

Justification

for 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
Imlunestrant (breast cancer, ER+, HER2-, with an ESR1-
mutation, progressive following prior endocrine therapy)

From 3 September 2026

Contents

1.	Legal basis.....	2
2.	Key points of the resolution.....	2
2.1	Additional benefit of the medicinal product in relation to the appropriate comparator therapy	3
2.1.1	Approved therapeutic indication of Imlunestrant (Inluriyo) in accordance with the product information.....	3
2.1.2	Appropriate comparator therapy.....	3
2.1.3	Extent and probability of the additional benefit.....	16
2.1.4	Summary of the assessment	24
2.2	Number of patients or demarcation of patient groups eligible for treatment	26
2.3	Requirements for a quality-assured application	26
2.4	Treatment costs	27
3.	Bureaucratic costs calculation.....	43
4.	Process sequence	43

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.

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 imlunestrant on 15 March 2026 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, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 of the Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 13 March 2026.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 June 2026 on the G-BA website at (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 imlunestrant 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 imlunestrant.

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 Imlunestrant (Inluriyo) in accordance with the product information

Inluriyo is indicated as monotherapy for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen.

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

Therapeutic indication of the resolution (resolution of 3 September 2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

- a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

Appropriate comparator therapy for imlunestrant as monotherapy:

- tamoxifen (only suitable for premenopausal patients who have not received tamoxifen during prior (neo-)adjuvant endocrine therapy; only suitable for postmenopausal patients if aromatase inhibitors are unsuitable)
- or
- letrozole
- or
- exemestane (only suitable for patients with disease progression following anti-oestrogen treatment)

¹ General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- or
- anastrozole
- or
- fulvestrant
- or
- everolimus in combination with exemestane (only suitable for patients without symptomatic visceral metastasis who have disease progression following 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

a2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

Appropriate comparator therapy for imlunestran as monotherapy:

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

b1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

Appropriate comparator therapy for imlunestran as monotherapy:

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

- tamoxifen
- letrozole
- exemestane
- anastrozole

- fulvestrant
- everolimus in combination with exemestane (only suitable for patients without symptomatic visceral metastasis who have disease progression following 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 ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

Appropriate comparator therapy for imlunestrant as monotherapy:

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal 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 for 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 for 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 camizestran, 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, leuporelin, goserelin, the protein kinase inhibitors everolimus, abemaciclib, palbociclib, ribociclib, 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 ovarian function suppression 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:

- Inavolisib: resolution of 19 February 2026

- Capivasertib: resolution of 3 April 2025
- Elacestrant: resolution of 2 May 2024
- Abemaciclib: resolutions of 19 May 2022 and 15 June 2023
- Palbociclib: resolutions of 18 May 2017, 21 March 2019 and 15 December 2022
- Ribociclib: resolutions of 4 July 2019 and 20 August 2020
- Alpelisib (in combination with fulvestrant): resolution of 18 February 2021
- Olaparib: resolution of 16 January 2020
- Talazoparib: resolution of 20 November 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 indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy"). A written statement by the Drugs Commission of the German Medical Association (AkdÄ) and a joint written statement by the Working Group for Gynaecological Oncology (AGO) of the German Cancer Society (DKG), the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Senology (DGS) are available.

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.

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

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). When determining the appropriate comparator therapy, a differentiation is thus made according to the following patient populations. Subgroup analyses of the biological menopausal status (pre-/perimenopausal; postmenopausal) should be presented for the patient populations of women.

a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the 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 anti-oestrogen fulvestrant is another recommended treatment option for initial endocrine therapy.

Moreover, according to the guidelines, and the written statement issued by the scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ), treatment with everolimus in combination with exemestane is available, which, according to its authorisation status, is indicated for patients without symptomatic visceral metastasis who have disease progression following 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 October 2024), the marketing authorisations for anastrozole, fulvestrant and everolimus do not formally exclude female patients whose menopause has been induced by surgery or medication. The appropriate comparator therapies determined here with anastrozole, fulvestrant and everolimus therefore include female 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 of any of these treatment options could be proven. A hint of 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 of 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, inavolisib, olaparib and talazoparib are explicitly approved in the presence of certain mutations or alterations (e.g. PIK3CA or BRCA 1/2 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 camizestrant is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 20 July 2026). According to the generally recognised state of medical knowledge, camizestrant is not determined as an appropriate comparator therapy for the present resolution.

