Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Alpelisib (Breast Cancer with PIK3CA Mutation, HR+, HER2-, Combination with Fulvestrant)

of 18 February 2021

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy 3

2.1.1 Approved therapeutic indication of alpelisib (Piqray) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 7

2.1.4 Summary of the assessment 19

2.2 Number of patients or demarcation of patient groups eligible for treatment 22

2.3 Requirements for a quality-assured application 23

2.4 Treatment costs 23

3. Bureaucratic costs 29

4. Process sequence 29

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient alpelisib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2020. 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 31 August 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 December 2020 on the website of the G-BA (www.g-ba.de), 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 alpelisib 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, and the written statements submitted in the written and oral hearing procedure as well as the addendum 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) according to 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 alpelisib.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of alpelisib (Piqray) in accordance with the product information

Piqray is indicated in combination with fulvestrant for the treatment of post-menopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

Therapeutic indication of the resolution (resolution of 18 February 2021):

See approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation:

- Ribociclib in combination with a non-steroidal aromatase inhibitor *or*
- Ribociclib in combination with fulvestrant *or*
- Anastrozole *or*
- Letrozole *or*
- Fulvestrant *or*
- Possibly tamoxifen if aromatase inhibitors are not suitable.

a2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation:

A therapy according to the doctor's instructions.

b1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

a further endocrine therapy depending on the previous therapy with:

- Abemaciclib in combination with fulvestrant *or*
- Ribociclib in combination with fulvestrant *or*
- Tamoxifen *or*
- Anastrozole *or*
- Fulvestrant as monotherapy; only for patients with relapse or progress after anti-oestrogen treatment *or*
- Letrozole; only for patients with relapse or progress after anti--oestrogen treatment *or*
- Exemestane; only for patients with progress after anti-oestrogen treatment *or*
- Everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

A therapy according to the doctor's instructions.

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 alpelisib, the following active ingredients are approved in the present therapeutic indication: Abemaciclib, anastrozole, everolimus, exemestane, fulvestrant, goserelin, letrozole, leuprorelin, medroxyprogesterone acetate, megestrol acetate, palbociclib, ribociclib, tamoxifen, and toremifene.

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

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

On 2. As non-medicinal therapies, surgical resection and/or radiotherapy are generally considered for the treatment of mammary carcinoma. 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:

- Abemaciclib (in combination with fulvestrant): Resolution of 3 September 2020
- Ribociclib (in combination with fulvestrant): Resolution of 20 August 2020
- Ribociclib (in combination with an aromatase inhibitor): Resolution of 20 August 2020
- Ribociclib (in combination with fulvestrant): Resolution of 4 July 2019
- Ribociclib (in combination with an aromatase inhibitor): Resolutions of 4 July 2019
- Abemaciclib (in combination with fulvestrant): Resolution of 2 May 2019
- Abemaciclib (in combination with an aromatase inhibitor): Resolution of 2 May 2019
- Palbociclib: Resolution of 22 March 2019
- Palbociclib: Resolution of 18 May 2017

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

For the present therapeutic indication, it is assumed 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. In addition, it is assumed that a change in treatment has taken place with regard to the active ingredients used for the initial endocrine therapy.

National and international guidelines recommend aromatase inhibitors for initial endocrine therapy in advanced or metastatic stages in post-menopausal women (a1). As an alternative in the case of aromatase inhibitor intolerance, tamoxifen, which is also approved, is an appropriate therapy.

In addition, the anti-oestrogen fulvestrant is another treatment option approved for this indication. In the context of a Cochrane Review[2] and the FIRST study[3] included therein, an advantage of fulvestrant compared with the aromatase inhibitor anastrozole is described with regard to overall survival. Also in international guidelines, monotherapy with fulvestrant is a recommended treatment option for initial endocrine therapy. In this treatment situation, fulvestrant is approved for post-menopausal patients who have not received previous endocrine therapy or who have had a relapse during or after adjuvant anti-oestrogen therapy.

Furthermore, in accordance with national guidelines, letrozole or fulvestrant can be combined with a CDK4/6 inhibitor for initial treatment in the advanced or metastatic stage. In previous benefit assessment procedures of the G-BA on CDK4/6 inhibitors for post-menopausal patients who have not previously received initial endocrine therapy, a hint for a minor additional benefit was found for ribociclib in combination with letrozole compared with letrozole and an indication of a minor additional benefit for ribociclib in combination with fulvestrant compared with fulvestrant.

In the therapy situation of disease progression in post-menopausal patients after endocrine pre-treatment, national and international guidelines unanimously recommend further endocrine therapy using an alternative active ingredient unless there is an

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

[3] Ellis MJ, Llombart Cussac A, Feltl D, et al. Fulvestrant 500 mg versus Anastrozole 1 mg for the First Line treatment of advanced breast cancer: Overall Survival Analysis from the Phase II First study. J Clin Oncol. 2015 Nov 10; 33(32): 3781–7.

indication for chemotherapy. With regard to the significance of gestagens, the corresponding statements in the guidelines are less clear compared with 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.

In addition, treatment with letrozole or fulvestrant, each in combination with a CDK4/6 inhibitor, is named in the national guidelines as an alternative to endocrine monotherapy for post-menopausal patients in the advanced or metastatic stage. For post-menopausal women with previous endocrine therapy, the benefit assessment of abemaciclib in combination with fulvestrant and for ribociclib in combination with fulvestrant found a hint for a minor additional benefit compared with fulvestrant in each case.

The marketing authorisation of fulvestrant provides for its use in post-menopausal women with progressive disease only after prior with anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in care; these are not based exclusively on previous therapy with antiestrogens but rather also on previous therapy with aromatase inhibitors. This fact was also presented in the written statements submitted by medical experts in the benefit assessment procedures already carried out in this therapeutic indication.

In this special therapy and medical treatment situation, the G-BA sees a sufficient medical factual reason that justifies the consideration of fulvestrant as a sufficiently suitable comparator in the present case despite remaining uncertainties.

