-free survival (PFS)

In the PALOMA-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) or death by any cause.

PFS in the palbociclib treatment group was statistically significantly longer by a median of 5.4 months compared with the control group (9.2 vs 3.8 months; HR: 0.42 [95% CI: 0.32; 0.56]; p < 0.001).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the PALOMA-3 study, the mortality endpoint component was calculated as an independent endpoint via the secondary endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging procedures (radiologically determined disease progression according to the RECIST criteria). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

For the interpretation of the PFS results, the data available on morbidity and health-related quality of life are used. Data on morbidity and health-related quality of life are potentially

relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life.

The data from the PALOMA-3 study show no overall advantage or disadvantage for palbociclib in the endpoints on morbidity and health-related quality of life. Accordingly, extended PFS under palbociclib was not associated with an advantage with regard to morbidity or quality of life. One limitation is that the corresponding endpoints were evaluated only up to progression and therefore allow statements to be made only up to the time of progression. In order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required.

The extent to which the extended PFS under palbociclib also translates into extended survival cannot be assessed at present – the final analysis of the overall survival endpoint is still pending.

With regard to the question of whether PFS can be regarded as a surrogate for overall survival, the analyses submitted by the pharmaceutical company in the dossier as well as in the written statement do not provide sufficient proof that 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 palbociclib – radiologically determined disease progression according to the RECIST criteria – is associated with an improvement in morbidity or health-related quality of life. Furthermore, the data available do not suggest that prolonged progression-free time is associated with a prolongation of survival.

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

Time to first subsequent (intravenous) chemotherapy

The endpoint “time to first subsequent (intravenous) chemotherapy” is defined as the period from randomisation to the start of first subsequent (intravenous) chemotherapy.

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.

Unlike the patients in first-line treatment in the PALOMA-2 study, however, about one third of the patients in the PALOMA-3 study had already received chemotherapy for treatment of the advanced/metastatic disease before the start of study: 30.8% of patients in the treatment group with palbociclib plus fulvestrant and 36.2% in the control group with fulvestrant.[9]

This endpoint thus addresses the first subsequent (intravenous) chemotherapy, but not specifically the subsequent (intravenous) chemotherapy used for the first time. This does not adequately reflect the transition from endocrine therapy to initial cytotoxic chemotherapy with this endpoint. For an adequate illustration in this respect, it would basically be assumed that the patients in the advanced/metastatic treatment situation have not yet received chemotherapy.

In addition, the results of the PALOMA-3 study for the endpoint time to first subsequent chemotherapy are also subject to serious uncertainty with regard to their significance.

[9] European Medicines Agency. Assessment report: IBRANCE. 15 September 2016

On one hand, mortality and morbidity were not taken into account in the corresponding evaluation.
On the other hand, the endpoint for PALOMA-3 was also defined *post hoc* in the benefit dossier on palbociclib. The pharmaceutical company does not describe significant information about the circumstances of the treatment decision for or against chemotherapy.

In the present benefit assessment, there are thus serious uncertainties in the interpretation of the results for the endpoint time to first subsequent (intravenous) chemotherapy.

Health status (EQ-5D visual analogue scale)

The general health status was assessed using the visual analogue scale of the EQ-5D. The mean values of the change between the start of study and end of treatment did not differ significantly between the study arms.

An additional benefit of palbociclib for the health status endpoint (EQ-5D-VAS) is therefore not proven.

Symptomatology

In the PALOMA-3 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.

The present assessment is based on the evaluation of the time to deterioration of the symptomatology (decrease of the score by at least 10 points compared with baseline).

For the endpoint “pain”, there was a statistically significant difference in favour of palbociclib (HR: 0.63 [95% CI: 0.48; 0.84]; p = 0.002). For the endpoint “burden of hair loss”, however, there was a statistically significant difference to the detriment of palbociclib (HR: 2.43 [95% CI: 1.17; 5.07]; p = 0.014). For all further endpoints presented, there was no statistically significant difference between the treatment groups.