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

The appropriate comparator therapy determined here includes several alternative 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 ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the 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 alpelisib, capivasertib, inavolisib, olaparib and talazoparib are explicitly approved in the presence of certain mutations or alterations (e.g. PIK3CA or BRCA 1/2 mutations or PIK3CA/AKT1/PTEN alterations). These active ingredients are not considered to be an appropriate comparator therapy in the present case.

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 evidence²³⁴, 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 active ingredient camizestrant is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 20 July 2026). According to the generally recognised state of medical knowledge, camizestrant is not determined as an appropriate comparator therapy for the present resolution.

In the overall analysis, the G-BA consider tamoxifen and palbociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole) as equally appropriate

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.

treatment options for men who have not yet received treatment at the locally advanced or metastatic stage.

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

b1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the 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 October 2024), the marketing authorisations for anastrozole, fulvestrant and everolimus do not formally exclude female 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 who have disease progression following 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^{1,2} 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, the G-BA determine the appropriate comparator therapy to be an individualised therapy specifically aimed at a change in endocrine therapy, specifying the relevant active ingredients.

In the case of prior therapy with an aromatase inhibitor, switching to treatment with an anti-oestrogen or an oestrogen receptor antagonist is adequate according to the guidelines². 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 guidelines² 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 recommendations².

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 less plausible 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.

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 of any of these treatment options could be proven. For postmenopausal women with previous endocrine therapy, ribociclib in combination with fulvestrant presented a hint of a minor additional benefit compared with fulvestrant, and abemaciclib in combination with

fulvestrant showed 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 consider 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 given at the locally advanced or metastatic stage.

About the active ingredient elacestrant: In this therapeutic indication, patients have received a line of endocrine therapy at the locally advanced or metastatic stage. An additional benefit for postmenopausal women who had undergone prior lines of endocrine therapy was not proven in the benefit assessment of elacestrant. A hint of a considerable additional benefit was found for postmenopausal women who had undergone two prior lines of endocrine therapy. Given that the appropriate comparator therapy is based on the treatment setting following a prior line of endocrine therapy, the active ingredient elacestrant is not determined as an appropriate comparator therapy, taking into account the results of the benefit assessment and in relation to the significance of the therapeutic options.

The active ingredients alpelisib, capivasertib, inavolisib, olaparib and talazoparib are explicitly approved in the presence of certain mutations or alterations (e.g. PIK3CA or BRCA 1/2 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 camizestrant is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 20 July 2026). According to the generally recognised state of medical knowledge, camizestrant is not determined as an appropriate comparator therapy for the present resolution.

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 suitable for patients without symptomatic visceral metastasis who have disease progression following 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.

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

Both a single-comparator study and a multi-comparator study with the selection of the above-mentioned treatment options may be suitable for the implementation of the appropriate comparator therapy. With regard to a single comparator study, individualised therapy can 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 the additional benefit in the total population.

In the case of a multi-comparator study design, the individualised treatment decision in relation to the comparator therapy should be made prior to group allocation (e.g. randomisation). This does not include necessary therapy adjustments in the course of the study (e.g. due to the onset of symptomatology or similar).

b2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the 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^{1,2} 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 the used 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.

The active ingredients alpelisib, capivasertib, inavolisib, olaparib and talazoparib are explicitly approved in the presence of certain mutations or alterations (e.g. PIK3CA or BRCA 1/2 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 camizestrant is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 20 July 2026). According to the generally recognised state of medical knowledge, camizestrant is not determined as an appropriate comparator therapy for the present resolution.

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).

Both a single-comparator study and a multi-comparator study with the selection of the above-mentioned treatment options may be suitable for the implementation of the appropriate comparator therapy. With regard to a single comparator study, individualised therapy can 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 the additional benefit in the total population.

In the case of a multi-comparator study design, the individualised treatment decision in relation to the comparator therapy should be made prior to group allocation (e.g. randomisation). This does not include necessary therapy adjustments in the course of the study (e.g. due to the onset of symptomatology or similar).

The determination of the off-label use of medicinal products as an appropriate comparator therapy by the 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.

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.