For men with breast cancer, the evidence on treatment options is extremely limited. According to the guidelines, the recommendations for the treatment of men with breast cancer are predominantly based on the recommendations for the treatment of women. However, tamoxifen is the recommended initial endocrine therapy for men. For further endocrine therapy after endocrine pre-treatment, for men, the guidelines recommend the active ingredient fulvestrant and aromatase inhibitors in addition to tamoxifen. However, aromatase inhibitors and fulvestrant are not approved for the present indication. There is a discrepancy between medicinal products approved in the indication and medicinal products used in care/recommended in guidelines.

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

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

The appropriate comparator therapy was originally determined as follows:

Post-menopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

Appropriate comparator therapy for alpelisib in combination with fulvestrant:

A further endocrine therapy with:

- Tamoxifen *or*
- Anastrozole *or*
- Fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment *or*
- Letrozole; only for patients with relapse or progress after anti-oestrogen treatment *or*
- Exemestane; only for patients with progress after anti-oestrogen treatment *or*
- Everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

At the beginning of dossier assessment of the IQWiG, it was noticed that the SOLAR-1 study, which was decisive for the marketing authorisation, included a patient population that was not covered by the originally determined appropriate comparator therapy. This patient population consisted of patients who had a relapse during or within 12 months after completion of (neo-)adjuvant endocrine therapy and who had not yet received therapy in the locally advanced or metastatic stage (i.e. patients who had received only adjuvant pretherapy). In contrast, the originally determined appropriate comparator therapy was aimed exclusively at patients who received the endocrine therapy as monotherapy in the metastatic or locally advanced stage.

It was therefore necessary to supplement the corresponding patient population and to determine the appropriate comparator therapy. In addition, the patient populations were delineated in terms of sex (women/men).

This was based on the fact that, particularly in the endocrine therapy phase, a joint assessment of women and men is not considered appropriate because, on one hand, there are differences between the therapy options considered as appropriate comparator therapy based on the relevant guideline recommendations. On the other hand, there is a difference in endocrine behaviour between the sexes. The present approved therapeutic indication for alpelisib is also explicitly aimed at the treatment of women and men.

Consequently, the delimitation according to sex was also carried out for the patient population on which the originally determined appropriate comparator therapy was based in order to be able to pursue a uniform question in this regard in the benefit assessment.

The pharmaceutical company and the IQWiG were informed about this change in the ongoing benefit assessment procedure. The appropriate comparator therapy in the amended version was published together with benefit assessment of the IQWiG on the website of the G-BA on 1 December 2020 and thus made available for comment.

This change in the appropriate comparator therapy neither effects this assessment of additional benefit nor does it require a re-assessment of the benefit assessment.

2.1.3 Extent and probability of the additional benefit

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

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present:

Indication of a minor benefit.

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present:

An additional benefit is not proven.

a3) Men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation:

An additional benefit is not proven.

b1) Post-menopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

Indication of a minor benefit.

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

An additional benefit is not proven.

Justification:

Description of the SOLAR-1 study

For the evidence of additional benefit of alpelisib in combination with fulvestrant compared with fulvestrant, the pharmaceutical company has presented results of the randomised, double-blind controlled SOLAR-1 Phase III study.

This multinational study included post-menopausal women and men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer. Patients had to have had a relapse or disease progression during or after endocrine therapy with an aromatase inhibitor; however, it did not have to be the last therapy received. The endocrine therapy could have been advanced, exclusively (neo-) adjuvant, or both. However, more than one endocrine therapy for advanced stage treatment was not allowed.

With a protocol amendment of 30 August 2016, patients with a relapse later than 12 months after completion of a (neo-)adjuvant endocrine therapy and without therapy for metastatic disease were excluded during the course of the study.

Patients were screened for the presence of a PIK3CA mutation. Of the total of 572 patients included in the SOLAR-1 study, 231 were assigned to the group without a PIK3CA mutation and 341 to the group with a PIK3CA mutation. Patients were randomised in a 1:1 ratio to treatment with either alpelisib + fulvestrant or placebo + fulvestrant stratified by prior CDK4/6 inhibitor therapy and the presence of lung and/or liver metastases.

A sub-population of 177 post-menopausal women received the study medication as first-line therapy in the advanced stage. It included 88 patients in the intervention arm and 89 patients in the comparator arm. This sub-population is the basis for the assessment of the additional benefit in patient populations a1 and a2. A sub-population of 161 post-menopausal women received the study medication as second-line therapy in the advanced stage; the intervention arm included 79 patients, and the comparator arm included 82 patients. This sub-population is decisive for the assessment of the additional benefit in patient population b1. Because only 1 man was included in the SOLAR-1 study, no data are available for the benefit assessment in the male patient populations (a3 and b2).

Treatment with the study medication was to continue until disease progression, unacceptable toxicity, withdrawal of consent, loss-to-follow-up, death, or discontinuation of treatment for any other reason. Discontinuation of fulvestrant treatment while continuing alpelisib or placebo was permitted in the study as was discontinuation of alpelisib or placebo while continuing fulvestrant treatment. A change of treatment from the comparator arm to the control arm was not allowed.

The primary endpoint of the study is progression-free survival (PFS) in the PIK3CA mutation group. Patient-relevant secondary endpoints include overall survival and endpoints on morbidity, health-related quality of life, and adverse events (AEs).

For the SOLAR-1 study, evaluations of three data cut-offs are available:

- 1st data cut-off (16 June 2018): planned final analysis after 243 PFS events
- 2nd data cut-off (30 September 2019): planned interim analysis after 151 deaths
- 3rd data cut-off (23 April 2020): planned final analysis after 178 PFS deaths

For the present benefit assessment, the results of the final 3rd data cut-off are used; this is the planned final analysis on overall survival.

Extent and probability of the additional benefit

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present:

and

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present:

Mortality

In the SOLAR-1 study overall survival was defined as the time from randomisation to the death of the patient regardless of the underlying cause of death.

When looking at the total population (a1 and a2), there is no statistically significant difference between the two treatment arms.

However, the pre-specified sub-group analysis for the characteristic “lung and/or liver metastases” shows an effect modification. Patients with lung and/or liver metastases had a statistically significant longer survival time under therapy with alpelisib + fulvestrant compared with fulvestrant (median survival of 40.6 months versus 22.2 months). In contrast, there was no statistically significant difference for the sub-group of patients who had no lung and/or liver metastases.