Furthermore, additional responder analyses on the symptom scales of EORTC-QLQ-C30 and -BR23 were subsequently submitted by the pharmaceutical company within the framework of the written statement procedure. These are not used because of their response criterion defined *post hoc* (for which no statements on validity are available) as well as the fact that they have already been prepared with knowledge of the data.

In the overall consideration of the results from the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23, an additional benefit of palbociclib + fulvestrant compared with fulvestrant regarding the change in symptomatology is not proven.

Quality of life

In the PALOMA-3 study, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23 were used to assess the health-related quality of life. The present assessment is based on the evaluation of the time to deterioration of quality of life (decrease of the score by at least 10 points compared with baseline).

For the endpoint “emotional functioning”, there was a statistically significant difference in favour of palbociclib plus fulvestrant (HR: 0.66 [95% CI: 0.48; 0.91]; p = 0.011). For the endpoint “sexual pleasure”, however, there was a statistically significant treatment effect to the detriment of palbociclib plus fulvestrant (HR: 1.78 [95% CI: 0.99; 3.21]; p = 0.0496). For all further endpoints presented, there was no statistically significant difference between the treatment groups.

With regard to the functional scales, the additional responder analyses later submitted by the pharmaceutical company within the framework of the written statement procedure are also not used for the present assessment for the reasons mentioned above.

In the overall consideration of the results from the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23, an additional benefit of palbociclib + fulvestrant compared with fulvestrant in terms of health-related quality of life is not proven.

Side effects

Adverse events (AE)

In the PALOMA-3 study, 98.9% of the patients in the intervention arm and 95.5% in the comparator arm experienced an adverse event.

Serious adverse events (SAE)

For the serious adverse events, there is no statistically significant treatment effect between palbociclib plus fulvestrant and fulvestrant.

Severe AE (CTCAE grade 3/4)

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 palbociclib plus fulvestrant (HR: 6.19 [95%-CI: 4.25; 9.02]; p < 0.001). In the intervention arm, severe AE occurred after 1.0 months (median; comparative arm: not reached).

Discontinuation because of AE

For the median time to “therapy discontinuation because of an adverse event”, there was no statistically significant difference between the treatment arms. This applies both to the discontinuation of palbociclib or placebo and the discontinuation of fulvestrant.

With regard to the assessment of the results in the endpoint category adverse events, it should be noted that the data on frequent adverse events and adverse events of special interest presented in the dossier were insufficiently presented. Only selective analyses were available for the SOC (system organ classes). Individual AE of CTCAE grade 3 or 4 were excluded. Survival time analyses are missing for individual serious adverse events (SAE). Even within the framework of the written statement procedure, these deficits were not completely eliminated by the analyses later submitted by the pharmaceutical company.

In the study, the side effects led to high rates of temporary discontinuation of medication in the palbociclib arm (see EPAR on Ibrance[10]). The transferability and significance of this study effect to medical practice is subject to uncertainty because in clinical studies, asymptomatic haematological laboratory parameters with short-term adjustment of the dose of ribociclib are more closely controlled than in medical practice. The EMA lists in particular the myelosuppressive side effects of palbociclib in the Risk Management Plan[11].

The side effect profile of palbociclib is qualitatively comparable to the side effect profile of cytotoxic chemotherapy (especially myelosuppression but also alopecia and fatigue) and differs significantly from the side effect profile of endocrine therapy in the comparator arm of the study.

In the overall consideration of the endpoints on side effects, an increase in severe AE (CTCAE grade 3 or 4) indicates negative effects of treatment with palbociclib plus fulvestrant compared with treatment with fulvestrant.

Overall assessment

From the PALOMA-3 study, results are available for assessing the extent of the additional benefit of palbociclib in combination with fulvestrant compared with fulvestrant in terms of mortality (overall survival), morbidity, quality of life, and side effects.