2.1.3 Extent and probability of the additional benefit

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

- a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

An additional benefit is not proven.

- a2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

An additional benefit is not proven.

- b1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

Hint of non-quantifiable additional benefit.

- b2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

An additional benefit is not proven.

Justification:

The pharmaceutical company presented the results of the open-label, randomised controlled EMBER-3 study for the benefit assessment.

In the ongoing triple-arm EMBER-3 study, imlunestrant (arm A) is being compared with fulvestrant or exemestane (arm B) and with imlunestrant in combination with abemaciclib (arm C), although the study arm with imlunestrant in combination with abemaciclib was only added retrospectively via a protocol amendment. This study arm is not relevant to the present benefit assessment and will not be described further below.

The study has been conducted in 243 study sites in Europe, North America, South America, Asia and Australia since October 2021.

Pretreated patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer were enrolled in the study. The previous endocrine therapy must have included an aromatase inhibitor, either as monotherapy or in combination with a CDK4/6 inhibitor.

A total of 874 patients were enrolled and randomly assigned in a 1:1:1 ratio to receive treatment with imlunestrant (N = 331), fulvestrant or exemestane (N = 330), or imlunestrant in combination with abemaciclib (N = 213). The decision on using fulvestrant or exemestane when allocating to the control arm was made by the principal investigator prior to

randomisation. Patients who had been pretreated with exemestane should be given fulvestrant. Patients who had been pretreated with fulvestrant were excluded from taking part in the study.

The relevant sub-population for the benefit assessment is defined on the basis of a confirmed ESR1-mutation, in accordance with the marketing authorisation. Within the relevant sub-population, 30 female patients had to be assigned to patient population a1 and 108 female patients to the patient population b1. No data are available for male patient populations.

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.

To date, a total of three data cut-offs have been carried out for the EMBER-3 study:

- 24 June 2024: pre-specified final analysis of PFS following approximately 480 observed PFS events in the ITT population; at the time of this analysis, approximately 192 PFS events were expected in the sub-population with an activating ESR1-mutation
- 30 January 2025: pre-specified interim analysis of overall survival, 6 months after the final analysis of PFS
- 18 August 2025: pre-specified interim analysis of overall survival following approximately 330 deaths in the ITT population; at the time of this analysis, approximately 125 events were expected in the sub-population with an activating ESR1-mutation

For the present benefit assessment, the results for the sub-population at the data cut-off from 18 August 2025 are used.

Limitations of the EMBER-3 study

A significant limitation is that the unblinded study showed relevant differences between the assessment of disease progression – primarily carried out by the principal investigators according to the study protocol – and the retrospective assessment by a Blinded Independent Central Review (BICR), both in terms of event rates and the median time to PFS event. Particularly in unblinded studies, it cannot be ruled out that the principal investigator's assessment may be influenced by their knowledge of the study medication. Therapy discontinuation and the follow-up of patient-reported endpoints and endpoints in the category of side effects are linked to the principal investigator's assessment. Consequently, differences in the assessment of disease progression may lead to bias in the results for endpoints in the categories of morbidity, health-related quality of life and side effects. Nor can it be ruled out that a study treatment that was still effective for a significant percentage of patients was discontinued prematurely. Consequently, the differences in the assessment of disease progression may also have an impact on the results for the overall survival endpoint.

The results for all patient-reported endpoints (PROs) are unusable because significant percentages of patients were excluded from the analysis and the return rates for all PROs decline sharply very early on.

Furthermore, there are limitations to the collection of AEs. The definition of AEs in the EMBER-3 study stipulates, in accordance with the study protocol, that progression, signs or symptoms of the investigated disease should not be collected as AEs unless they were more serious than would have been expected given the patients' condition. The study protocol did not define any default, objective criteria for this assessment. Particularly in an unblinded study, this may

result in the collection of AEs being potentially unsystematic and/or incomplete, and may also potentially lead to a bias in the results. This applies equally to SAEs and severe AEs. The EMA had already expressed this criticism in the EPAR for imlunestrant.