However, in the pre-specified subgroup analysis for the more broadly defined characteristic “visceral metastases”, which also or mainly include lung and/or liver metastases but also visceral metastases of other localisations, no effect modification is shown.

In the present study, stratified randomisation was used for the characteristic “lung and/or liver metastases”, which is why there is a lower risk of random imbalances. The characteristic “visceral metastases” was not randomised in a stratified manner.

The two characteristics – “lung and/or liver metastases” and “visceral metastases” – are, in principle, suitable for investigating different effects depending on the severity of the disease. From the written statements of clinical experts in the present procedure, it can be inferred that the clinical significance of both characteristics is similar. Moreover, it can be inferred from the written statements that there is no clear priority of one over the other.

Against the background of the overall significant data on overall survival in the present study and taking into consideration the size of the effect in the relevant sub-group, the G-BA considers the sub-group results on lung and/or liver metastases to be sufficiently robust for the present assessment in order to be able to make a correspondingly separate assessment of the additional benefit with the necessary certainty. However, uncertainties remain regarding the assessment of the magnitude of the effect.

In the sub-group of patients without lung and/or liver metastases, there is no statistically significant difference in overall survival. An additional benefit is therefore not proven for this patient population.

In the sub-group of patients with lung and/or liver metastases, there is a statistically significant prolongation in overall survival, which is assessed as a relevant, but not conclusively quantifiable improvement.

Morbidity

Progression-free survival

Progression-free survival (PFS) was the primary endpoint of the SOLAR-1 study and was operationalised as the time from randomisation to the first documented progression or death regardless of the underlying cause of death. The occurrence of disease progression was surveyed using imaging techniques and based on the RECIST criteria (version 1.1). The evaluation was done by the investigator. In addition, a tumour assessment by a blinded independent central review (BICR) was performed in a selected sub-population.

The result shows a statistically significant prolongation of PFS by treatment with alpelisib in combination with fulvestrant compared with fulvestrant.

In the present study, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint overall survival. The morbidity component “disease progression” was assessed solely by means of imaging techniques (radiologically determined disease progression according to the RECIST criteria). Morbidity is thus not assessed primarily on the basis of disease symptoms but rather solely on the basis of asymptomatic, not directly patient-relevant findings.

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

Because radiologically determined disease progression may be associated with effects on morbidity and/or quality of life, the data available on morbidity and health-related quality of life are used for further interpretation of the PFS results. 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.

In the SOLAR-1 study, the prolonged PFS with alpelisib in combination with fulvestrant was not associated with an advantage in terms of morbidity or quality of life; however, there were disadvantages for alpelisib in combination with fulvestrant in terms of symptomatology and quality of life in the “social functioning” functional scale. It should be taken into consideration that the corresponding endpoints were surveyed only up to progression and therefore allow statements only up to the time of progression. However, in order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under alpelisib in combination with fulvestrant is associated with an improvement in morbidity or health-related quality of life. The results on the endpoint PFS are not therefore used in this assessment.

Symptomatology

In the SOLAR-1 study, the symptomatology of the patients was surveyed using the symptom scales of the EORTC QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration (response criterion: 10 points). These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

Within the written statement procedure, the pharmaceutical company submitted responder analyses of the symptom scales of the questionnaire EORTC QLQ-C30 operationalised as time to first deterioration. Deterioration was defined by a response criterion of 15% of the scale span. These are used here for the present assessment.

For post-menopausal patients who received endocrine therapy in the neo-(adjuvant) therapy situation, there was a significant difference to the disadvantage of alpelisib in combination with fulvestrant for the symptom scales “nausea and vomiting”, “loss of appetite”, and “diarrhoea”.

For the symptom scales “fatigue”, “insomnia”, “pain”, and “constipation”, there was no significant difference between the treatment groups.

Overall, there is therefore a disadvantage for alpelisib in combination with fulvestrant in terms of symptomatology.

Pain (BPI-SF)

In the SOLAR-1 study, a survey of pain was carried out using the Brief Pain Inventory-Short Form (BPI-SF) questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration. These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

For the present assessment, the analyses submitted by the pharmaceutical company within the framework of the written statement procedure on the items “strongest pain”, “pain severity index”, and “pain interference index”, operationalised as time to first deterioration of the disease symptomatology, are used. This was defined as the time from randomisation to the occurrence of a clinically relevant deterioration; an increase of at least 2 points from baseline was considered a clinically relevant deterioration.

For post-menopausal patients who received endocrine therapy in the neo-(adjuvant) therapy situation, there was no significant difference between the treatment groups for the scale “strongest pain”.

No usable data are available for the scales “pain intensity” and “impairment due to pain”.

Overall, there is no advantage or disadvantage for alpelisib in combination with fulvestrant with regard to the pain endpoint.

Health status (EQ-5D VAS)

In the SOLAR-1 study, health status was surveyed using the EQ-5D VAS questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration. These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

The responder analyses, operationalised as the time from randomisation to first deterioration, submitted by the pharmaceutical company in the context of the written statement procedure are used. Deterioration was defined by a response criterion of 15% of the scale span.

For post-menopausal patients who received endocrine therapy in the neo-(adjuvant) therapy situation, there was no significant difference between the treatment groups.

With regard to the health status endpoint, there is therefore no advantage or disadvantage for alpelisib in combination with fulvestrant.

Quality of life

In the SOLAR-1 study, health-related quality of life was assessed using the global health status and functional scales of the EORTC QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration (response criterion: 10 points). These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

For the present assessment, the evaluation of the time to first deterioration of the quality of life submitted by the pharmaceutical company within the framework of the written statement procedure is used. This was defined as the time from randomisation to the occurrence of a clinically relevant deterioration. Deterioration was operationalisation by a response criterion of 15% of the scale span. These are used here for the present assessment.

For post-menopausal patients who received endocrine therapy in the neo-(adjuvant) therapy situation, there was a significant effect to the disadvantage of alpelisib in combination with fulvestrant for the function scale “social functioning”. The median time to deterioration was 5.6 months in the intervention arm compared with 16.5 months in the control arm.

For the functional scales “physical functioning”, “role functioning”, “emotional functioning”, and “cognitive functioning” as well as the global health status, there was no significant difference between the treatment groups.

