Gemeinsamer Bundesausschuss

Justification

to 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) and

Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Inavolisib (breast cancer, PIK3CA-mutated, ER+, HER2-, locally advanced or metastatic, recurrence < 12 months after adjuvant endocrine therapy, combination with palbociclib and fulvestrant)

of 19 February 2026

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 studies the pharmaceutical company have 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,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide 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 inavolisib on 15 August 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 1 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 8 August 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 November 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 inavolisib compared to 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. In order to determine the extent of the additional benefit, the G-BA have 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 inavolisib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made 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 Inavolisib (Itovebi) in accordance with the product information

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment.

There should be an interval of at least 12 months between discontinuation of the CDK4/6 inhibitor and detection of recurrence in patients who have previously been treated with a CDK4/6 inhibitor as part of (neo)adjuvant treatment.

In pre/perimenopausal women and in men, endocrine therapy should be combined with an LHRH agonist (LHRH = luteinising hormone-releasing hormone).

Therapeutic indication of the resolution (resolution of 19.02.2026):

See the approved therapeutic indication

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Appropriate comparator therapy for inavolisib in combination with palbociclib and 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

or

- everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis, followed by progression after a non-steroidal aromatase inhibitor)

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

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Appropriate comparator therapy for inavolisib in combination with palbociclib and fulvestrant:

- Tamoxifen

or

- 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 they determine 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 inavolisib, 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 cancer.

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:
- Capivasertib: resolution of 03.04.2025
- 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 systematic 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.

For the present therapeutic indication, it is assumed that patients have not previously received endocrine therapy in the advanced or metastatic stage, and 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.

Furthermore, it is assumed that there is no indication for (secondary) resection or radiotherapy with a curative objective.

It is assumed that a change of treatment has taken place with regard to the active ingredients used for the initial previous adjuvant endocrine therapy.

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 according to sex (women; men). When determining the appropriate comparator therapy, a differentiation is thus made according to the following patient populations:

a) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

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 anti-oestrogen fulvestrant is another recommended treatment option for initial endocrine therapy.

Moreover, according to the guidelines, treatment with everolimus in combination with exemestane is available, which, according to its authorisation status, is indicated for patients without symptomatic visceral metastasis, showing progression on treatment with a non-steroidal aromatase inhibitor.

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.

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. The results of the benefit assessment procedures to date for the CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) in the present therapeutic indication can be summarised as follows: For pre/perimenopausal women, no additional benefit could be proven for any of these treatment options. A hint for a minor additional benefit of ribociclib in combination with letrozole in comparison with letrozole could be shown, while an indication of a minor additional benefit of ribociclib in combination with fulvestrant in comparison with fulvestrant could be shown. 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 thereof 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 consider 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 recommendation can be derived on the basis of the available evidence with regard to a renewed therapy with a CDK4/6 inhibitor in the locally advanced or metastatic stage after adjuvant therapy with a CDK4/6 inhibitor.

The active ingredients alpelisib, capivasertib, olaparib and talazoparib are explicitly approved in the presence of certain mutations or alterations (e.g. PIK3CA or BRCA1/2 mutations or PIK3CA/AKT1/PTEN alterations). These active ingredients are not considered to be an appropriate comparator therapy in the present case.

The active ingredient alpelisib is explicitly approved for the present therapeutic indication in the presence of a PIK3CA mutation. However, alpelisib is not available on the German market and, according to the statement of clinical experts, it plays a minor role in earlier procedures for advanced or metastatic breast cancer. Alpelisib is therefore not considered to be an appropriate comparator therapy.

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

The appropriate comparator therapy determined here includes several therapeutic alternatives. 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.

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

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 alpelisib, capivasertib, olaparib and talazoparib are explicitly approved in the presence of certain mutations or alterations (e.g. PIK3CA or BRCA1/2 mutations or PIK3CA/AKT1/PTEN alterations). These active ingredients are not considered to be an appropriate comparator therapy in the present case.

The active ingredient alpelisib is explicitly approved for the present therapeutic indication in the presence of a PIK3CA mutation. However, alpelisib is not available on the German market and, according to the statement of clinical experts, it plays a minor role in earlier procedures for advanced or metastatic breast cancer. Alpelisib is therefore not considered to be an appropriate comparator therapy.

