Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Capivasertib (breast cancer, ER+, HER2-, PIK3CA/AKT1/PTEN alteration(s), after prior therapy, combination with fulvestrant)

of 3 April 2025

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 all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

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

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

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient capivasertib on 1 October 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 30 September 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2025 on the G-BA website (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 capivasertib 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 statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the

extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of capivasertib.

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

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

2.1.1 Approved therapeutic indication of Capivasertib (Truqap) in accordance with the product information

TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen.

In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

For men, administration of LHRH agonist according to current clinical practice standards should be considered.

Therapeutic indication of the resolution (resolution of 25.03.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Appropriate comparator therapy for capivasertib in combination with fulvestrant:

- Tamoxifen (only for premenopausal patients who have not received tamoxifen in previous (neo-)adjuvant endocrine therapy; only for postmenopausal patients if aromatase inhibitors are unsuitable)
  or
- letrozole
  or
- exemestane (only for patients with progression after anti-oestrogen treatment)
  or
- anastrozole
  or
- fulvestrant

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

or
- ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)
or
- abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)
or
- Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)
or
- ribociclib in combination with fulvestrant
or
- abemaciclib in combination with fulvestrant
or
- palbociclib in combination with fulvestrant

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Appropriate comparator therapy for capivasertib in combination with fulvestrant:

- tamoxifen
or
- Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Appropriate comparator therapy for capivasertib in combination with fulvestrant:

Individualised therapy, taking into account a change of endocrine therapy to

- tamoxifen
- letrozole
- exemestane
- anastrozole
- fulvestrant
- everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis, followed by progression after a non-steroidal aromatase inhibitor)
- ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)
- abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

- ribociclib in combination with fulvestrant
- abemaciclib in combination with fulvestrant
- palbociclib in combination with fulvestrant

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Appropriate comparator therapy for capivasertib in combination with fulvestrant:

Individualised therapy, taking into account a change of endocrine therapy to

- tamoxifen
- aromatase inhibitor in combination with a GnRH analogue
- fulvestrant
- Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. The anti-oestrogens tamoxifen, fulvestrant, elacestrant and toremifene and the aromatase inhibitors anastrozole, letrozole and exemestane are approved for this therapeutic indication. Other approved active ingredients are megestrol acetate, medroxyprogesterone acetate, leuprorelin, goserelin, the protein kinase inhibitors everolimus, abemaciclib, palbociclib, ribociclib and capivasertib and the PARP inhibitors olaparib and talazoparib.

The active ingredients alpelisib and toremifene are approved for this therapeutic indication, but are not available on the German market.

Medicinal products with explicit marketing authorisation for HER2-positive breast cancer are not considered here.

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

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

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:
- Elacestrant: resolution of 02.05.2024
- Abemaciclib: resolutions of 19.05.2022 and 15.06.2023
- Palbociclib: resolutions of 21.03.2019 and 15.12.2022
- Ribociclib: resolutions of 04.07.2019 and 20.08.2020
- Alpelisib (in combination with fulvestrant): resolution of 18.02.2021
- Olaparib: resolution of 16.01.2020
- Talazoparib: resolution of 20.11.2020

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the

comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

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

On 2 July 2024, the G-BA held an expert meeting with clinical experts and BfArM on the research question "Differences between pre- and postmenopausal patients with HR-positive breast cancer as well as natural and induced menopause". A written summary of this expert meeting is attached to the "Information on the appropriate comparator therapy" document. The expert meeting was used for the present determination of the appropriate comparator therapy as a further information basis for the assessment by the G-BA with regard to the research question of a subdivision into patient groups by menopausal status (pre-/perimenopausal and postmenopausal patients) in the appropriate comparator therapy. The expert meeting on specific medical questions in this regard, taking into account the marketing authorisation aspects, represents a necessary information basis that goes beyond the relevant information from the "Research and synopsis of the evidence for determining the appropriate comparator therapy according to Section 35a SGB V".

For the present therapeutic indication, it is assumed that an (if applicable, additional) endocrine therapy is indicated for the patients and in particular that there is no indication for chemotherapy for achieving a necessary, quick remission.

It is also assumed that pre-/perimenopausal patients receive ovarian suppression with a GnRH analogue.

In the view of the G-BA, there are patient populations to be considered separately for the present indication according to the current state of medical knowledge, which differ with regard to the treatment setting after previous endocrine therapy (adjuvant; locally advanced/ metastatic) and sex (women; men). Taking into account the results of the expert meeting, a subdivision into patient groups by menopausal status is not made. However, subgroup analyses regarding the biological menopausal status (pre-/perimenopausal; postmenopausal) must be presented. When determining the appropriate comparator therapy, a differentiation is thus made according to the following patient populations:

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

According to the available evidence, aromatase inhibitors show relevant significance for women who have not yet received therapy in locally advanced or metastatic stage. Therefore, the aromatase inhibitors letrozole, exemestane and anastrozole were determined as the appropriate comparator therapy. The restriction to patients with progression after anti-oestrogen treatment with exemestane reflects the authorisation status, whereby the term "progression" can also be considered to include a relapse after anti-oestrogen treatment according to the product information for exemestane.

Treatment with tamoxifen is considered for premenopausal women who have not received tamoxifen in previous (neo-)adjuvant endocrine therapy. In this regard, according to the available evidence, it should be noted that re-therapy may also be an option, depending on the time interval between re-therapy and a previous therapy with tamoxifen. In this regard, it is stated that premenopausal patients can be treated with tamoxifen in combination with cessation of ovarian function if previous tamoxifen therapy was terminated more than 12 months ago. Tamoxifen is an alternative for postmenopausal women if aromatase inhibitors are unsuitable.

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

The active ingredients anastrozole and fulvestrant are explicitly approved for use in postmenopausal women. According to information from the BfArM (on 22.10.2024), the marketing authorisations for anastrozole and fulvestrant do not formally exclude patients whose menopause has been induced by surgery or medication. The appropriate comparator therapies determined here with anastrozole or fulvestrant therefore include patients who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication.

The guidelines also recommend the CDK4/6 inhibitors abemaciclib, palbociclib and ribociclib in combination with endocrine therapy.

The CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) are approved in combination with either a non-steroidal aromatase inhibitor or fulvestrant. In pre-/perimenopausal women, treatment should be given in combination with an LHRH agonist in accordance with the marketing authorisation. For pre-/perimenopausal women, no additional benefit could be proven for any of these treatment options in the benefit assessments to date. The results of the benefit assessment procedures to date for the CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) for postmenopausal women can be summarised as follows: A hint for a minor additional benefit was shown for ribociclib in combination with letrozole in comparison with letrozole, while an indication of a minor additional benefit was shown for ribociclib in combination with fulvestrant in comparison with fulvestrant. A hint for a minor additional benefit of abemaciclib in combination with anastrozole or letrozole over anastrozole or letrozole was identified. In the benefit assessments of palbociclib and abemaciclib in combination with fulvestrant, no additional benefit could be proven in postmenopausal women.

The guidelines equally recommend all three currently approved CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) for both pre-/perimenopausal and postmenopausal women, or do not state any specific preference.

In the overall analysis, the G-BA considers the three CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) in the respectively approved combinations to be equally appropriate treatment options for women who have not yet received treatment in the locally advanced or metastatic stage.

No conclusions can be drawn on the basis of the available evidence with regard to a renewed therapy with a CDK4/6 inhibitor in locally advanced or metastatic stage after adjuvant therapy with a CDK4/6 inhibitor.

The appropriate comparator therapy determined here includes several therapy options. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be

considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

Any therapy option that is not restricted by the bracketed patient and disease characteristics can be used for demonstrating the additional benefit for the total population.

In contrast, the sole comparison with a therapy option that only represents a comparator therapy for part of the patient population is generally insufficient to demonstrate the additional benefit for the total population.

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Male breast cancer is a very rare disease; the incidence is about 0.5 - 1% of all diagnosed breast cancers. The evidence on treatment options for men with breast cancer is extremely limited.

The guidelines recommend CDK4/6 inhibitors in combination with aromatase inhibitors or fulvestrant for the treatment of men, partly depending on the previous therapy. In this therapeutic indication, only the CDK4/6 inhibitor palbociclib in combination with aromatase inhibitors is also approved for men.

For men, the guidelines also recommend the active ingredients tamoxifen, fulvestrant and aromatase inhibitors.

Aromatase inhibitors and fulvestrant are only approved for women in this indication. Accordingly, the use of aromatase inhibitors and fulvestrant in the patient group of men represents an off-label use. 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, against the background of an overall poor body of evidence[2,3], it cannot be inferred from the guidelines that the off-label use of fulvestrant and aromatase inhibitors + GnRH analogue would generally be preferable to the medicinal products previously approved for the patient group of men according to the generally recognised state of medical knowledge.

The requirements for exceptionally determining the off-label use of fulvestrant and aromatase inhibitors + GnRH analogue as appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) are therefore not met.

The appropriate comparator therapy determined here includes several therapy options. These therapeutic alternatives are equally appropriate for the comparator therapy.

[2] Burstein HJ, Somerfield MR, Barton DL, Dorris A, Fallowfield LJ, Jain D, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. J Clin Oncol 2021;39(35):3959-3977

[3] Hassett MJ, Somerfield MR, Giordano SH. Management of male breast cancer: ASCO guideline summary. JCO Oncol Pract 2020;16(8):e839-e843

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

In the event of disease progression on or after previous endocrine therapy, the available evidence recommends further endocrine therapy using an alternative active ingredient. Anti-oestrogens, oestrogen receptor antagonists, aromatase inhibitors and the mTOR inhibitor everolimus as well as the CDK4/6 inhibitors abemaciclib, palbociclib and ribociclib are mentioned as potential treatment options.

The active ingredients anastrozole, fulvestrant and everolimus are explicitly approved for use in postmenopausal women. According to information from the BfArM (on 22.10.2024), the marketing authorisations for anastrozole, fulvestrant and everolimus do not formally exclude patients whose menopause has been induced by surgery or medication. The appropriate comparator therapies determined here with anastrozole, fulvestrant or everolimus therefore include patients who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication.

Treatment with everolimus in combination with exemestane is limited to patients without symptomatic visceral metastasis, followed by progression after a non-steroidal aromatase inhibitor, which reflects the authorisation status.

The available evidence for the progestogens, which are also approved, is considered inadequate in relation to the other treatment options to determine them as an appropriate comparator therapy.

The marketing authorisations for fulvestrant, letrozole and exemestane only provide for use in this therapeutic indication after prior anti-oestrogen treatment. Accordingly, the use of fulvestrant, letrozole and exemestane after previous aromatase inhibitor treatment, constitutes an off-label use.

In this regard, the available guidelines[2] show that a change of the substance class used is recommended as an essential part of the therapy algorithm in the context of endocrine therapy of advanced HR-positive breast cancer. Against this background, when determining the appropriate comparator therapy, the G-BA specifically focussed on a change in endocrine therapy, naming the corresponding active ingredients.

In the case of prior therapy with an aromatase inhibitor, the guidelines[2] recommend switching to treatment with an anti-oestrogen or an oestrogen receptor antagonist. In this regard, the guidelines specifically state that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors. This fact was also presented in the statements submitted by medical experts in the benefit assessment procedures of the G-BA already carried out in this therapeutic indication.

With regard to the use of the aromatase inhibitors letrozole and exemestane, it is also clear from the available guidelines[2] that the change of aromatase inhibitor from a steroidal to a non-steroidal aromatase inhibitor or vice versa is also explicitly recommended in the treatment algorithm for this therapeutic indication.

For the indication area following prior therapy with a non-steroidal aromatase inhibitor, monotherapy with the steroidal aromatase inhibitor exemestane is therefore adequate in view of the guideline recommendations[2].

It should also be taken into account that the use of a (renewed) therapy with a non-steroidal aromatase inhibitor after a possible previous therapy with a non-steroidal

aromatase inhibitor in combination with a CDK4/6 inhibitor is considered implausible in the sense of the standard case according to the current state of medical knowledge. This also applies to the indication area after previous therapy with a steroidal aromatase inhibitor in combination with a CDK4/6 inhibitor with regard to (renewed) therapy with the steroidal aromatase inhibitor exemestane.

Overall, it can therefore be concluded that the use of fulvestrant, letrozole and exemestane for the indication area after previous therapy with an endocrine therapy other than anti-oestrogens, in particular after previous therapy with aromatase inhibitors, should generally be preferred to the approved endocrine therapies, in accordance with Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). Therefore, it is appropriate to determine the above-mentioned active ingredients in the off-label use for this indication area as the appropriate comparator therapy.

The CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) in combination with a non-steroidal aromatase inhibitor or fulvestrant are also approved treatment options for women with locally advanced or metastatic breast cancer following previous endocrine therapy in the therapeutic indication. In pre-/perimenopausal women, treatment should be given in combination with an LHRH agonist in accordance with the marketing authorisation.