With regard to the endpoint category mortality, the data on the overall survival endpoint are preliminary, and therefore no assessment of effectiveness can as yet be drawn for the overall survival endpoint category. Final analyses on the endpoint of overall survival are pending. Based on the data available, an additional benefit of palbociclib in combination with fulvestrant is not proven for overall survival.
Based on the overall consideration of the results for the endpoint category morbidity (endpoint health status, symptomatology), an additional benefit for palbociclib plus fulvestrant compared with fulvestrant is not proven. Likewise, in the overall view of the effects of the treatments on health-related quality of life, an additional benefit is not proven for palbociclib plus fulvestrant.

Because of the serious uncertainties described in interpreting the results available at the endpoint time to first subsequent (intravenous) chemotherapy, these are not considered valid and are therefore not included in the present benefit assessment.

In terms of side effects, there is a significant disadvantage of palbociclib plus fulvestrant compared with fulvestrant with regard to the endpoint severe adverse events (CTCAE grade 3 or 4), particularly with regard to the pronounced myelosuppression caused by palbociclib. The overall side effect profile of palbociclib differs significantly from the side effect profile of endocrine therapy in the comparator arms of the studies.

In the study, the side effects often led to a temporary discontinuation of the medication in the palbociclib arm. In clinical studies asymptomatic haematological laboratory parameters with short-term adjustment of the dose of palbociclib are more closely controlled than in health care practice. The side effects are therefore underestimated based on study results, and the

[10] European Medicines Agency. Assessment report: IBRANCE. 15 September 2016, page 116
[11] European Medicines Agency. Assessment report: IBRANCE. 15 September 2016, page 131

transferability and significance of this study effect to medical practice is subject to uncertainty.

In the overall view, the G-BA concludes that for palbociclib in combination with fulvestrant for the treatment of post-menopausal and pre-/peri-menopausal patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer with previous endocrine therapy, an additional benefit compared with fulvestrant is not proven. The extent to which the negative side effects and the prolonged progression-free survival have an effect on overall survival cannot yet be assessed.

2.1.4 Limitation of the period of validity of the resolution

a1) Post-menopausal patients in first-line treatment:

The limitation of the period of validity of the resolution on the benefit assessment of palbociclib has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

For this assessment, the overall survival data from the PALOMA-2 study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending.

Because clinical data on overall survival relevant for the benefit assessment of the medicinal product are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific insight on the additional benefit of palbociclib in combination with an aromatase inhibitor is available. The limitation allows the expected final results from the PALOMA-2 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

For this purpose, the G-BA considers a limitation of the resolution until 1 March 2019 to be appropriate.

Conditions of the limitation:

After the deadline, the final study results for all endpoints from the currently ongoing PALOMA-2 study used to demonstrate an additional benefit should be submitted in the dossier for the renewed benefit assessment.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment for the medicinal product palbociclib in combination with an aromatase inhibitor shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of palbociclib in combination with an aromatase inhibitor in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, no. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for the medicinal product palbociclib can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2–4 VerfO) remains unaffected by this.

b1) Post-menopausal patients with progression after previous endocrine therapy:

and

b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy:

The limitation of the period of validity of the resolution on the benefit assessment of palbociclib has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

For this assessment, the overall survival data from the PALOMA-3 study are preliminary. There were small number of events at the time of this data cut-off. The final results from the current study are still pending.

There are no results on symptoms, health-related quality of life, and adverse events for the most recent data presented.

Because clinical data on overall survival relevant for the benefit assessment of the medicinal product are expected in the future, the G-BA considers it appropriate to limit the period of validity of the resolution until further scientific insight on the additional benefit of palbociclib in combination with fulvestrant is available. The limitation allows the expected final results from the PALOMA-3 study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

For this purpose, the G-BA considers a limitation of the resolution until 1 October 2018 to be appropriate.

Conditions of the limitation:

After the deadline, the final study results for all endpoints from the currently ongoing PALOMA-3 study used to demonstrate an additional benefit should be submitted in the dossier for the renewed benefit assessment.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment for the medicinal product palbociclib in combination with fulvestrant shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline proving an additional benefit of palbociclib in combination with fulvestrant in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the dossier is not submitted or submitted incompletely, the G-BA may come to the finding that an additional benefit is not proven.