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.

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

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][4], 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 therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy.

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

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

[2] Oncology guideline programme, German Cancer Society (DKG), German Cancer Aid (DKH), Association of the Scientific-Medical Societies (AWMF). Early detection, diagnosis, therapy and follow-up of breast cancer, interdisciplinary S3 guideline, long version 4.4 [online]. AWMF registry number 032-045OL. Berlin (GER): Oncology guideline programme; 2021.

[3] 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.

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

2.1.3 Extent and probability of the additional benefit

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

a) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

   a1) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have not received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

   Hint for a considerable additional benefit

   a2) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

   An additional benefit is not proven.

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

   An additional benefit is not proven.

Justification:

INAVO120 study

The INAVO120 study is an ongoing, multicentre, double-blind, randomised, controlled phase III study comparing inavolisib in combination with palbociclib and fulvestrant to placebo in combination with palbociclib and fulvestrant.

The study has been conducted in 123 study sites in Europe, North and South America, Asia and Australia since January 2020.

The patients enrolled in the study had to have experienced recurrence on adjuvant endocrine treatment or up to a maximum of 12 months after completion of this treatment. If a CDK4/6 inhibitor was part of the neoadjuvant or adjuvant treatment, progression had to occur > 12 months after completion of therapy with the CDK4/6 inhibitor.

A total of 325 patients who were randomised in a 1:1 ratio were enrolled in the study: Randomisation was stratified by the presence of visceral disease (yes vs no), endocrine resistance (primary vs secondary) and region (North America/ Western Europe vs Asia vs others).

Only 6 men were enrolled in the study in total. For research question a (women), the total study population is used because it is assumed that the few men enrolled do not significantly affect the reliability of data of the evaluations for women.

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 assessed.

The results of the INAVO120 study at the 2nd data cut-off from 15.11.2024 are used for the benefit assessment.

Limitations of the INAVO120 study

The study has limitations in terms of the exclusion of patients with type 1 and type 2 diabetes mellitus requiring treatment, particularly given the fact that the data on adverse events in the study show an increase in hyperglycaemia in the inavolisib treatment group.

Another limitation is that almost all of the patients enrolled had already received adjuvant or neoadjuvant treatment, with CDK4/6 inhibitors being used in only 3 cases. Due to the resulting very limited information on re-therapy with CDK4/6 inhibitors, uncertainties remain regarding the efficacy of CDK4/6 inhibitors, particularly palbociclib, in patients who have previously been treated with CDK4/6 inhibitors in the (neo)adjuvant setting. This criticism is particularly evident in the four dissenting votes of the CHMP in the EPAR.

The G-BA therefore consider it appropriate to conduct a separate assessment of the additional benefit for women with or without prior treatment with a CDD4/6 inhibitor as part of (neo)adjuvant treatment.

Extent and probability of the additional benefit

a1) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have not received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

Mortality

In the INAVO120 study, overall survival is defined as the time between randomisation and death from any cause.

There was a statistically significant difference between the treatment arms, with an advantage of inavolisib, the extent of which is considered a significant improvement.

The subgroup analysis showed an effect modification by the "age" characteristic. There was a statistically significant difference to the advantage of inavolisib in subjects < 65 years, while there was no statistically significant difference between the treatment groups in subjects ≥ 65 years. These subgroup results are considered a relevant outcome of the present benefit assessment. This is however considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, the effect modification is not evident for other patient-relevant endpoints.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the INAVO120 study. It is defined as the time from randomisation to the earliest time of the first documentation of disease progression (defined according to RECIST 1.1 criteria) or death from any cause, whichever occurred first.

For the PFS, there was a statistically significant difference to the advantage of inavolisib.

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 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 PFS endpoint.

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

Symptomatic skeletal events

The skeletal events endpoint of the INAVO120 study is a composite endpoint with the individual components:

- pathological fracture,
- radiotherapy on the bone,
- cancer-related surgery on the bone and
- spinal cord compression.