About the implementation of the appropriate comparator therapy for patient group b1

With regard to the implementation of the individualised therapy for patient group b1, fulvestrant or exemestane as monotherapy was used in the comparator arm of the EMBER-3 study, although only one patient received exemestane. In patient group b1, all female patients had previously received an aromatase inhibitor, over 25% of them had received tamoxifen, and well over 80% of patients had been pretreated with CDK4/6 inhibitors. The current S3 guideline recommends endocrine therapy as first-line therapy, preferably in combination with a CDK4/6 inhibitor. The S3 guideline does not recommend re-therapy with CDK4/6 inhibitors following disease progression whilst on CDK4/6 inhibitors. CDK4/6 inhibitors, as part of the comparator therapy, are therefore not an option for the patients enrolled in the study who already showed disease progression whilst on CDK4/6 inhibitors. 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 is considered an adequate implementation of an individualised therapy, taking into account a change in endocrine therapy. The G-BA have therefore based this assessment on the data for assessing the additional benefit across the entire patient group b1.

Extent and probability of the additional benefit

- a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

Mortality

Overall survival

The endpoint of overall survival was defined in the EMBER-3 study as the time from randomisation to death from any cause. There was no statistically significant difference between the study arms.

Morbidity

Progression-free survival (PFS)

Progression-free survival is the primary endpoint of the EMBER-3 study. It is defined as the time from randomisation to the first documented disease progression or death from any cause in the absence of disease progression. Progression events were primarily collected by principal investigators in accordance with the RECIST v.1.1 criteria. In addition, a retrospective BICR was carried out.

For PFS as assessed by the BICR as well as the principal investigator, there was a statistically significant difference to the advantage of imlunestrant.

The PFS endpoint is a composite endpoint comprising 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, symptom scales)

Symptomatology was assessed in the EMBER-3 study using the symptom scales of the EORTC QLQ-C30 questionnaire.

Due to the low patient number at baseline and the sharp, very early decline in questionnaire return rates, 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.

Due to the low patient number at baseline and the sharp, very early decline in questionnaire return rates, the results are unsuitable and are not used for the assessment.

Health status (EQ-5D VAS)

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

Due to the low patient number at baseline and the sharp, very early decline in questionnaire return rates, the results are unsuitable and are not used for the assessment.

Quality of life

EORTC QLQ-C30

Health-related quality of life was assessed in the EMBER-3 study using the functional scales of the EORTC QLQ-C30 questionnaire.

Due to the low patient number at baseline and the sharp, very early decline in questionnaire return rates, the results are unsuitable and are not used for the assessment.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

Due to the relevant above-described limitations regarding the collection of AEs in the EMBER-3 study, the data are unsuitable overall for the quantitative benefit assessment of imlunestrant compared with the comparator therapy.

PRO-CTCAE

In accordance with the EMBER-3 study protocol, two symptomatic AEs were collected from the PRO-CTCAE system: Diarrhoea, as well as pain and swelling at the injection site. The study protocol does not explain the procedure for selecting the items.

The PRO-CTCAE questionnaire is not used for the benefit assessment due to the lack of transparency in the selection process for symptomatic AEs.

Overall assessment/conclusion

Results on mortality, morbidity, health-related quality of life and side effects from the randomised controlled EMBER-3 study are available for the assessment of the additional benefit of imlunestrant in female patients with ER-positive, HER2-negative, locally advanced

or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy and who have not previously received treatment at the locally advanced or metastatic stage. The study compared imlunestrant with endocrine therapy, with the selection of fulvestrant or exemestane.

For this sub-population from the EMBER-3 study, usable results are available only for the endpoint of overall survival, and these do not show any statistically significant difference between the treatment groups. The results for the patient-reported endpoints on symptomatology (EORTC QLQ-C30, symptom scales), worst pain (BPI-SF item 3) and health status (EQ-5D VAS), as well as health-related quality of life (EORTC QLQ-C30, functional scales) are unusable due to a sharp, very early decline in return rates and the fact that a significant percentage of patients were excluded from the analysis (approximately 22 to 32% depending on the endpoint).

Due to the relevant limitations in the collection of adverse events (AEs) in the EMBER-3 study, the data on side effects are unsuitable overall for the quantitative benefit assessment of imlunestrant compared with the comparator therapy.

Due to the very low patient number (30 vs 23 female patients) and the few usable analyses from the EMBER-3 study, only very limited conclusions can be drawn regarding the first-line treatment setting in the present therapeutic indication.