In the quality of life category, a disadvantage can thus be determined overall for alpelisib in combination with fulvestrant.

Side effects

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

Adverse events (AE)

In the SOLAR-1 study, 100.0% of post-menopausal patients who received endocrine therapy in the neo-(adjuvant) therapy situation experienced an adverse event in the intervention arm. In the comparator arm, this was 92.1% of patients.

Serious adverse events

For the serious adverse events, a statistically significant differences to the disadvantage of alpelisib in combination with fulvestrant was observed.

Severe AE (CTCAE grade ≥ 3)

With regard to the time to severe adverse events with CTCAE grade ≥ 3, there was a statistically significant difference between the treatment groups to the detriment of alpelisib in combination with fulvestrant.

Discontinuation because of AE

In the SOLAR-1 study, therapy discontinuation was defined as termination of therapy with alpelisib or placebo and/or fulvestrant.

For the median time to therapy discontinuation because of an AE, there was a statistically significant difference to the disadvantage of alpelisib in combination with fulvestrant.

Specific AE

A detailed examination of the specific AEs shows that the time to the occurrence of the specific AEs "severe hyperglycaemia" (SMQ, severe AEs), "severe skin rash" (CMQ, severe AEs) in patients in the intervention arm was significantly shorter than in patients in the control arm. Similarly, for the other specific AEs "taste disorders" (PT, AEs), "alopecia" (PT, AEs), "gastrointestinal disorders" (SOC, AEs), "mucosa inflammation" (PT, AEs), "peripheral oedema" (PT, AEs), "diarrhoea" (PT, severe AEs), "hypertension" (PT, severe AEs), "weight decreased" (PT, AEs) and "metabolism and nutrition disorders" (SOC, severe AEs), there is a statistical difference to the disadvantage of alpelisib in combination with fulvestrant compared with fulvestrant.

With regard to the specific AE "gastrointestinal disorders" (SOC, AEs), there is an effect modification with regard to the characteristics "lung and/or liver metastases" and "visceral metastases". Accordingly, the disadvantage is more pronounced in patients with "lung and/or liver metastases" or "visceral metastases".

For the endpoint "gamma-glutamyltransferase increased" (PT, severe AEs), there is a statistically significant advantage for alpelisib in combination with fulvestrant.

In the overall consideration of the endpoints on side effects, there were almost exclusively statistically significant disadvantages of alpelisib in combination with fulvestrant. Overall, a significant disadvantage is found for treatment with alpelisib in combination with fulvestrant.

<u>Overall assessment</u>

For the assessment of the additional benefit of alpelisib in combination with fulvestrant in the patient population of post-menopausal women who have received endocrine therapy as monotherapy in the (neo-) adjuvant therapy situation, results on mortality, morbidity (symptomatology and health status), quality of life, and side effects are available from the SOLAR-1 study compared with fulvestrant.

For the endpoint overall survival, there was no statistically significant difference between the two treatment arms for the total population (patient populations a1 and a2). However, the pre-specified sub-group analysis for the characteristic "lung and/or liver metastases" shows an effect modification. Patients with lung and/or liver metastases had a statistically significant longer survival time under therapy with alpelisib + fulvestrant compared with fulvestrant. In contrast, there was no statistically significant difference for the sub-group of patients who had no lung and/or liver metastases. These sub-group results are considered sufficiently robust in order to be able to make a corresponding separate assessment of additional benefit with the necessary certainty. However, uncertainties remain regarding the assessment of the magnitude of the effect.

In the area of morbidity, there is a disadvantage in therapy with alpelisib in combination with fulvestrant because of statistically significant disadvantages in the endpoints "nausea and vomiting", "loss of appetite" and "diarrhoea".

In the quality of life category, there is a significant disadvantage for alpelisib in combination with fulvestrant for the function scale “social functioning”.

The endpoints on side effects consistently show almost exclusively significant disadvantages. Overall, a significant disadvantage in side effects is noted for treatment with alpelisib in combination with fulvestrant compared with fulvestrant.

Because of the results for the endpoint overall survival, a separate assessment of the additional benefit is made in the overall assessment depending on whether lung and/or liver metastases are present:

For patients without lung and/or liver metastases (patient population a1), there is no statistically significant difference in overall survival. An additional benefit in terms of overall survival is therefore not proven for this patient population.

The endpoints on symptomatology, quality of life, and side effects showed exclusively negative effects. In terms of side effects overall, a significant disadvantage of treatment with alpelisib in combination with fulvestrant compared with fulvestrant was found.

For the above reasons, it is therefore reasonable to conclude that alpelisib in combination with fulvestrant for the patient population of post-menopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast carcinoma with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation in whom no lung and/or liver metastases are present has a lower benefit than the appropriate comparator therapy.

For patients with lung and/or liver metastases (patient population a2), there is a statistically significant prolongation in overall survival, which is assessed as a relevant, but not conclusively quantifiable improvement. This advantage is counterbalanced by exclusively negative effects in the endpoints on symptomatology, quality of life, and side effects. In terms of side effects overall, a significant disadvantage of treatment with alpelisib in combination with fulvestrant compared with fulvestrant was found.

In a balancing decision, the G-BA concluded that, in this case, the advantage in terms of overall survival does not outweigh the disadvantages overall. As a result, for the patient population of post-menopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast carcinoma with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation, in whom lung and/or liver metastases are present, it is determined that an additional benefit is not proven.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind SOLAR-1 Phase III study.

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

The risk of bias at the study level is assessed to be low. Likewise, the risk of bias at the endpoint level is assessed as low.

For the results on severe AEs and morbidity, there is also a high degree of endpoint-specific reliability of data because of the large extent of the effects.

With regard to the results on health-related quality of life, the negative effect is based on the difference in only one of the investigated domains on health-related quality of life, which is why for the overall statement on health-related quality of life, there is assumed to be a low reliability of data.

Thus, in the overall view, the reliability of data for the minor benefit determined in the overall assessment is classified as an “indication”.

a3) Men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation:

No data are available for the assessment of the additional benefit of alpelisib in combination with fulvestrant compared with the appropriate comparator therapy in men who have received endocrine therapy in the (neo-)adjuvant therapy situation. The characterisation of the study population shows that only one man was included in the SOLAR-1 study. There is no sufficient data basis to assess the additional benefit.

b1) Post-menopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

Mortality

In the SOLAR-1 study overall survival was defined as the time from randomisation to the death of the patient regardless of the underlying cause of death.