In principle, the endpoint of symptomatic skeletal events is relevant for the benefit assessment. However, the dossier lacks information on the occurrence of the individual subcomponents for the INAVO120 study. Furthermore, it is unclear from the available data whether the present operationalisation actually reflects symptomatic skeletal events. Furthermore, according to the requirements in the study protocol, the use of local radiotherapy is subject to certain conditions or additional consultations, which means that it remains unclear whether all relevant events have been included in the analysis.

During the written statement procedure, the pharmaceutical company was unable to address the points of criticism raised.

Due to the uncertainties described, the results for the endpoint of skeletal events are not used for the assessment.

Symptomatology

EORTC QLQ-C30 and EORTC QLQ-BR23

Symptomatology was assessed in the INAVO120 study using the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.

As the return rates to the questionnaires are too low at an early stage and also vary greatly between the treatment arms, the results are unsuitable and are not used for the assessment.

Worst pain

BPI-SF item 3

The endpoint of worst pain was assessed using item 3 of the BPI-SF.

The pharmaceutical company did not present any relevant results in the dossier because data was collected using the tool with an incorrect time reference (7 days instead of 24 hours). However, this item is also included in the more comprehensive long form of the BPI, which is also collected by the pharmaceutical company and for which the evaluation manual specifies a recall period of 7 days. The differing time reference alone is therefore not a reason for data exclusion.

However, the data for the BPI-SF questionnaire cannot be used due to the low return rates at an early stage and the large differences in the return rates between the treatment arms, as described above under symptomatology, in line with the EORTC questionnaires.

Health status

EQ-5D VAS

No suitable data are available for the health status, assessed using the EQ-5D VAS.

The data on health status are unusable overall as the return rates to the VAS of the EQ-5D are too low at an early stage and also vary greatly between the treatment arms.

Quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23

Health-related quality of life was assessed in the INAVO120 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.

The results are unsuitable and are not used for the assessment as the return rates to the questionnaires are too low at an early stage and also vary greatly between the treatment arms.

Side effects

Adverse events (AEs) in total

In the INAVO120 study, an AE occurred in all patients of both study arms. The results are only presented additionally.

Serious AEs (SAEs) and severe AEs

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

Therapy discontinuation due to AEs

For the endpoint of discontinuation due to AEs, there was a statistically significant disadvantage of inavolisib in combination with palbociclib and fulvestrant compared to the control arm.

Specific AEs

For the endpoints of stomatitis, hyperglycaemia, decreased appetite, non-infectious diarrhoea, thrombocytopenia, metabolism and nutrition disorders, and gastrointestinal disorders, there was a statistically significant difference to the disadvantage of inavolisib.

PRO-CTCAE

In accordance with the study protocol, side effects were also collected in the INAVO120 study using the PRO-CTCAE tool, specifically 7 symptomatic AEs and one item on the general burden of side effects. In Module 4, the pharmaceutical company did not provide any information on PRO-CTCAE.

Overall, it is not clear what criteria were used to select the items and whether the side effects of inavolisib, palbociclib or fulvestrant are adequately represented. Therefore, the PRO-CTCAE endpoint is not used for the assessment.

Conclusion on side effects

For SAEs and severe AEs in the endpoint category of side effects, there were no statistically significant differences between the treatment arms. For the endpoint "Therapy discontinuation due to AEs", there was a disadvantage of inavolisib. In detail, for specific AEs, there were disadvantages of the inavolisib combination.

In the overall analysis of the results on side effects, a disadvantage is derived overall for the endpoint category of side effects.

Overall assessment

Results on mortality, morbidity, health-related quality of life and side effects from the INAVO120 study are available for the assessment of the additional benefit of inavolisib in combination with palbociclib and fulvestrant for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, if there was recurrence on or within 12 months of completing adjuvant endocrine treatment and there was no prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment. In this RCT, inavolisib in combination with palbociclib and fulvestrant was compared with palbociclib in combination with fulvestrant.

For overall survival, there was a statistically significant difference to the advantage of inavolisib, the extent of which is considered a significant improvement. The subgroup analysis showed an effect modification by the "age" characteristic. There was a statistically significant difference to the advantage of inavolisib in patients < 65 years, while there was no statistically significant difference between the treatment groups in patients ≥ 65 years. These subgroup results are considered a relevant outcome of the present benefit assessment. This is however considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, the effect modification is not evident for other patient-relevant endpoints.