According to the recommendations of the guidelines, endocrine-based therapy with a CDK4/6 inhibitor should be carried out either in combination with an aromatase inhibitor or with fulvestrant, even after endocrine therapy has already been carried out, if CDK4/6 inhibitors have not been used before. According to the available evidence, re-therapy with a CDK4/6 inhibitor is not considered.

For pre-/perimenopausal women, no additional benefit could be proven for any of these treatment options in the benefit assessments to date. The results of the benefit assessment procedures to date for the CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) for postmenopausal women in the therapeutic indication can be summarised as follows: For postmenopausal women with previous endocrine therapy, ribociclib in combination with fulvestrant presents a hint for a minor additional benefit compared with fulvestrant, and abemaciclib in combination with fulvestrant was found to have an indication of a minor additional benefit compared with fulvestrant. In the benefit assessments of palbociclib in combination with a non-steroidal aromatase inhibitor or fulvestrant and of ribociclib in combination with an aromatase inhibitor, no additional benefit could be proven in postmenopausal women with previous endocrine therapy.

The guidelines equally recommend all three currently approved CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) for both pre-/perimenopausal and postmenopausal women, or do not state any specific preference.

Therefore, the G-BA considers the three CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) in the respectively approved combinations to be equally suitable treatment options for women with disease progression on or after endocrine therapy which was carried out in the locally advanced or metastatic stage.

In summary, the appropriate comparator therapy is determined to be an individualised therapy considering a change of endocrine therapy to tamoxifen, letrozole, exemestane, anastrozole, fulvestrant, everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis followed by progression after a non-steroidal aromatase inhibitor), ribociclib in combination with a non-

steroidal aromatase inhibitor (anastrozole, letrozole), abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole), palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole), ribociclib in combination with fulvestrant, abemaciclib in combination with fulvestrant and palbociclib in combination with fulvestrant.

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available. However, for the present patient population, individualised therapy can also be carried out using an active ingredient as the sole comparator therapy, taking into account the previous therapy and provided that a change in treatment has taken place with regard to the active ingredients used for the initial endocrine therapy, thus enabling proof of additional benefit in the total population.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Male breast cancer is a very rare disease; the incidence is about 0.5 - 1% of all diagnosed breast cancers. The evidence on treatment options for men with breast cancer is extremely limited.

The active ingredients tamoxifen, fulvestrant, aromatase inhibitors + GnRH analogue as well as CDK4/6 inhibitors are recommended in the guidelines[2,3] for the patient group of men. In this therapeutic indication, only tamoxifen and the CDK4/6 inhibitor palbociclib in combination with aromatase inhibitors are approved for men. However, aromatase inhibitors and fulvestrant are only approved for use in women. Accordingly, the use of aromatase inhibitors and fulvestrant in the patient group of men represents an off-label use.

With regard to the approved active ingredient tamoxifen, it can be assumed that the vast majority of patients have already received treatment with tamoxifen at an earlier stage of the disease or earlier in the treatment sequence.

The available guidelines also indicate that a change of substance class is recommended as an essential part of the treatment algorithm for endocrine therapy of advanced HR-positive breast cancer. According to the available evidence, re-therapy with a CDK4/6 inhibitor is not considered.

In view of the therapy algorithm, this results in a relevant indication for the patient group of men in the present therapeutic indication, for which the authorised medicinal products are not considered for the reasons mentioned above. In this therapeutic indication, the use of fulvestrant and aromatase inhibitors + GnRH analogue should therefore generally be preferred to tamoxifen and palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole), in accordance with Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). It is therefore appropriate to determine the off-label use of the above-mentioned medicinal products as appropriate comparator therapy.

In summary, the appropriate comparator therapy is determined to be an individualised therapy, taking into account a change of endocrine therapy to tamoxifen, aromatase inhibitors in combination with a GnRH analogue, fulvestrant and palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole).

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available. However, for the present patient population, individualised therapy can also be carried out using an active ingredient as the sole comparator therapy, taking into account the previous therapy and provided that a change in treatment has taken place with regard to the active ingredients used for the initial endocrine therapy, thus enabling proof of additional benefit in the total population.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

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

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

2.1.3 Extent and probability of the additional benefit

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

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

An additional benefit is not proven.

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

An additional benefit is not proven.

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Indication of a considerable additional benefit.

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

An additional benefit is not proven.

Justification:

For the proof of additional benefit of capivasertib, the pharmaceutical company presented the results of the CAPItello-291 and FAKTION studies.

CAPItello-291 study

The CAPItello-291 study is an ongoing, multicentre, phase III randomised controlled trial (RCT) comparing capivasertib in combination with fulvestrant versus placebo in combination with fulvestrant.

The study has been conducted in 181 study sites in Europe, North and South America, Asia and Australia since June 2020.

Adult patients (pre-/perimenopausal and postmenopausal) and patients with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, unresectable, locally advanced or metastatic breast cancer were enrolled in the study. Patients had to have a recurrence or progression on or after treatment with an aromatase inhibitor. If neoadjuvant or adjuvant therapy has taken place, a recurrence or progression must have occurred on therapy or within 12 months of the end of therapy. In addition, the study participants were not allowed to have received more than 2 previous lines of endocrine therapy and no more than 1 previous line of chemotherapy in the unresctable, locally advanced or metastatic stage.

The PIK3CA/AKT1/PTEN alteration status was determined by means of a test at the time of enrolment in the study.

Patients were randomised in a 1:1 ratio and stratified according to the characteristics of liver metastases, previous therapy with cyclin-dependent kinase (CDK)4/6 inhibitors, and by geographical location.

The CAPItello-291 study comprises a global cohort and a China extension cohort, which recruited additional patients in China and Taiwan post randomisation of the global cohort. A total of 708 patients were enrolled in the global cohort. The relevant sub-population with PIK3CA/AKT1/PTEN alterations according to the marketing authorisation of capivasertib comprises 155 patients in the intervention arm and 134 in the comparator arm of the global cohort. A total of 134 patients were enrolled in the China extension cohort. The relevant sub-population with PIK3CA/AKT1/PTEN alterations comprises 24 patients in the intervention arm and 22 patients in the comparator arm. Chinese and Taiwanese patients who were randomised into the extension cohort before the planned end of recruitment of the global cohort are part of both the global cohort and the extension cohort.

In addition to the primary endpoint of progression-free survival (PFS), overall survival and endpoints in the categories of morbidity, health-related quality of life and side effects were also assessed. Furthermore, the PFS2 was assessed as part of the study.