There is no statistically significant difference between the two treatment arms. With alpelisib in combination with fulvestrant, the median survival time was 37.2 months and with fulvestrant, 31.2 months.

For the endpoint overall survival, an additional benefit of alpelisib in combination with fulvestrant compared with fulvestrant is therefore not proven in the present patient population.

Morbidity

Progression-free survival

Progression-free survival (PFS) was the primary endpoint of the SOLAR-1 study and was operationalised as the time from randomisation to the first documented progression or death regardless of the underlying cause of death. The occurrence of disease progression was surveyed using imaging techniques and based on the RECIST criteria (version 1.1). The evaluation was done by the investigator. In addition, a tumour assessment by a blinded independent central review (BICR) was performed in a selected sub-population.

The result shows a statistically significant prolongation of PFS by treatment with alpelisib in combination with fulvestrant compared with fulvestrant.

In the present study, the endpoint component “mortality” was surveyed as an independent endpoint using the endpoint overall survival. The morbidity component “disease progression” was assessed solely by means of imaging techniques (radiologically determined disease progression according to the RECIST criteria). Morbidity is thus not assessed primarily on the basis of disease symptoms but rather solely on the basis of asymptomatic, not directly patient-relevant findings.

Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint.

Because radiologically determined disease progression may be associated with effects on morbidity and/or quality of life, the data available on morbidity and health-related quality of life are used for further interpretation of the PFS results. 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.

In the SOLAR-1 study, the prolonged PFS with alpelisib in combination with fulvestrant was associated with disadvantages in terms of symptomatology and the “social functioning” scale. An advantage was shown for the endpoint “dyspnoea”. It should be taken into consideration that the corresponding endpoints were surveyed only up to progression and therefore allow statements only up to the time of progression. However, in order to assess the possible effects of a radiologically determined progression on quality of life and morbidity, reliable analyses of data before and after the time of the radiologically determined progression are required.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under alpelisib in combination with fulvestrant is associated with an improvement in morbidity or health-related quality of life. The results on the endpoint PFS are not therefore used in this assessment.

Symptomatology

In the SOLAR-1 study, the symptomatology of the patients was surveyed using the symptom scales of the EORTC QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration (response criterion: 10 points). These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

Within the written statement procedure, the pharmaceutical company submitted responder analyses of the symptom scales of the questionnaire EORTC QLQ-C30 operationalised as time to first deterioration. Deterioration was defined by a response criterion of 15% of the scale span. These are used here for the present assessment.

For post-menopausal patients who have already received endocrine therapy in the locally advanced or metastatic therapy situation, a statistically significant difference was shown for the symptom scales “nausea and vomiting” and “diarrhoea” as well as “loss of appetite” to the disadvantage of alpelisib in combination with fulvestrant.

For the symptom scale “dyspnoea”, there was a statistically significant difference to the advantage of alpelisib + fulvestrant.

For the symptom scales “fatigue”, “pain”, “insomnia”, and “constipation”, there was no significant difference between the treatment groups.

In summary, the disadvantages outweigh the advantage, which is why there is an overall disadvantage for alpelisib in combination with fulvestrant in terms of symptomatology.

Pain (BPI-SF)

In the SOLAR-1 study, a survey of pain was carried out using the Brief Pain Inventory-Short Form (BPI-SF) questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration. These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

For the present assessment, the analyses submitted by the pharmaceutical company within the framework of the written statement procedure on the items “strongest pain”, “pain severity index”, and “pain interference index” operationalised as time to first deterioration of the disease symptomatology, are used. This was defined as the time from randomisation to the occurrence

of a clinically relevant deterioration; an increase of at least 2 points from baseline was considered a clinically relevant deterioration.

For post-menopausal patients who have already received endocrine therapy in the locally advanced or metastatic therapy situation, there was no significant difference between the treatment groups for the scale “strongest pain”.

No usable data are available for the scales “pain intensity” and “impairment due to pain”.

Overall, there is no advantage or disadvantage for alpelisib in combination with fulvestrant with regard to the pain endpoint.

Health status (EQ-5D VAS)

In the SOLAR-1 study, health status was surveyed using the EQ-5D VAS questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration. These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

The responder analyses, operationalised as the time from randomisation to first deterioration, submitted by the pharmaceutical company in the context of the written statement procedure are used. Deterioration was defined by a response criterion of 15% of the scale span.

For post-menopausal patients who have already received endocrine therapy in the locally advanced or metastatic therapy situation, there was no significant difference between the treatment groups.

With regard to the health status endpoint, there is therefore no advantage or disadvantage for alpelisib in combination with fulvestrant.

Quality of life

In the SOLAR-1 study, health-related quality of life was assessed using the global health status and functional scales of the EORTC QLQ-C30 questionnaire.

In the dossier, the pharmaceutical company presented responder analyses; these were operationalised as time to permanent deterioration (response criterion: 10 points). These are not used; because of the difference in the number of follow-up surveys between the two study arms, it can be assumed that it is mainly a comparison of a one-time deterioration in the comparator arm with a persistent deterioration in the intervention arm.

For the present assessment, the evaluation of the time to first deterioration of the quality of life submitted by the pharmaceutical company within the framework of the written statement procedure is used. This was defined as the time from randomisation to the occurrence of a clinically relevant deterioration. Deterioration was operationalisation by a response criterion of 15% of the scale span. These are used here for the present assessment.

For post-menopausal patients who have already received endocrine therapy in the locally advanced or metastatic therapy situation, there was a significant effect for the functional scale “social functioning” to the disadvantage of alpelisib in combination with fulvestrant.

For the functional scales “physical functioning”, “role functioning”, “emotional functioning”, and “cognitive functioning” as well as the global health status, there was no significant difference between the treatment groups.

In the quality of life category, a disadvantage can thus be determined overall for alpelisib in combination with fulvestrant.

Side effects

Adverse events (AE)

In the SOLAR-1 study, 98.7% of post-menopausal patients in the intervention arm who had already received endocrine therapy in the locally advanced or metastatic stage experienced an adverse event. In the comparator arm, this was 88.9% of patients.