In the morbidity endpoint category, no suitable data were available for the endpoint "symptomatic skeletal events" as well as for symptomatology, assessed using EORTC QLQ-C30 and EORTC QLQ-BR23, worst pain, assessed using BPI-SF item 3, and health status, assessed using the EQ-5D VAS, as the return rates to the questionnaires are too low at an early stage and also vary greatly between the treatment arms.

No suitable data were available with regard to health-related quality of life (assessed using EORTC QLQ-C30 and –BR23).

For SAEs and severe AEs in the endpoint category of side effects, there were no statistically significant differences between the treatment arms. For the endpoint "Therapy discontinuation due to AEs", there was a disadvantage of inavolisib. In detail, for the specific AEs, there were disadvantages of the inavolisib combination. In the overall analysis of the results on side effects, a disadvantage is derived overall for the endpoint category of side effects.

Based on the significant advantage in overall survival, the G-BA conclude overall the presence of a considerable additional benefit of inavolisib in combination with palbociclib and fulvestrant compared to palbociclib and fulvestrant for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, if there was recurrence on or within 12 months of completing adjuvant endocrine treatment and there was no prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment.

Reliability of data (probability of additional benefit)

The randomised, multicentre, controlled INAVO120 study forms the basis of the present benefit assessment.

Overall, the risk of bias at the study level is rated as low.

A relevant uncertainty in the reliability of data results for the total patient population due to the effect modification by the "age" characteristic in the endpoint of overall survival.

Furthermore, no suitable data on disease-specific symptomatology and health-related quality of life are available from the INAVO120 study. This means that it is not possible to assess the effect the therapy with inavolisib in combination with palbociclib and fulvestrant compared to palbociclib and fulvestrant has on symptomatology and health-related quality of life of patients.

In summary, the G-BA derive a hint for the identified additional benefit with regard to the reliability of data.

a2) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

The study population of the INAVO120 study comprises only 3 patients who have received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment. This means that adequate data to assess the additional benefit for the patient population in question is not available.

The G-BA therefore conclude that an additional benefit of inavolisib in combination with palbociclib and fulvestrant over palbociclib and fulvestrant is not proven for women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment and prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment.

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

In the INAVO120 study, the therapy in the comparator arm does not correspond to the appropriate comparator therapy determined by the G-BA for the patient group of men. Furthermore, only 6 men were enrolled in total. This means that appropriate data to assess the additional benefit for the patient population in question is not available.

The G-BA therefore conclude that an additional benefit of inavolisib in combination with palbociclib and fulvestrant over palbociclib and fulvestrant is not proven for men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Itovebi with the active ingredient inavolisib in combination with palbociclib and fulvestrant.

The therapeutic indication assessed here is as follows: Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment.

There should be an interval of at least 12 months between discontinuation of the CDK4/6 inhibitor and detection of recurrence in patients who have previously been treated with a CDK4/6 inhibitor as part of (neo)adjuvant treatment.

The pharmaceutical company submitted the results of the INAVO120 study for the benefit assessment.

The G-BA made separate assessments of the additional benefit, depending on sex and prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment:

a1) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have not received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

The G-BA determined palbociclib in combination with fulvestrant as the appropriate comparator therapy.

The results of the INAVO120 study submitted by the pharmaceutical company are used for patients who have not received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment.

For overall survival, there was a statistically significant difference to the advantage of inavolisib, the extent of which is considered a significant improvement. The subgroup analysis showed an effect modification by the "age" characteristic. There was a statistically significant difference to the advantage of inavolisib in patients < 65 years, while there was no statistically significant difference between the treatment groups in patients ≥ 65 years. These subgroup events are considered a relevant outcome of the present benefit assessment. This is however considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, the effect modification is not evident for other patient-relevant endpoints.

In the morbidity endpoint category, no suitable data were available for the endpoint "symptomatic skeletal events" as well as for symptomatology, assessed using EORTC QLQ-C30 and EORTC QLQ-BR23, worst pain, assessed using BPI-SF item 3, and health status, assessed using the EQ-5D VAS, as the return rates to the questionnaires are too low at an early stage and also vary greatly between the treatment arms.