The possibility that a benefit assessment for the medicinal product palbociclib can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1, paragraph 2, Nos. 2 – 4 VerfO) remains unaffected by this.

2.2 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 its resolution, the G-BA follows the assessment of the IQWiG that the total patient numbers submitted by the pharmaceutical company is an underestimate. The patient numbers were therefore adjusted without deduction of deaths for 5 years from the 5-year prevalence and without transferring the proportion of patients receiving endocrine therapy in the treatment reality. The patient numbers are nevertheless subject to great uncertainty, particularly with regard to their upper limit. This is because the stage distribution related to the new diseases was applied to both incidence (lower limit) and prevalence (upper limit). This results in an overestimation of the number of patients with regard to the upper limit because an advanced stage is associated with an unfavourable prognosis and thus a higher proportion is to be assumed for the incidence than for the prevalence.

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: 12 April 2017):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/003853/WC500217196.pdf

Treatment with palbociclib 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 May 2017).

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy 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.

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is different for each individual patient and/or is shorter on average.

The recommended dose for palbociclib is 125 mg. Palbociclib 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.

a1) Post-menopausal patients in first-line treatment:

Designation of the therapy	Treatment mode	Number of treatments per patient	Treatment days per patient per year
Medicinal product to be assessed			
Palbociclib	continuously	1 × daily	273
Aromatase inhibitor[12]	continuously	1 × daily	365
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Appropriate comparator therapy			
Aromatase inhibitor			
Anastrozole	continuously	1 × daily	365
Letrozole	continuously	1 × daily	365
Anti-oestrogens			
Tamoxifen	continuously	1 × daily	365

[12] Aromatase inhibitor: Anastrozole, letrozole or exemestane

a2) Pre-/peri-menopausal patients in first-line treatment:

Designation of the therapy	Treatment mode	Number of treatments per patient	Treatment days per patient per year
Medicinal product to be assessed			
Palbociclib	continuously	1 × daily	273
Aromatase inhibitor	continuously	1 × daily	365
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Goserelin	continuously	every 28 days	13
Leuprorelin	continuously	1 × every 3 months	4
Appropriate comparator therapy			
Anti-oestrogens			
Tamoxifen	continuously	1 × daily	365
LHRH[13] analogue			
Goserelin	continuously	every 28 days	13
Leuprorelin	continuously	1 × every 3 months	4

b1) Post-menopausal patients with progression after previous endocrine therapy:

Designation of the therapy	Treatment mode	Number of treatments per patient	Treatment days per patient per year
Medicinal product to be assessed			
Palbociclib	continuously	1 × daily	273
Aromatase inhibitor	continuously	1 × daily	365

[13] Luteinizing Hormone Releasing Hormone

Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Appropriate comparator therapy			
Aromatase inhibitor			
Anastrozole	continuously	1 × daily	365
Exemestane	continuously	1 × daily	365
Letrozole	continuously	1 × daily	365
Anti-oestrogens			
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Tamoxifen	continuously	1 × daily	365
Protein kinase inhibitors			
Everolimus	continuously	1 × daily	365

b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy:

Designation of the therapy	Treatment mode	Number of treatments per patient	Treatment days per patient per year
Medicinal product to be assessed			
Palbociclib	continuously	1 × daily	273

Aromatase inhibitor	continuously	1 × daily	365
Fulvestrant	First year of treatment: 1st month: 500 mg i.m. on Day 1 and 15 From the 2nd month: 500 mg i.m. 1 × monthly Following year: 500 mg i.m.	1st month: 2 × monthly From the 2nd month: 1 × monthly 1 × monthly	13 12
Goserelin	continuously	every 28 days	13
Leuprorelin	continuously	1 × every 3 months	4
Appropriate comparator therapy			
Aromatase inhibitor			
Exemestane	continuously	1 × daily	365
Letrozole	continuously	1 × daily	365
Anti-oestrogens			
Tamoxifen	continuously	1 × daily	365
Gestagens			
Medroxyprogester-one acetate	continuously	1 × daily	365
Megestrol acetate	continuously	1 × daily	365
LHRH analogue			
Goserelin	continuously	every 28 days	13
Leuprorelin	continuously	1 × every 3 months	4