Serious adverse events

For the serious adverse events, a statistically significant differences to the disadvantage of alpelisib in combination with fulvestrant was observed.

Severe AE (CTCAE grade ≥ 3)

With regard to the time to severe adverse events with CTCAE grade ≥ 3, there was a statistically significant difference between the treatment groups to the detriment of alpelisib in combination with fulvestrant.

Discontinuation because of AE

In the SOLAR-1 study, therapy discontinuation was defined as termination of therapy with alpelisib or placebo and/or fulvestrant.

For the median time to therapy discontinuation because of an AE, there was a statistically significant difference to the disadvantage of alpelisib in combination with fulvestrant.

Specific AE

A detailed examination of the specific AEs shows that the time to the occurrence of the specific AEs “severe hyperglycaemia” (SMQ, severe AEs), “severe skin rash” (CMQ, severe AEs) in patients in the intervention arm was significantly shorter than in patients in the control arm. Similarly, for the other specific AEs “Alopecia” (PT, AEs), “Pruritus” (PT, AEs), “Gastrointestinal disorders” (SOC, AEs), “Mucosa inflammation” (PT, AEs), “Weight decreased” (PT, AEs), “Stomatitis” (PT, AEs), “Musculoskeletal and connective tissue disorders” (SOC, SAEs), “Diarrhoea” (PT, severe AEs), “General disorders and administration site conditions” (SOC, severe AEs), “Investigations” (SOC, severe AEs) and “Hypokalaemia” (PT, severe AEs), there was a statistically significant difference to the disadvantage of alpelisib in combination with fulvestrant compared with fulvestrant. Thus, there are only disadvantages with regard to the specific AEs.

In the overall consideration of the endpoints on side effects, statistically significant disadvantages of alpelisib in combination with fulvestrant are shown throughout. Overall, a significant disadvantage is found for treatment with alpelisib in combination with fulvestrant.

<u>Overall assessment</u>

For the assessment of the additional benefit of alpelisib in combination with fulvestrant in the patient population of post-menopausal women who have already received endocrine therapy in the locally advanced or metastatic stage, results for mortality (overall survival), morbidity (symptomatology and health status), quality of life, and side effects are available from the SOLAR-1 study compared with fulvestrant.

For the endpoint overall survival, there was no statistically significant difference between the treatments.

In the area of morbidity, therapy with alpelisib in combination with fulvestrant shows a disadvantage with regard to the endpoints “nausea and vomiting” and “diarrhoea” as well as “loss of appetite”. For the endpoint “dyspnoea”, there is an advantage for alpelisib in combination fulvestrant compared with fulvestrant. The disadvantages outweigh the advantage, which is why there is an overall disadvantage for alpelisib in combination with fulvestrant in terms of symptomatology.

In the quality of life category, there was a disadvantage with alpelisib in combination with fulvestrant in relation to the dimension “social functioning” assessed by the EORTC QLQ-C30.

The endpoints on side effects consistently show statistically significant disadvantages. Overall, a significant disadvantage in side effects is noted for treatment with alpelisib in combination with fulvestrant compared with fulvestrant.

In the overall view, there was no statistically significant difference in overall survival for alpelisib in combination with fulvestrant, although there were disadvantages in terms of symptomatology, quality of life, and side effects. In terms of side effects overall, a significant disadvantage of treatment with alpelisib in combination with fulvestrant compared with fulvestrant was found.

For the above reasons, it can therefore be reasonably concluded that alpelisib in combination with fulvestrant for post-menopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast carcinoma with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastatic stage, has a lower benefit than the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind SOLAR-1 Phase III study.

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

The risk of bias at the study level is assessed to be low. Likewise, the risk of bias at the endpoint level is assessed as low.

For the results on severe AEs and morbidity, there is also a high degree of endpoint-specific reliability of data because of the large extent of the effects.

With regard to the results on health-related quality of life, the negative effect is based on the difference in only one of the investigated domains on health-related quality of life, which is why for the overall statement on health-related quality of life, there is assumed to be a low reliability of data.

Thus, in the overall view, the reliability of data for the minor benefit determined in the overall assessment is classified as an “indication”.

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage:

No data are available for the assessment of the additional benefit of alpelisib in combination with fulvestrant compared with the appropriate comparator therapy in men who have already received endocrine therapy in the locally advanced or metastatic stage. The characterisation of the study population shows that only one man was included in the SOLAR-1 study. There is no sufficient data basis to assess the additional benefit.

2.1.4 Summary of the assessment

This assessment refers to the benefit assessment of the new medicinal product Piqray® with the active ingredient alpelisib.

Alpelisib in combination with fulvestrant is approved for the treatment of post-menopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation when the disease has progressed after endocrine therapy as monotherapy.

In the therapeutic indication to be considered, five patient groups were distinguished:

a1) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are not present

a2) Post-menopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation; lung and/or liver metastases are present

a3) Men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the (neo-)adjuvant therapy situation

b1) Post-menopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

b2) Men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, which took place in the locally advanced or metastasised stage

Patient population a1)

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

- Ribociclib in combination with a non-steroidal aromatase inhibitor *or*
- Ribociclib in combination with fulvestrant *or*
- Anastrozole *or*
- Letrozole *or*
- Fulvestrant *or*
- Possibly tamoxifen if aromatase inhibitors are not suitable.

The pharmaceutical company presents results of the SOLAR-1 randomised controlled study comparing alpelisib in combination with fulvestrant with placebo in combination with fulvestrant. The results of a relevant sub-population of the study are used.

In the mortality category, the pre-specified subgroup analysis for the characteristic “lung and/or liver metastases” shows an effect modification in the endpoint overall survival for the overall population (patient population a1 and a2). Because of this, a separate assessment of the additional benefit is made depending on whether lung and/or liver metastases are present.

For patients without lung and/or liver metastases, there is no statistically significant difference in overall survival. An additional benefit in terms of overall survival is therefore not proven for this patient population.

The endpoints on symptomatology, quality of life, and side effects showed exclusively negative effects. In terms of side effects overall, a significant disadvantage of treatment with alpelisib in combination with fulvestrant compared with fulvestrant was found.