No suitable data were available with regard to health-related quality of life (assessed using EORTC QLQ-C30 and –BR23).

For SAEs and severe AEs in the endpoint category of side effects, there were no statistically significant differences between the treatment arms. For the endpoint "Therapy discontinuation due to AEs", there was a disadvantage of inavolisib. In detail, for specific AEs,

there were disadvantages of the inavolisib combination. In the overall analysis of the results on side effects, a disadvantage is derived overall for the endpoint category of side effects.

A considerable additional benefit is identified overall, particularly due to the significant advantage in overall survival.

The reliability of data of the additional benefit identified is classified in the "hint" category.

a2) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

The study population of the INAVO120 study comprises only 3 patients who have received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment. This means that adequate data to assess the additional benefit for the patient population in question is not available.

An additional benefit is therefore not proven for this sub-population.

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

In the INAVO120 study, the therapy in the comparator arm does not correspond to the appropriate comparator therapy determined by the G-BA for the patient group of men. Furthermore, only 6 men were enrolled in total.

This means that appropriate data to assess the additional benefit for the patient population in question is not available.

An additional benefit is therefore not proven for this sub-population.

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 is subject to uncertainty, as subjects who fell ill before the analysis year were not taken into account, the approach to determine the percentage values of recurrences was inappropriate, the representativeness of the populations on which the percentage values of endocrine resistance are based is unclear, the PIK3CA mutational status of untested subjects is unclear, and the interval of at least 12 months between discontinuation of any CDK4/6 inhibitor used for (neo)adjuvant treatment and detection of recurrence was not taken into account.

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 Itovebi (active ingredient: inavolisib) at the following publicly accessible link (last access: 18 November 2025):

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

Treatment with inavolisib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists from other specialist groups participating in the Oncology Agreement.

Patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer should be selected for treatment with inavolisib based on the presence of one or more PIK3CA mutations in a tumour or plasma sample. Detection of PIK3CA mutation(s) must be performed using a CE-marked in vitro diagnostic (IVD) device 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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 December 2025).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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

It is assumed that pre/perimenopausal patients receive ovarian suppression with a GnRH analogue. According to the product information, treatment with inavolisib should also be combined with a GnRH analogue in men. Leuprorelin and goserelin are explicitly approved for use in women in the metastatic stage according to the respective product information. Against this background, LHRH agonists are not shown in the cost representation in patient group b) as part of the appropriate comparator therapy.

Treatment period:

a) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed: *Inavolisib in combination with palbociclib and fulvestrant*				
Inavolisib	Continuously, 1 x daily	365.0	1	365.0
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: 1 x monthly	12.0	1 - 3	14.0
Plus GnRH analogue, if applicable				
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Leuprorelin	Continuously, 1 x every 3 months	4.0	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Anti-oestrogens				
Tamoxifen[5]	Continuously, 1 x daily	365.0	1	365.0
fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2: 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
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,	365.0	1	365.0

[5] 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
	1 x daily			
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: 1 x monthly	12.0	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: 1 x monthly	12.0	1-2	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: 1 x monthly	12.0	1 - 3	14.0
Everolimus in combination with exemestane				
Everolimus	Continuously, 1 x daily	365.0	1	365.0
Exemestane	Continuously, 1 x daily	365.0	1	365.0
All therapies, plus GnRH analogue, if applicable				
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Leuprorelin	Continuously, 1 x every 3 months	4.0	1	4.0

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed: *Inavolisib in combination with palbociclib and fulvestrant*				
Inavolisib	Continuously, 1 x daily	365.0	1	365.0
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: 1 x monthly	12.0	1 - 3	14.0
Plus GnRH analogue				
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Leuprorelin	Continuously, 1 x every 3 months	4.0	1	4.0
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

Consumption:

a) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed: *Inavolisib in combination with palbociclib and fulvestrant*					
Inavolisib	9 mg	9 mg	1 x 9 mg	365.0	365 x 9 mg
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
Plus GnRH analogue, if applicable					
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13.0	13 x 3.6 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 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					
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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	13.0	26 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
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
All therapies, plus GnRH analogue, if applicable					
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13.0	13 x 3.6 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