Usage and consumption:

a1) Post-menopausal patients in first-line treatment:

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package[14]	Average annual consumption by potency
Medicinal product to be assessed				
Palbociclib	125 mg	125 mg	21 tablets (3x7)	273 tablets
Aromatase inhibitor	1–25 mg	1–25 mg	120 tablets each	365 tablets each
Fulvestrant	250 mg	500 mg	2 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Appropriate comparator therapy				
Aromatase inhibitor				
Anastrozole	1 mg	1 mg	120 tablets	365 tablets
Letrozole	2.5 mg	2.5 mg	120 tablets	365 tablets
Anti-oestrogens				
Tamoxifen	20 mg	20 mg	100 tablets	365 tablets

a2) Pre-/peri-menopausal patients in first-line treatment:

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package	Average annual consumption by potency
Medicinal product to be assessed				
Palbociclib	125 mg	125 mg	21 tablets (3x7)	273 tablets
Aromatase inhibitor	1–25 mg	1–25 mg	120 tablets each	365 tablets each
Fulvestrant	250 mg	500 mg	2 prefilled syringes	First year of treatment: 26 prefilled syringes Following year:

[14] Largest pack in each case

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package	Average annual consumption by potency
				24 prefilled syringes
Goserelin	3.6 mg	3.6 mg	3 prefilled syringes	13 prefilled syringes
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes
Appropriate comparator therapy				
Anti-oestrogens				
Tamoxifen	20 mg	20 mg	100 tablets	365 tablets
LHRH analogue				
Goserelin	3.6 mg	3.6 mg	3 prefilled syringes	13 prefilled syringes
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes

b1) Post-menopausal patients with progression after previous endocrine therapy:

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package	Average annual consumption by potency
Medicinal product to be assessed				
Palbociclib	125 mg	125 mg	21 tablets (3x7)	273 tablets
Aromatase inhibitor	1–25 mg	1–25 mg	120 tablets each	365 tablets each
Fulvestrant	250 mg	500 mg	2 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Appropriate comparator therapy				
Aromatase inhibitor				

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package	Average annual consumption by potency
Anastrozole	1 mg	1 mg	120 tablets	365 tablets
Exemestane	25 mg	25 mg	120 tablets	365 tablets
Letrozole	2.5 mg	2.5 mg	120 tablets	365 tablets
Anti-oestrogens				
Fulvestrant	250 mg	500 mg	2 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Tamoxifen	20 mg	20 mg	100 tablets	365 tablets
Protein kinase inhibitors				
Everolimus	10 mg	10 mg	90 tablets	365 tablets

b2) Pre-/peri-menopausal patients with progression after previous endocrine therapy:

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package	Average annual consumption by potency
Medicinal product to be assessed				
Palbociclib	125 mg	125 mg	21 tablets (3x7)	273 tablets
Aromatase inhibitor	1–25 mg	1–25 mg	120 tablets each	365 tablets each
Fulvestrant	250 mg	500 mg	2 prefilled syringes	First year of treatment: 26 prefilled syringes Following year: 24 prefilled syringes
Goserelin	3.6 mg	3.6 mg	3 prefilled syringes	13 prefilled syringes
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes

Designation of the therapy	Potency	Dose per patient per treatment day	Quantity per package	Average annual consumption by potency
Appropriate comparator therapy				
Aromatase inhibitor				
Exemestane	25 mg	25 mg	120 tablets	365 tablets
Letrozole	2.5 mg	2.5 mg	120 tablets	365 tablets
Anti-oestrogens				
Tamoxifen	20 mg	20 mg	100 tablets	365 tablets
Gestagens				
Medroxypro-gesterone acetate	500 mg	300–1,000 mg	100 tablets	365–730 tablets
Megestrol acetate	160 mg	160 mg	30 tablets	365 tablets
LHRH analogue				
Goserelin	3.6 mg	3.6 mg	3 prefilled syringes	13 prefilled syringes
Leuprorelin	11.25 mg	11.25 mg	2 prefilled syringes	4 prefilled syringes