In the CAPItello-291 study, a data cut-off was collected for the global cohort on 15.08.2022 (primary PFS data cut-off) and on 27.03.2023 (safety data cut-off) respectively. The primary PFS data cut-off of the extension cohort was performed on 08.05.2023.

As part of the written statement procedure, data which included postmenopausal patients and patients defined as pre-/perimenopausal in the studies were subsequently submitted for patient groups a1 and b1, and the two cohorts of the CAPItello-291 study were subject to meta-analytic summary at the patient-individual data level. A PIK3CA/AKT1/PTEN-altered sub-population with 16 patients in the control arm and 28 patients in the intervention arm is considered for patient group a1, and a PIK3CA/AKT1/PTEN-altered sub-population with 124 patients in the control arm and 156 patients in the intervention arm is considered for patient group b1. The subsequently submitted analyses of the AEs for the global cohort are based on the pre-specified data cut-off from 15.08.2022. The data subsequently submitted are used for the benefit assessment.

FAKTION study

The ongoing FAKTION study is a 2-part study with an initial dose escalation phase followed by a double-blind, multicentre phase II study. The randomised part of the study in which capivasertib in combination with fulvestrant was compared with placebo in combination with fulvestrant was used in the benefit assessment.

The study has been ongoing in the UK since March 2015.

Adult postmenopausal patients with ER-positive, HER2-negative, unresectable, locally advanced or metastatic breast cancer were enrolled. Patients should show disease progression during treatment with an aromatase inhibitor in the locally advanced or metastatic stage or a recurrence of metastatic disease during treatment with an aromatase inhibitor in the adjuvant treatment setting. In addition, the study participants were not allowed to have received more than 3 previous lines of endocrine therapy and no more than 1 previous line of chemotherapy in the unresctable, locally advanced or metastatic stage.

The PIK3CA/AKT1/PTEN alteration status was determined using various tests and a pre-specified, additional analysis of the samples for further relevant mutations of the PIK3CA/AKT1/PTEN signalling pathway was carried out for the publication Howell et al. The patient population identified by means of extended testing was submitted by the pharmaceutical company and used for the benefit assessment.

Patients were randomised in a 1:1 ratio, based on PIK3CA alteration status, PTEN expression status, measurable vs non-measurable disease and primary vs secondary resistance to an aromatase inhibitor of the 3rd generation.

The PIK3CA/AKT1/PTEN-altered sub-population with 37 patients in the control arm and 39 patients in the intervention arm is considered for the present benefit assessment.

In addition to the primary endpoint PFS, overall survival and endpoints on side effects were also assessed.

In the FAKTION study, data was collected on 30.01.2019 and 25.11.2021. The pharmaceutical company presented analyses of the publication by Howell et al. at the data cut-off from 25.11.2021; these analyses were used for the present benefit assessment.

On the implementation of the appropriate comparator therapy for patient groups b1) and b2)

The pharmaceutical company used fulvestrant as a comparator. In the CAPItello-291 study, patients were pretreated with aromatase inhibitors, CDK4/6 inhibitors or tamoxifen. For enrolment in the FAKTION study, patients had to show disease progression or recurrence on treatment with an aromatase inhibitor. The prerequisite that a change of treatment has taken place with regard to the active ingredients used for the initial endocrine therapy has been fulfilled by the fulvestrant treatment. Therefore, the use of fulvestrant for both patient groups

is considered to be an adequate implementation of individualised therapy, taking into account a change in endocrine therapy.

Extent and probability of the additional benefit

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

The results for this patient group are based on the analyses of the CAPItello-291 study.

Mortality

Overall survival is defined in the CAPItello-291 study as the time between randomisation and death from any cause. Overall survival was the secondary endpoint in the study.

There was no statistically significant difference in terms of overall survival of the female patients in the CAPItello-291 study. The median survival has not yet been reached due to the low number of events.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the CAPItello-291 study. It is defined as the time from randomisation to the first RECIST 1.1-defined radiological disease progression or death from any cause without prior progression, regardless of whether the female patient discontinued therapy or received other antineoplastic therapy prior to progression.

For the PFS, there was a statistically significant difference to the advantage of capivasertib in combination with fulvestrant compared to fulvestrant.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The mortality endpoint component is already assessed via the overall survival endpoint as an independent endpoint. The morbidity component is assessed according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The available data on morbidity and health-related quality of life are used to interpret the PFS results. These results are potentially relevant in the present case because radiologically disease progression may be associated to effects on morbidity and/or quality of life.

The prolonged PFS with capivasertib in combination with fulvestrant was not associated with an advantage in terms of morbidity or quality of life in the CAPItello-291 study.

In summary, the available data do not indicate that the statistically significant prolonged time of progression-free survival with capivasertib in combination with fulvestrant – radiologically determined disease progression according to RECIST criteria – is associated with an improvement in morbidity or health-related quality of life.

The results for the PFS endpoint are not used in the present assessment.

Symptomatology

EORTC QLQ-C30 and EORTC QLQ-BR23

Disease symptomatology was surveyed in the CAPItello-291 study using the EORTC QLQ-C30 questionnaire and the EORTC QLQ-BR23 additional module. The evaluations on the time to first deterioration by ≥ 10 points is used for the benefit assessment.

For the endpoint of diarrhoea, there was a statistically significant difference to the disadvantage of capivasertib in combination with fulvestrant compared to fulvestrant.

There were no differences for the other symptoms of fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss and constipation, surveyed using the EORTC QLQ-C30, as well as the side effects of systemic therapy, chest symptoms and arm symptoms, surveyed using the EORTC QLQ-BR23. No suitable data were available for the symptom of burden due to hair loss.

PGIS

No suitable data were available for the endpoint of symptomatology assessed using PGIS.

Health status

EQ-5D, visual analogue scale

The health status was surveyed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

For health status surveyed using EQ-5D VAS, there was no statistically significant difference between the treatment arms.

PGIC

No suitable data were available for the endpoint of health status surveyed using PGIC.

In the endpoint category of morbidity, a disadvantage was identified due to the negative effect on the endpoint of diarrhoea.

Quality of life

Health-related quality of life was surveyed in the CAPItello-291 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. The evaluations on the time to first deterioration by ≥ 10 points is used for the benefit assessment.

There was no statistically significant difference for the scales of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning, surveyed using the EORTC QLQ-C30, as well as the scales of body image, sexual activity and future prospects, surveyed using the EORTC QLQ-BR23.

No suitable data were available for the sexual pleasure scale, surveyed using the EORTC QLQ BR23, as no baseline or post-baseline score was available for 81% or 93% of patients.