In the overall assessment, it can be reasonably concluded that alpelisib in combination with fulvestrant has a lower benefit than the appropriate comparator therapy.

The risk of bias is classified as low. Thus, an indication can be derived with regard to the reliability of data.

Overall, an indication of a minor benefit is thus found for alpelisib in combination with fulvestrant.

Patient population a2)

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

- Ribociclib in combination with a non-steroidal aromatase inhibitor *or*
- Ribociclib in combination with fulvestrant *or*
- Anastrozole *or*
- Letrozole *or*
- Fulvestrant *or*
- Possibly tamoxifen if aromatase inhibitors are not suitable.

The pharmaceutical company presents results of the SOLAR-1 randomised controlled study comparing alpelisib in combination with fulvestrant with placebo in combination with fulvestrant. The results of a relevant sub-population of the study are used.

In the mortality category, the pre-specified subgroup analysis for the characteristic “lung and/or liver metastases” shows an effect modification in the endpoint overall survival for the overall population (patient population a1 and a2). Because of this, a separate assessment of the additional benefit is made depending on whether lung and/or liver metastases are present.

For patients with lung and/or liver metastases, there is a statistically significant prolongation in overall survival, which is assessed as a relevant, but not conclusively quantifiable improvement.

This advantage is counterbalanced by exclusively negative effects in the endpoints on symptomatology, quality of life, and side effects. In terms of side effects overall, a significant disadvantage of treatment with alpelisib in combination with fulvestrant compared with fulvestrant was found.

In a balancing decision, the G-BA concluded that, in this case, the advantage in terms of overall survival does not outweigh the disadvantages overall. As a result, it is stated that an additional benefit for alpelisib in combination with fulvestrant is not proven.

Patient population a3)

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

A therapy according to the doctor’s instructions.

There are no data from the SOLAR-1 study on which to base the assessment of the patient population.

Thus, an additional benefit for alpelisib in combination with fulvestrant is not proven.

Patient population b1)

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

- Abemaciclib in combination with fulvestrant *or*

- Ribociclib in combination with fulvestrant *or*
- Tamoxifen *or*
- Anastrozole *or*
- Fulvestrant as monotherapy; only for patients with relapse or progress after anti-oestrogen treatment *or*
- Letrozole; only for patients with relapse or progress after anti--oestrogen treatment *or*
- Exemestane; only for patients with progress after anti-oestrogen treatment *or*
- Everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

The pharmaceutical company presents results of the SOLAR-1 randomised controlled study comparing alpelisib in combination with fulvestrant with placebo in combination with fulvestrant. The results of a relevant sub-population of the study are used.

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

In the morbidity category, there are predominantly disadvantages with alpelisib in combination with fulvestrant.

There is also a disadvantage with regard to the quality of life category.

The endpoints on side effects consistently show statistically significant disadvantages. In terms of side effects overall, a significant disadvantage of treatment with alpelisib in combination with fulvestrant compared with fulvestrant was found.

In the overall assessment, it can be reasonably concluded that alpelisib in combination with fulvestrant has a lower benefit than the appropriate comparator therapy.

The risk of bias is classified as low. Thus, an indication can be derived with regard to the reliability of data.

Overall, an indication of a minor benefit is thus found for alpelisib in combination with fulvestrant.

Patient population b2)

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

A therapy according to the doctor's instructions.

There are no data from the SOLAR-1 study on which to base the assessment of the patient population.

Thus, an additional benefit for alpelisib in combination with fulvestrant 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 in principle to the derivation of the target population used as a basis in the resolution on the benefit assessment of palbociclib (resolution of 18 May 2017) for the calculation of the number of patients.

However, because treatment with alpelisib, in contrast to palbociclib, is limited to patients already receiving previous endocrine monotherapy and who have a PIK3CA mutation, the target population was further narrowed using the proportional values provided by the pharmaceutical company.

Furthermore, as was already the case in the resolution on ribociclib of 20 August 2020, the use of more up-to-date data on the incidence and prevalence of breast cancer in Germany and the consideration of the current proportion of patients in the SHI target population of 87.7% result in further minor deviations.

The calculation of the number of men in the SHI target population is based on the calculation of the number of women. For the proportion of patients with PIK3CA mutation, the mean value of the range 11.8–36% was used despite uncertainties because of limited sources. Applying the proportional value of 0.9% men with breast carcinoma to all those affected with breast carcinoma used by the pharmaceutical company as well as applying the other proportional values used by the pharmaceutical company for HR-positive and HER2-negative breast carcinoma and for the SHI proportion and the proportion of patients with PIK3CA mutation, the patient numbers for men were recalculated.

This range takes into account the existing uncertainties in the data basis and reflects the minimum and maximum values obtained during derivation.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Piqray (active ingredient: alpelisib) at the following publicly accessible link (last access: 11 November 2020):

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

Treatment with alpelisib 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.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material. The training material for health professionals prescribing Piqray includes, in particular, instructions on the management of severe hyperglycaemia, including ketoacidosis, potentially occurring with alpelisib.

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 February 2021).

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

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

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Alpelisib	continuously, 2 × daily	365	1	365
plus fulvestrant				
Fulvestrant	Cycle 1: 1 × on Day 1, 15, and 29 From Cycle 2: 1 × monthly	14	1	14
Appropriate comparator therapy for patient populations a1) and a2)				
Ribociclib in combination with a non-steroidal aromatase inhibitor or with fulvestrant				
Ribociclib	On Day 1–21 of a 28-day cycle	13	21	273
Anastrozole	continuously, 1 × daily	365	1	365
Letrozole	continuously, 1 × daily	365	1	365
Fulvestrant	continuous, Cycle 1: 1 × on Day 1, 15, and 29 From Cycle 2: 1 × monthly	14	1	14
Anastrozole				
Anastrozole	continuously, 1 × daily	365	1	365
Letrozole				
Letrozole	continuously, 1 × daily	365	1	365
Fulvestrant				
Fulvestrant	continuous, Cycle 1: 1 x on Day 1 and 15	13	1	13