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: *Inavolisib in combination with palbociclib and fulvestrant*					
Inavolisib	9 mg	9 mg	1 x 9 mg	365.0	365 x 9 mg
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
Plus GnRH analogue					
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	13.0	13 x 3.6 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 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
Appropriate comparator therapy					
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

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Inavolisib	28 FCT	€ 15,458.58	€ 1.77	€ 879.55	€ 14,577.26
Palbociclib	21 FCT	€ 1,884.89	€ 1.77	€ 104.35	€ 1,778.77
Fulvestrant 250 mg[6]	1 IPFS	€ 175.68	€ 1.77	€ 13.00	€ 160.91
Goserelin 3.6 mg	3 IMP	€ 681.20	€ 1.77	€ 37.09	€ 642.34
Leuprorelin 11.25 mg	2 SRM	€ 1,010.55	€ 1.77	€ 55.32	€ 953.46
Appropriate comparator therapy					
Abemaciclib 150 mg	168 FCT	€ 6,068.30	€ 1.77	€ 343.27	€ 5,723.26
Anastrozole 1 mg[6]	100 FCT	€ 43.68	€ 1.77	€ 2.56	€ 39.35
Everolimus 10 mg	30 TAB	€ 419.63	€ 1.77	€ 19.38	€ 398.48
Exemestane 25 mg[6]	100 CTA	€ 127.53	€ 1.77	€ 9.19	€ 116.57
Fulvestrant 250 mg[6]	1 IPFS	€ 175.68	€ 1.77	€ 13.00	€ 160.91
Goserelin 3.6 mg	3 IMP	€ 681.20	€ 1.77	€ 37.09	€ 642.34
Letrozole 2.5 mg[6]	120 FCT	€ 61.68	€ 1.77	€ 3.98	€ 55.93
Leuprorelin 11.25 mg	2 SRM	€ 1,010.55	€ 1.77	€ 55.32	€ 953.46

[6] 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
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[6]	100 FCT	€ 28.05	€ 1.77	€ 1.32	€ 24.96
Abbreviations: FCT = film-coated tablets; IPFS = solution for injection in a pre-filled syringe; IMP = implant; SRM = sustained-release microcapsules and suspending agents; DSS = dry substance; CTA = coated tablets					

LAUER-TAXE® last revised: 15 December 2025

Costs for additionally required SHI services:

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

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

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

2.5 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 designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

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 have 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 have 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 have 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 PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have not received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA have identified at least considerable additional benefit for the combination with the assessed medicinal product in the present resolution:

- Palbociclib (Ibrance)

a2) Women with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment, who have received prior treatment with a CDK4/6 inhibitor as part of (neo)adjuvant treatment

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment".

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:

Product information for inavolisib (Itovebi); Itovebi®; last revised: January 2026

b) Men with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment".

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:

Product information for inavolisib (Itovebi); Itovebi®; last revised: January 2026

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product inavolisib is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed

who participated at study sites within the scope of SGB V (German Social Security Code) is < 5% of the total number of study participants.

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

The plenum determined the appropriate comparator therapy at their session on 4 April 2024.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products newly determined the appropriate comparator therapy at their session on 29 July 2025.

On 8 August 2025, the pharmaceutical company submitted a dossier for the benefit assessment of inavolisib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 11 August 2025 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 inavolisib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 November 2025, and the written statement procedure was initiated with publication on the G-BA website on 17 November 2025. The deadline for submitting written statements was 8 December 2025.

The oral hearing was held on 12 January 2026.

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 subcommittee session on 10 February 2026, and the draft resolution was approved.

At their session on 19 February 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Plenum	4 April 2024	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	29 July 2025	New determination of the appropriate comparator therapy
Working group Section 35a	7 January 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2026	Conduct of the oral hearing
Working group Section 35a	21 January 2026 4 February 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	10 February 2026	Concluding discussion of the draft resolution
Plenum	19 February 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 February 2026

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

Prof. Hecken