With regard to health-related quality of life, there was no overall advantage or disadvantage of capivasertib in combination with fulvestrant.

Side effects

Adverse events (AEs) in total

In the CAPItello-291 study, one AE occurred in all patients in the capivasertib arm and in 80% of patients in the control arm respectively. The results were only presented additionally.

Serious AEs (SAEs) and severe AEs

There were no statistically significant differences between the treatment groups for the endpoint of SAEs and severe AEs.

Therapy discontinuation due to AEs and PRO-CTCAE

No information is available as to whether therapy discontinuation due to AEs involves the discontinuation of at least one or all active ingredient(s). The results are unsuitable for the benefit assessment due to the absence of data on discontinuations separately for each active ingredient.

The PRO-CTCAE questionnaire is not used to depict the symptomatic AEs of capivasertib and fulvestrant due to the non-transparent selection process and the incomprehensible selection of items.

Specific AEs

Diarrhoea (AEs), maculopapular rash (AEs), stomatitis (AEs), gastrointestinal disorders (severe AEs)

For the endpoints of diarrhoea, maculopapular rash and stomatitis as well as for the endpoint of gastrointestinal disorders, there was a statistically significant difference between the treatment groups to the disadvantage of capivasertib in combination with fulvestrant.

With regard to side effects, there is no overall advantage or disadvantage of capivasertib in combination with fulvestrant.

Overall assessment

Results on mortality, morbidity, health-related quality of life and side effects from the CAPItello-291 study were available for the assessment of the additional benefit of capivasertib in patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), after recurrence of the disease on or after (neo-)adjuvant endocrine therapy and who have not yet received treatment in the locally advanced or metastatic stage. In this multicentre, randomised, controlled phase III study, capivasertib in combination with fulvestrant was compared with placebo in combination with fulvestrant.

The results for the overall survival endpoint showed no statistically significant difference.

In the endpoint category of morbidity, symptomatology (EORTC QLQ-C30 and -BR23) and health status (EQ-5D VAS, PGIC) were surveyed. In this respect, there was a statistically significant disadvantage for capivasertib in combination with fulvestrant for the diarrhoea symptom.

For health-related quality of life (EORTC QLQ-C30 and -BR23), neither an advantage nor a disadvantage of capivasertib in combination with fulvestrant was identified.

With regard to the endpoints of SAEs and severe AEs, there were no differences between the treatment groups and no suitable data were available for the endpoint of therapy discontinuation due to AEs. No suitable data were available for the PRO-CTCAE questionnaire either. In detail, there were disadvantages in the specific AEs. No advantage or disadvantage was identified in the side effects category.

In the overall analysis, the G-BA concludes that an additional benefit of capivasertib in combination with fulvestrant compared to placebo in combination with fulvestrant is not proven for the treatment of patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), after recurrence of the

disease on or after (neo-)adjuvant endocrine therapy and who have not previously received treatment in the locally advanced or metastatic stage.

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

The pharmaceutical company did not submit any data for the assessment of the additional benefit of capivasertib in comparison with the appropriate comparator therapy.

The G-BA therefore concludes that an additional benefit of capivasertib in combination with fulvestrant compared to placebo in combination with fulvestrant is not proven in men with PIK3CA/AKT1/PTEN alteration(s), ER-positive, HER2-negative, locally advanced or metastatic breast cancer and recurrence of the disease on or after (neo-)adjuvant endocrine therapy, who have not previously received treatment in the locally advanced or metastatic stage.

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

For this patient group, the results for overall survival and PFS are based on the CAPItello-291 and FAKTION studies. A meta-analytic summary of the data was performed for the two endpoints, with 156 patients in the intervention arm and 124 patients in the control arm of the CAPItello-291 study and 39 patients in the intervention arm and 37 patients in the control arm of the FAKTION study.

No suitable data on the endpoint categories of morbidity, health-related quality of life or side effects were available from the FAKTION study, or the endpoints were not assessed. For the other endpoints, only results from the CAPItello-291 study are therefore available.

On the meta-analytic evaluation of the CAPItello-291 and FAKTION studies

With regard to the meta-analytical summary, it should be noted that the CAPItello-291 and FAKTION studies differ with regard to various inclusion criteria. For example, there are differences with regard to the definition of the ER-positive characteristic and also with regard to previous therapy with CDK4/6 inhibitors. The two studies also differ with regard to the identification of patients who are to be assigned to the respective PIK3CA/AKT1/PTEN-altered sub-population. However, these differences do not preclude a meta-analytic summary of the two studies.

The start of capivasertib therapy delayed by 14 days compared to fulvestrant in the intervention arm of the FAKTION study in comparison with the CAPItello-291 study also does not preclude a meta-analytic summary, as it is not assumed that the delayed start of treatment with capivasertib has a significant influence on the results of the "overall survival" endpoint.

A meta-analytic summary of the results of the global cohort and the extension cohort of the CAPItello-291 study and the FAKTION study is considered appropriate and used despite the differences described.

Mortality

In the CAPItello-291 and FAKTION studies, overall survival was defined as the time between randomisation and death from any cause. In both studies, overall survival was a secondary endpoint.

The meta-analytic evaluation showed a statistically significant difference between the treatment arms to the advantage of capivasertib in combination with fulvestrant for the endpoint of overall survival. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the CAPItello-291 and FAKTION studies. It is defined as the time from randomisation to the first RECIST 1.1-defined radiological disease progression or death from any cause without prior progression, regardless of whether the female patient discontinued therapy or received other antineoplastic therapy prior to progression.

There was no statistically significant difference between the treatment groups for the PFS endpoint.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The mortality endpoint component is already assessed via the overall survival endpoint as an independent endpoint. The morbidity component is assessed according to RECIST criteria and thus predominantly by means of imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS.

The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

EORTC QLQ-C30 and EORTC QLQ-BR23

Disease symptomatology was surveyed in the CAPItello-291 study using the EORTC QLQ-C30 questionnaire and the EORTC QLQ-BR23 additional module. The evaluations on the time to first deterioration by ≥ 10 points is used for the benefit assessment.

For the constipation symptom, there was a statistically significant advantage of capivasertib in combination with fulvestrant.

For the symptoms of appetite loss, diarrhoea as well as nausea and vomiting, there was a statistically significant difference to the disadvantage of capivasertib in combination with fulvestrant compared with fulvestrant.

Neither advantages nor disadvantages were identified for the other symptoms of fatigue, pain, dyspnoea and insomnia, surveyed using the EORTC QLQ-C30, as well as side effects of systemic therapy, chest symptoms and arm symptoms, surveyed using the EORTC QLQ-BR23. No suitable data were available for the symptom of burden due to hair loss.