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	From Cycle 2: 1 × monthly			
Possibly tamoxifen				
Tamoxifen	continuously, 1 × daily	365	1	365
Appropriate comparator therapy for patient population a3)				
Therapy according to the doctor's instructions – Tamoxifen [a]				
	continuously, 1 × daily	365	1	365
Appropriate comparator therapy for patient population b1)				
Abemaciclib in combination with fulvestrant				
Abemaciclib	continuously, 2 × daily	365	1	365
Fulvestrant	Cycle 1: 1 x on Day 1 and 15 From Cycle 2: 1 × monthly	13	1	13
Ribociclib in combination with fulvestrant				
Ribociclib	On Day 1–21 of a 28-day cycle	13	21	273
Fulvestrant	Cycle 1: 1 x on Day 1, 15, and 29 From Cycle 2: 1 × monthly	14	1	14
Tamoxifen				
Tamoxifen	continuously, 1 × daily	365	1	365
Anastrozole				
Anastrozole	continuously, 1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Fulvestrant as monotherapy				
Fulvestrant	Cycle 1: 1 x on Day 1 and 15 From Cycle 2: 1 × monthly	13	1	13
Letrozole				
Letrozole	continuously, 1 × daily	365	1	365
Exemestane				
Exemestane	continuously, 1 × daily	365	1	365
Everolimus in combination with exemestane				
Everolimus	continuously, 1 × daily	365	1	365
Exemestane	continuously, 1 × daily	365	1	365
Appropriate comparator therapy for patient population b2)				
Therapy according to the doctor's instructions - Tamoxifen [a]				
	continuously, 1 × daily	365	1	365
[a] Costs are shown only for the active ingredient tamoxifen. In addition to tamoxifen, aromatase inhibitors in combination with a GnRH analogue and fulvestrant are also suitable comparators for the present benefit assessment in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products.				

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Alpelisib	300 mg	300 mg	2 × 150 mg	365	730 × 150 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
plus fulvestrant					
Fulvestrant	500 mg	500 mg	2 × 250 mg	14	28 × 250 mg
Appropriate comparator therapy for patient populations a1) and a2)					
Ribociclib in combination with a non-steroidal aromatase inhibitor or with fulvestrant					
Ribociclib	600 mg	600 mg	3 × 200 mg	273	819 × 200 mg
Anastrozole	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Fulvestrant	500 mg	500 mg	2 × 250 mg	14	28 × 250 mg
Anastrozole					
Anastrozole	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Letrozole					
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Fulvestrant					
Fulvestrant	500 mg	500 mg	2 × 250 mg	13	26 × 250 mg
Possibly tamoxifen					
Tamoxifen	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg
Appropriate comparator therapy for patient population a3)					
Therapy according to the doctor's instructions					
- Tamoxifen[a]	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg
Appropriate comparator therapy for patient population b1)					
Abemaciclib in combination with fulvestrant					
Abemaciclib	150 mg	300 mg	2 × 150 mg	365	730 × 150 mg
Fulvestrant	500 mg	500 mg	2 × 250 mg	13	26 × 250 mg
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 × 200 mg	273	819 × 200 mg
Fulvestrant	500 mg	500 mg	2 × 250 mg	14	28 × 250 mg
Tamoxifen					
Tamoxifen	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg
Anastrozole					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Anastrozole	1 mg	1 mg	1 × 1 mg	365	365 × 1 mg
Fulvestrant as monotherapy					
Fulvestrant	500 mg	500 mg	2 × 250 mg	13	26 × 250 mg
Letrozole					
Letrozole	2.5 mg	2.5 mg	1 × 2.5 mg	365	365 × 2.5 mg
Exemestane					
Exemestane	25 mg	25 mg	1 × 25 mg	365	365 × 25 mg
Everolimus in combination with exemestane					
Everolimus	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
Exemestane	25 mg	25 mg	1 × 25 mg	365	365 × 25 mg
Appropriate comparator therapy for patient population b2)					
Therapy according to the doctor's instructions - Tamoxifen[a]	20 mg	20 mg	1 × 20 mg	365	365 × 20 mg

[a] Costs are shown only for the active ingredient tamoxifen. In addition to tamoxifen, aromatase inhibitors in combination with a GnRH analogue and fulvestrant are also suitable comparators for the present benefit assessment in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products.

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Alpelisib	56 FCT	€ 6,383.56	€ 1.77	€ 361.29	€ 6,020.50
Fulvestrant	6 SFI	€ 1,895.93	€ 1.77	€ 90.00	€ 1,804.16
Appropriate comparator therapy					
Abemaciclib	168 FCT	€ 7,270.15	€ 1.77	€ 411.92	€ 6,856.46
Anastrozole[4]	100 FCT	€ 57.27	€ 1.77	€ 3.66	€ 51.84
Everolimus	30 TAB	€ 1,433.71	€ 1.77	€ 67.52	€ 1,364.42

[4] Fixed reimbursement rate

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Exemestane	100 FCT	€ 127.26	€ 1.77	€ 9.19	€ 116.30
Fulvestrant	6 SFI	€ 1,895.93	€ 1.77	€ 90.00	€ 1,804.16
Letrozole[4]	120 FCT	€ 61.40	€ 1.77	€ 3.98	€ 55.65
Ribociclib	189 FCT	€ 7,270.15	€ 1.77	€ 411.92	€ 6,856.46
Tamoxifen[4]	100 FCT	€ 22.19	€ 1.77	€ 0.88	€ 19.54
Abbreviations: FCT = film-coated tablets, SFI = solution for injection, TAB = tablets					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services:

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

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

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

3. Bureaucratic costs

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

4. Process sequence

At its session on 26 March 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

At the time of the consultation, the appropriate comparator therapy established by the G-BA was reviewed on the basis of the planned/applied for therapeutic indication. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 26 October 2020.

On 31 August 2020, the pharmaceutical company submitted a dossier for the benefit assessment of alpelisib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 September 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient alpelisib.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 November 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2020. The deadline for submitting written statements was 22 December 2020.

The oral hearing was held on 12 January 2021.

By letter dated 13 January 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 2 February 2021.

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 February 2021, and the proposed resolution was approved.

At its session on 18 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 March 2019	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	26 October 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	5 January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 January 2021 2 February 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 February 2021	Concluding discussion of the draft resolution
Plenum	18 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 18 February 2021

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

Prof. Hecken