Neither an advantage nor a disadvantage in terms of overall survival was observed in the overall analysis. No suitable data are available for the other endpoint categories. An additional benefit of imlunestrant compared with endocrine therapy with the selection of either fulvestrant or exemestane is therefore not proven for female patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy and who have not previously received treatment at the locally advanced or metastatic stage.

a2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

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

The G-BA therefore conclude that an additional benefit of imlunestrant is not proven in men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy and who have not previously received treatment at the locally advanced or metastatic stage.

- b1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

Mortality

Overall survival

The endpoint of overall survival was defined in the EMBER-3 study as the time from randomisation to death from any cause. There was a statistically significant difference to the advantage of imlunestrant compared with fulvestrant. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

Progression-free survival is the primary endpoint of the EMBER-3 study. It is defined as the time from randomisation to the first documented disease progression or death from any cause in the absence of disease progression. Progression events were primarily collected by principal investigators in accordance with the RECIST v.1.1 criteria. In addition, a retrospective BICR was carried out.

No statistically significant difference was observed for PFS as assessed by BICR, whereas a statistically significant difference to the advantage of imlunestrant was observed for PFS as assessed by the principal investigator.

The PFS endpoint is a composite endpoint comprising 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, symptom scales)

Symptomatology was assessed in the EMBER-3 study using the symptom scales of the EORTC QLQ-C30 questionnaire.

Due to the sharp, very early decline in questionnaire return rates, 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.

Due to the sharp, very early decline in questionnaire return rates, the results are unsuitable and are not used for the assessment.

Health status (EQ-5D VAS)

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

Due to the sharp, very early decline in questionnaire return rates, the results are unsuitable and are not used for the assessment.

Quality of life

EORTC QLQ-C30

Health-related quality of life was assessed in the EMBER-3 study using the functional scales of the EORTC QLQ-C30 questionnaire.

Due to the sharp, very early decline in questionnaire return rates, the results are unsuitable and are not used for the assessment.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

Due to the relevant limitations in the collection of adverse events (AEs) in the EMBER-3 study, the data on side effects are unsuitable overall for the quantitative benefit assessment of imlunestrant compared with the comparator therapy.

PRO-CTCAE

In accordance with the EMBER-3 study protocol, two symptomatic AEs were collected from the PRO-CTCAE system: Diarrhoea, as well as pain and swelling at the injection site. The study protocol does not explain the procedure for selecting the items.

The PRO-CTCAE questionnaire is not used for the benefit assessment due to the lack of transparency in the selection process for symptomatic AEs.

Overall assessment/conclusion

Results on mortality, morbidity, health-related quality of life and side effects from the EMBER-3 study are available for the assessment of the additional benefit of imlunestrant in female patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy, which was given at the locally advanced or metastatic stage. The study compared imlunestrant with fulvestrant or exemestane, although only one patient received exemestane.

For this sub-population from the EMBER-3 study, usable results are available only for the endpoint of overall survival. The results for the patient-reported endpoints on symptomatology (EORTC QLQ-C30, symptom scales), worst pain (BPI-SF item 3) and health status (EQ-5D VAS), as well as health-related quality of life (EORTC QLQ-C30, functional scales) are unusable due to a sharp, very early decline in return rates and the fact that a significant percentage of patients were excluded from the analysis (20 to 37% depending on the endpoint).

A significant improvement in terms of the overall survival endpoint was observed in the overall assessment. No suitable data are available on other patient-relevant endpoints.

Due to the relevant limitations in the collection of adverse events (AEs) in the EMBER-3 study, the data on side effects are unsuitable overall for the quantitative benefit assessment of imlunestrant compared with the comparator therapy.

However, based on the information on the side effects of imlunestrant provided in the EMA's EPAR and the statements from scientific-medical societies, these side effects are not expected

to call into question the advantage in terms of overall survival. Nevertheless, there is significant difficulty in carrying out the benefit-risk assessment of imlunestrant.

In the overall benefit-risk assessment, quantification of the additional benefit is not possible due to the generally very limited data basis available.

Consequently, a non-quantifiable additional benefit of imlunestrant compared with endocrine therapy with the selection of fulvestrant or exemestane has been identified for patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage.