PGIS

No suitable data were available for the endpoint of symptomatology assessed using PGIS.

Health status

EQ-5D, visual analogue scale

The health status was surveyed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

For the health status, there was no statistically significant difference between the treatment arms.

PGIC

No suitable data were available for the endpoint of health status surveyed using PGIC.

In the endpoint category of morbidity, an overall disadvantage was identified due to the negative effects.

Quality of life

Health-related quality of life was surveyed in the CAPItello-291 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. The evaluations on the time to first deterioration by ≥ 10 points is used for the benefit assessment.

For the endpoint of social functioning, there was a statistically significant difference between the treatment groups to the disadvantage of capivasertib in combination with fulvestrant.

There was no statistically significant difference for the scales of global health status, physical functioning, role functioning, emotional functioning and cognitive functioning, assessed using the EORTC QLQ-C30, as well as the scales of body image, sexual activity and future prospects, surveyed using the EORTC QLQ-BR23.

No suitable data were available for the sexual pleasure scale, surveyed using the EORTC QLQ BR23, as no baseline or post-baseline score was available for 83% or 81% of patients.

With regard to health-related quality of life, neither an advantage nor a disadvantage of capivasertib in combination with fulvestrant was derived.

Side effects

Adverse events (AEs) in total

In the CAPItello-291 study, one AE occurred in almost all patients in the capivasertib arm and in 85% of patients in the control arm respectively. The results were only presented additionally.

Serious AEs (SAEs)

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

Severe AEs

With regard to severe AEs, there was a statistically significant difference between the treatment groups to the disadvantage of capivasertib in combination with fulvestrant.

Therapy discontinuation due to AEs and PRO-CTCAE

No information is available as to whether therapy discontinuation due to AEs involves the discontinuation of at least one or all active ingredient(s). The results are unsuitable for the benefit assessment due to the absence of data on discontinuations separately for each active ingredient.

The PRO-CTCAE questionnaire is not used to depict the symptomatic AEs of capivasertib and fulvestrant due to the non-transparent selection process and the incomprehensible selection of items.

Specific AEs

Diarrhoea (AEs and severe AEs), maculopapular rash (AEs and severe UEs), stomatitis (AEs), nausea (AEs)

For the endpoints of diarrhoea, maculopapular rash, stomatitis and nausea, there was a statistically significant difference to the disadvantage of capivasertib in combination with fulvestrant.

In terms of side effects, there was an overall disadvantage of capivasertib in combination with fulvestrant.

Overall assessment

Results on mortality, morbidity, health-related quality of life and side effects were available for the assessment of the additional benefit of capivasertib in patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy, which took place in the locally advanced or metastatic stage. A meta-analytic evaluation of the CAPItello-291 and FAKTION studies was performed for the endpoints of overall survival and PFS. Results from the CAPItello-291 study were available for the other endpoints.

The results for the overall survival endpoint show a statistically significant difference to the advantage of capivasertib in combination with fulvestrant, which is considered a significant improvement.

In the endpoint category of morbidity, symptomatology (EORTC QLQ-C30 and -BR23) and health status (EQ-5D VAS, PGIC) were surveyed. There was a statistically significant advantage of capivasertib in combination with fulvestrant compared to fulvestrant for the symptom of constipation and there were statistically significant disadvantages for the symptoms of appetite loss, diarrhoea as well as nausea and vomiting. Overall, a disadvantage of capivasertib in combination with fulvestrant was therefore identified.

With regard to health-related quality of life (EORTC QLQ-C30 and -BR23), neither an advantage nor a disadvantage of capivasertib in combination with fulvestrant was identified.

For the endpoint of serious AEs, there was no difference between the treatment groups. With regard to severe AEs, there was a disadvantage of capivasertib in combination with fulvestrant. No suitable data on therapy discontinuation due to AEs and PRO-CTCAE were available. In detail, there were disadvantages in the specific AEs. In the category of side effects, one disadvantage was therefore derived overall.

In the overall analysis, the positive effect in overall survival is offset by negative effects in the endpoint categories of morbidity and side effects. The overall assessment when weighing up the disadvantages is that they do not call into question the extent of the additional benefit due to the significant improvement in overall survival.

The G-BA concluded the presence of a considerable additional benefit of capivasertib in combination with fulvestrant compared with fulvestrant for the treatment of women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy, which took place in the locally advanced or metastatic stage.

Reliability of data (probability of additional benefit)

For the present patient group b1, the results for overall survival and PFS are based on the results of the CAPItello-291 and FAKTION studies. A meta-analytic summary of the data was performed for the two endpoints.

For the other endpoints, only results from the CAPItello-291 study were available.

The risk of bias at study level is rated as low overall for the CAPItello-291 and FAKTION studies.

The risk of bias for the endpoint of overall survival from the CAPItello-291 study is rated as low, whereas it is rated as high in the FAKTION study due to the lack of information on subsequent therapies.

For the patient-reported endpoints on symptomatology, health status and health-related quality of life, the risk of bias is rated as high, as no baseline value or no value was available for some of the patients during the course of the study and the percentage differs between the arms.

In summary, the G-BA derives an indication for the identified additional benefit with regard to the significance.

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

The CAPItello-291 study can generally be considered for a direct comparison between capivasertib in combination with fulvestrant and the appropriate comparator therapy. However, only 2 men in the intervention arm of the global cohort were enrolled in the study, so that no statements on an additional benefit are possible based on this evidence.

The G-BA therefore concluded that an additional benefit of capivasertib in combination with fulvestrant compared with placebo in combination with fulvestrant is not proven for the treatment of men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy, which took place in the locally advanced or metastatic stage.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Truqap with the active ingredient capivasertib.

Capivasertib is indicated for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen.

In the therapeutic indication under consideration, 4 patient groups were differentiated according to their sex (women or men) and the time of recurrence or progression of the disease (on or after (neo-)adjuvant endocrine therapy, no treatment to date in the locally advanced or metastatic stage or progression of the disease on or after endocrine therapy which took place in the locally advanced or metastatic stage).

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

The G-BA determined fulvestrant as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presented the CAPItello-291 RCT, which compared capivasertib in combination with fulvestrant with placebo in combination with fulvestrant.

There was no statistically significant difference for the overall survival.

In the morbidity category, symptomatology (EORTC QLQ-C30 and -BR23) and health status (EQ-5D VAS, PGIC) were surveyed. In this respect, there was a statistically significant disadvantage for the diarrhoea symptom.