Costs:

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy sales price according to potency and package size)	Costs after deduction of statutory rebates
Palbociclib	€ 5,425.89 125 mg, 21 tablets	€ 5,117.52 [€ 1.77[15]; € 306.60[16]]
Anastrozole	€ 109.29[17] 1 mg, 120 tablets	€ 99.74 [€ 1.77[15]; € 7.78[16]]
Everolimus	€ 14,051.64 10 mg, 90 tablets	€ 13,250.65 [€ 1.77[15]; € 799.22[16]]
Exemestane	€ 150.23[17] 25 mg, 120 tablets	€ 137.45 [€ 1.77[15]; € 11.01[16]]
Fulvestrant	€ 849.34 250 mg, 2 prefilled syringes	€ 807.77 [€ 1.77[15]; € 39.80[16]]
Goserelin	€ 547.46 3.6 mg, 3 prefilled syringes	€ 515.99 [€ 1.77[15]; € 29.70[16]]
Letrozole	€ 104.17[17] 2.5 mg, 120 tablets	€ 95.03 [€ 1.77[15]; € 7.37[16]]
Leuprorelin	€ 932.29 11.25 mg, 2 prefilled syringes	€ 879.51 [€ 1.77[15]; € 51.01[16]]
Medroxyprogesterone acetate	€ 339.75 500 mg, 100 tablets	€ 296.38 [€ 1.77[15]; € 41.60[16]]
Megestrol acetate	€ 471.89 160 mg, 30 tablets	€ 444.60 [€ 1.77[15]; € 25.52[16]]
Tamoxifen	€ 22.13[17] 20 mg, 100 tablets	€ 19.48 [€ 1.77[15]; € 0.88[16]]

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 May 2017

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product have been taken into account if, when using the medicinal product to be assessed, there are regular differences in the necessary use of medical treatment or in the prescription of other services as indicated in the product or package information. Regular laboratory services or medical fees that do not exceed the scope of the usual expenses in the course of oncological treatment were not taken into account.

Medical treatment costs, costs incurred for routine examinations, and medical fees are not shown.

[15] Rebate according to Section 130 SGB V
[16] Rebate according to Section 130a SGB V
[17] Fixed reimbursement rate Level I

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 January 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy. The consultation meeting took place on 13 January 2016.

Following the granting of the positive opinion by the European Medicines Agency (EMA) on 15 September 2016, a review of the appropriate comparator therapy defined by the G-BA at the time of the consultation on the basis of the planned/applied therapeutic indication took place.

On 22 November 2016, 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, number 1, sentence 2 VerfO.

By letter dated 23 November 2016 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 palbociclib.

The dossier assessment by the IQWiG was submitted to the G-BA on 24 February 2017, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2017. The deadline for submitting written statements was 22 March 2017.

The oral hearing was held on 11 April 2017.

By letter dated 12 April 2017, the IQWiG was commissioned with a supplementary assessment of data submitted in the dossier as well as in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 28 April 2017.

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 9 May 2017, and the proposed resolution was approved.

At its session on 18 May 2017, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 January 2016	Determination of the appropriate comparator therapy
Working group Section 35a	1 November 2016 15 November 2015	Review of the appropriate comparator therapy after granting the positive opinion
Subcommittee on Medicinal Products	22 November 2016	Change of the appropriate comparator therapy
Working group Section 35a	4 April 2017	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	11 April 2017	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 April 2017 2 May 2017	Consultation on the dossier assessment by the IQWiG and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 May 2017	Concluding discussion of the draft resolution
Plenum	18 May 2017	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 18 May 2017

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

Prof. Hecken