Reliability of data (probability of the additional benefit)

The risk of bias across endpoints in the EMBER-3 study is rated as high. In the unblinded EMBER-3 study, there are significant differences between the principal investigators' assessment of disease progression and the retrospective assessment by BICR. Particularly in unblinded studies, it cannot be ruled out that the principal investigator's assessment may be influenced by their knowledge of the study medication. Therapy discontinuation and the follow-up of patient-reported endpoints and endpoints in the category of side effects are linked to the principal investigator's assessment. Consequently, differences in the assessment of disease progression may lead to bias in the results for endpoints in the categories of morbidity, health-related quality of life and side effects. Nor can it be ruled out that a study treatment that was still effective for a significant percentage of patients was discontinued prematurely. Consequently, the differences in the assessment of disease progression may also have an impact on the results for the overall survival endpoint.

No usable data are available for the endpoints in the categories of morbidity, health-related quality of life and side effects.

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

b2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

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

The G-BA therefore conclude that an additional benefit of imlunestrant is not proven in men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy, which was given at 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 Inluriyo with the active ingredient imlunestrant.

Imlunestrant is indicated for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen.

In the therapeutic indication under consideration, four patient groups were distinguished on the basis of gender (women; men) and treatment setting following prior endocrine therapy (adjuvant; locally advanced/ metastatic).

a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

The G-BA determined the appropriate comparator therapy to be various monotherapies and combination therapies (alternate comparator therapies), including letrozole, fulvestrant or ribociclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole) or abemaciclib in combination with fulvestrant.

For this patient group, the pharmaceutical company presented the EMBER-3 RCT, which compared imlunestrant with endocrine therapy with the selection of either fulvestrant or exemestane.

Usable results are available only for the overall survival endpoint, and these do not show any statistically significant difference between the treatment groups. The results on symptomatology, worst pain and health status, as well as health-related quality of life, are unusable due to a sharp, very early decline in return rates and the fact that a significant percentage of patients were excluded from the analysis.

Due to the relevant limitations in the collection of adverse events (AEs) in the EMBER-3 study, the data on side effects are unsuitable overall for the quantitative benefit assessment of imlunestrant compared with the comparator therapy.

Given the very low patient number and the few usable analyses, the EMBER-3 study results only allow very limited conclusions to be drawn regarding the first-line treatment setting in the present therapeutic indication.

In the overall analysis, the G-BA conclude that an additional benefit is not proven for this sub-population.

a2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the 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 conclude that an additional benefit is not proven for this sub-population.

b1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

The appropriate comparator therapy is an individualised therapy, taking into account a change of endocrine therapy to various monotherapies and combination therapies, including tamoxifen, exemestane, fulvestrant, abemaciclib in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole) or palbociclib in combination with fulvestrant.

For this patient group, the pharmaceutical company presented the EMBER-3 RCT, which compared imlunestrant with endocrine therapy with the selection of either fulvestrant or exemestane.

Usable results are available only for the overall survival endpoint, and these show a statistically significant difference to the advantage of imlunestrant compared with fulvestrant (only one patient received exemestane). The results on symptomatology, worst pain and health status, as well as health-related quality of life, are unusable due to a sharp, very early decline in return rates and the fact that a significant percentage of patients were excluded from the analysis.

Due to the relevant limitations in the collection of adverse events (AEs) in the EMBER-3 study, the data on side effects are unsuitable overall for the quantitative benefit assessment of imlunestrant compared with the comparator therapy.

However, based on the information on the side effects of imlunestrant provided in the EMA's EPAR and the statements from scientific-medical societies, these side effects are not expected to call into question the advantage in terms of overall survival. Nevertheless, there is significant difficulty in carrying out the benefit-risk assessment of imlunestrant.

In the overall benefit-risk assessment, a non-quantifiable additional benefit is identified due to the generally very limited data basis available.

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

b2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

The appropriate comparator therapy is 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).

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

The G-BA therefore conclude that an additional benefit is 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).

For the patient groups a1 and b1 (both women), the G-BA take into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties. Uncertainties arise from:

- the unclear transferability of various percentages across several steps of the estimate,
- partially unsuitable percentages for determining the number of female patients in the respective sub-populations, and
- an uncertain operationalisation of the suitability of further endocrine therapy.

Overall, the patient numbers for patient groups a1 and b1 (both women) are within a plausible range despite the uncertainties.