Neither an advantage nor a disadvantage was found for health-related quality of life (EORTC QLQ-C30 and -BR23).

With regard to the endpoints of SAEs and severe AEs, there were no differences in each case and no suitable data were available for therapy discontinuation due to AEs. No suitable data were available for the PRO-CTCAE questionnaire either. In detail, there were disadvantages in the specific AEs. No advantage or disadvantage was identified in the side effects category.

In the overall analysis, the G-BA concludes that an additional benefit of capivasertib in combination with fulvestrant compared with placebo in combination with fulvestrant is not proven.

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

The G-BA determined tamoxifen or palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole) as the appropriate comparator therapy.

No data were available for the assessment of the additional benefit.

The G-BA therefore concludes that an additional benefit of capivasertib in combination with fulvestrant compared with placebo in combination with fulvestrant is not proven.

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

The G-BA determined fulvestrant as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presented the RCTs CAPItello-291 and FAKTION, which compared capivasertib in combination with fulvestrant with placebo in combination with fulvestrant. In addition, a meta-analytic summary of both studies for overall survival and PFS was presented.

With regard to overall survival, there was a statistically significant difference to the advantage of capivasertib in combination with fulvestrant, which is considered a significant improvement.

For the morbidity category, symptomatology (EORTC QLQ-C30 and -BR23) and health status (EQ 5D VAS, PGIC) were surveyed. There was a statistically significant advantage for the constipation symptom and there were statistically significant disadvantages for the symptoms of appetite loss, diarrhoea as well as nausea and vomiting. Overall, a disadvantage was therefore identified.

Neither an advantage nor a disadvantage was found for health-related quality of life (EORTC QLQ-C30 and -BR23).

There was no difference for the endpoint of serious AEs and no suitable data were available for therapy discontinuation due to AEs. With regard to severe AEs, there was a disadvantage of capivasertib in combination with fulvestrant. No appropriate data were available for the PRO-CTCAE questionnaire. In detail, there were disadvantages in the specific AEs. In the category of side effects, one disadvantage was therefore derived overall.

In the overall analysis, the positive effect in overall survival is offset by negative effects in the endpoint categories of morbidity and side effects. The overall assessment when weighing up the disadvantages is that they do not call into question the extent of the additional benefit due to the significant improvement in overall survival.

The G-BA concludes the presence of an indication of a considerable additional benefit of capivasertib in combination with fulvestrant compared with placebo in combination with fulvestrant.

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

The G-BA determined fulvestrant as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presented the CAPItello-291 RCT, which compared capivasertib in combination with fulvestrant with fulvestrant.

However, only 2 men were enrolled in the CAPItello-291 study, so that no statements on an additional benefit can be made based on this evidence.

The G-BA therefore concludes that an additional benefit of capivasertib in combination with fulvestrant compared with placebo 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).

The G-BA base their resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The information provided by the pharmaceutical company for patient groups a1 and b1 is subject to uncertainties due to the unclear transferability of various percentage values, a lack of restriction of the target population to patients with progression or recurrence on or after endocrine therapy and an uncertain operationalisation of the suitability of another endocrine therapy. Patients from previous years with progression to the locally advanced or metastatic stage are not considered for the lower limit of the patient numbers. Patient groups a2 and b2 are also subject to uncertainties in the stated patient numbers, as the pharmaceutical company transfers the percentage values for women to men and the transferability is unclear.

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 Truqap (active ingredient: capivasertib) at the following publicly accessible link (last access: 05 February 2025):

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

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

Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with capivasertib based on the presence of one or more PIK3CA/AKT1/PTEN alteration(s), which should be detected using a CE-marked IVD with the appropriate intended use. If a CE-marked IVD is not available, an alternative validated test must be used.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 01 March 2025).

The costs for the first year of treatment are shown for the cost representation in the resolution.

For the patient population b1, the use of fulvestrant, letrozole and exemestane, in particular after previous aromatase inhibitor treatment, constitutes an off-label use. The cost representation is based on the guideline[4].

In the patient populations a2) and b2), aromatase inhibitors and fulvestrant are only approved for women in the present indication. The cost representation is based on the guidelines[4,5].

Treatment period:

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

[4] Burstein HJ, Somerfield MR, Barton DL, Dorris A, Fallowfield LJ, Jain D, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. J Clin Oncol 2021;39(35):3959-3977.

[5] Hassett MJ, Somerfield MR, Giordano SH. Management of male breast cancer: ASCO guideline summary. JCO Oncol Pract 2020;16(8):e839-e843.

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Capivasertib	Continuously, 2 x daily on day 1 - 4 of a 7-day cycle	52.1	4	208.4
Fulvestrant	Continuously, cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0
Appropriate comparator therapy				
Anti-oestrogens				
Tamoxifen[7]	Continuously, 1 x daily	365.0	1	365.0
fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2 onwards: 1 x monthly	13.0[6]	1	13.0
Non-steroidal aromatase inhibitors				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Steroidal aromatase inhibitors				
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Ribociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Abemaciclib	Continuously, 1 x daily	365.0	1	365.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0

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

[7] only for premenopausal patients who have not received tamoxifen in previous (neo-)adjuvant endocrine therapy; only for postmenopausal patients if aromatase inhibitors are unsuitable

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Ribociclib in combination with fulvestrant				
Ribociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0
Abemaciclib in combination with fulvestrant				
Abemaciclib	Continuously, 1 x daily	365.0	1	365.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2 onwards: 1 x monthly	13.0[6]	1	13.0
Palbociclib in combination with fulvestrant				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Capivasertib	Continuously, 2 x daily on day 1 - 4 of a 7-day cycle	52.1	4	208.4
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0
Appropriate comparator therapy				
Anti-oestrogens				
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Capivasertib	Continuously, 2 x daily on day 1 - 4 of a 7-day cycle	52.1	4	208.4
Fulvestrant	Continuously, cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0
Appropriate comparator therapy				
Individualised therapy, taking into account a change of endocrine therapy to				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Anti-oestrogens				
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2 onwards: 1 x monthly	13.0	1	13.0
Non-steroidal aromatase inhibitors				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Steroidal aromatase inhibitors				
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Everolimus in combination with exemestane[8]				
Everolimus	Continuously, 1 x daily	365.0	1	365.0
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Ribociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Abemaciclib	Continuously, 1 x daily	365.0	1	365.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Ribociclib in combination with fulvestrant				
Ribociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Fulvestrant	Continuously,	12.0[6]	1 - 3	14.0

[8] only for patients without symptomatic visceral metastasis, followed by progression after a non-steroidal aromatase inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly			
Abemaciclib in combination with fulvestrant				
Abemaciclib	Continuously, 1 x daily	365.0	1	365.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2 onwards: 1 x monthly	13.0[6]	1	13.0
Palbociclib in combination with fulvestrant				
Palbociclib	Continuously, 1 x on day 1 – 21 of a 28-day cycle	13.0	21	273.0
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Capivasertib	Continuously, 2 x daily on day 1 - 4 of a 7-day cycle	52.1	4	208.4
Fulvestrant	Continuously, Cycle 1: 1 x on day 1, 15 and 29 From cycle 2 onwards: 1 x monthly	12.0[6]	1 - 3	14.0
Appropriate comparator therapy				
Individualised therapy, taking into account a change of endocrine therapy to				
Anti-oestrogens				
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Fulvestrant	Continuously,	13.0[6]	1	13.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Cycle 1: 1 x on day 1 and 15 From cycle 2 onwards: 1 x monthly			
Aromatase inhibitor in combination with a GnRH analogue				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Leuprorelin	Continuously, 1 x every 28 days	13.0	1	13.0
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)				
Palbociclib	Continuously, 1 x on day 1 - 21 of a 28-day cycle	13.0	21	273.0
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Letrozole	Continuously, 1 x daily	365.0	1	365.0

Consumption:

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Capivasertib	400 mg	800 mg	4 x 200 mg	208.4	833.6 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Appropriate comparator therapy					
Anti-oestrogens					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Non-steroidal aromatase inhibitors					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Steroidal aromatase inhibitors					

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Ribociclib	600 mg	600 mg	3 x 200 mg	273.0	819 x 200 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 x 200 mg	273.0	819 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Abemaciclib in combination with fulvestrant					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Palbociclib in combination with fulvestrant					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Capivasertib	400 mg	800 mg	4 x 200 mg	208.4	833.6 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Appropriate comparator therapy					

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Anti-oestrogens					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Capivasertib	400 mg	800 mg	4 x 200 mg	208.4	833.6 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Appropriate comparator therapy					
Individualised therapy, taking into account a change of endocrine therapy to					
Anti-oestrogens					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Non-steroidal aromatase inhibitors					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Steroidal aromatase inhibitors					
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg
Everolimus in combination with exemestane					
Everolimus	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg
Ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Ribociclib	600 mg	600 mg	3 x 200 mg	273.0	819 x 200 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Ribociclib in combination with fulvestrant					
Ribociclib	600 mg	600 mg	3 x 200 mg	273.0	819 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Abemaciclib in combination with fulvestrant					
Abemaciclib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Palbociclib in combination with fulvestrant					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Capivasertib	400 mg	800 mg	4 x 200 mg	208.4	833.6 x 200 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	14.0	28 x 250 mg
Appropriate comparator therapy					
Individualised therapy, taking into account a change of endocrine therapy to					
Anti-oestrogens					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Aromatase inhibitor in combination with a GnRH analogue					

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg
Leuprorelin	3.75 mg	3.75 mg	1 x 3.75 mg	13.0	13 x 3.75 mg
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13.0	13 x 3.6 mg
Palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole)					
Palbociclib	125 mg	125 mg	1 x 125 mg	273.0	273 x 125 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Patient populations a1), a2), b1) and b2)

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Capivasertib 200 mg	64 FCT	€ 7,490.43	€ 1.77	€ 424.49	€ 7,064.17
Fulvestrant 250 mg[9]	1 PFS	€ 175.68	€ 1.77	€ 13.00	€ 160.91
Appropriate comparator therapy					
Abemaciclib 150 mg	168 FCT	€ 6,338.77	€ 1.77	€ 358.72	€ 5,978.28
Anastrozole 1 mg[9]	120 FCT	€ 48.87	€ 1.77	€ 2.97	€ 44.13
Everolimus 10 mg	30 TAB	€ 422.22	€ 1.77	€ 19.50	€ 400.95
Exemestane 25 mg[9]	100 CTA	€ 127.53	€ 1.77	€ 9.19	€ 116.57
Fulvestrant 250 mg[9]	1 PFS	€ 175.68	€ 1.77	€ 13.00	€ 160.91
Goserelin 3.6 mg	3 IMP	€ 632.16	€ 1.77	€ 34.37	€ 596.02
Letrozole 2.5 mg[9]	120 FCT	€ 61.68	€ 1.77	€ 3.98	€ 55.93

[9] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Leuprorelin 3.75 mg	3 SRM	€ 501.87	€ 1.77	€ 27.16	€ 472.94
Palbociclib 125 mg	21 FCT	€ 1,884.89	€ 1.77	€ 104.35	€ 1,778.77
Ribociclib 200 mg	189 FCT	€ 6,846.14	€ 1.77	€ 0.00	€ 6,844.37
Tamoxifen 20 mg[9]	100 FCT	€ 22.47	€ 1.77	€ 0.88	€ 19.82
Abbreviations: FCT = film-coated tablets; IPFS = solution for injection in a pre-filled syringe; IMP = implant; SRM = sustained-release microcapsules and suspending agents; CTA = coated tablets					

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Costs for additionally required SHI services:

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

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

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

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c,

sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive

marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and

pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information for capivasertib (Truqap); TRUQAP® 160mg/-200mg film-coated tablets; last revised: June 2024

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information for capivasertib (Truqap); TRUQAP® 160mg/-200mg film-coated tablets; last revised: June 2024

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information for capivasertib (Truqap); TRUQAP® 160mg/-200mg film-coated tablets; last revised: June 2024

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for capivasertib (Truqap); TRUQAP® 160mg/-200mg film-coated tablets; last revised: June 2024

3. Bureaucratic costs calculation

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

4. Process sequence

At their session on 26 November 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 September 2024, the pharmaceutical company submitted a dossier for the benefit assessment of capivasertib 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 October 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient capivasertib.

The dossier assessment by the IQWiG was submitted to the G-BA on 1 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2025. The deadline for submitting written statements was 23 January 2025.

The oral hearing was held on 10 February 2025.

By letter dated 12 February 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by the IQWiG was submitted to the G-BA on 12 March 2025 and 14 March 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 25 March 2025, and the proposed draft resolution was approved.

At their session on 3 April 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 November 2024	Determination of the appropriate comparator therapy
Working group Section 35a	4 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 February 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 February 2025 4 March 2025 18 March 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 March 2025	Concluding discussion of the draft resolution
Plenum	3 April 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 April 2025

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

Prof. Hecken