For patient groups a2 and b2 (both men), the ranges reported by the pharmaceutical company are subject to uncertainties. This is because – in addition to the uncertainties listed for patient groups a1 and b1 – the pharmaceutical company extrapolates the percentages for women to men, and the extent of this extrapolation is unclear.

In order to ensure a consistent determination of the patient numbers for the patient group b2 (men) in the present therapeutic indication, the G-BA refer to the derivation of the target population used as a basis in the resolution on the benefit assessment of elacestrant (resolution of 2 May 2024).

For patient group a2 (men), the resolution is based on the patient numbers corrected by the pharmaceutical company during the written statement procedure, taking into account newly diagnosed patients with metastatic disease.

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 Inluriyo (active ingredient: imlunestrant) at the following publicly accessible link (last access: 25 August 2026):

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

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

Patients should be selected for treatment with imlunestrant if an activating ESR1-mutation, which has been detected using a CE-marked in vitro diagnostic (IVD) with an appropriate intended use, is present in the plasma samples. If an IVD with CE marking is not available, the presence of an activating ESR1-mutation in the plasma samples should be detected by an alternative validated test.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 July 2026). 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.

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 guideline⁵.

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^{5,6}.

It is assumed that pre-/perimenopausal patients receive ovarian suppression with a GnRH analogue. According to the product information, treatment with imlunestrant should also be combined with a GnRH analogue in men.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different 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.

a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the 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:				
Imlunestrant	Continuously, 1 x daily	365.0	1	365.0
Plus GnRH analogue, if applicable				
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Leuprorelin	Continuously,	4.0	1	4.0

⁵ 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.

⁶ Hassett MJ, Somerfield MR, Giordano SH. Management of male breast cancer: ASCO guideline summary. JCO Oncol Pract 2020;16(8):e839-e843.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 3 months			
Appropriate comparator therapy				
Tamoxifen (only suitable for premenopausal patients who have not received tamoxifen during prior (neo-)adjuvant endocrine therapy; only suitable for postmenopausal patients if aromatase inhibitors are unsuitable)				
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Letrozole				
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Exemestane (only for patients with progression after anti-oestrogen treatment)				
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Anastrozole				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Fulvestrant				
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2: 1 x monthly	12.0	1 – 2	13.0
Everolimus in combination with exemestane (only suitable for patients without symptomatic visceral metastasis who have disease progression following a non-steroidal aromatase inhibitor)				
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)				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Abemaciclib	Continuously, 2 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, 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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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

a2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the 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:				
Imlunestrant	Continuously, 1 x daily	365.0	1	365.0
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				
Tamoxifen				
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 ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the 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:				
Imlunestrant	Continuously, 1 x daily	365.0	1	365.0
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
Appropriate comparator therapy				
Individualised therapy, taking into account a change of endocrine therapy to				
Tamoxifen				
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Letrozole				
Letrozole	Continuously, 1 x daily	365.0	1	365.0
Exemestane				
Exemestane	Continuously, 1 x daily	365.0	1	365.0
Anastrozole				
Anastrozole	Continuously, 1 x daily	365.0	1	365.0
Fulvestrant				
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15 From cycle 2: 1 x monthly	12.0	1 – 2	13.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Everolimus in combination with exemestane (only suitable for patients without symptomatic visceral metastasis who have disease progression following a non-steroidal aromatase inhibitor)				
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, 2 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, Cycle 1: 1 x on day 1, 15 and 29 From cycle 2: 1 x monthly	12.0	1 – 3	14.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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
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

b2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the 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:				
Imlunestrant	Continuously, 1 x daily	365.0	1	365.0
Plus GnRH analogue				
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Leuprorelin	Continuously,	4.0	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 3 months			
Appropriate comparator therapy				
Individualised therapy, taking into account a change of endocrine therapy to				
Tamoxifen				
Tamoxifen	Continuously, 1 x daily	365.0	1	365.0
Aromatase inhibitor in combination with a GnRH analogue				
Aromatase inhibitor:				
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
GnRH analogues:				
Goserelin	Continuously, 1 x every 28 days	13.0	1	13.0
Leuprorelin	Continuously, 1 x every 3 months	4.0	1	4.0
Fulvestrant				
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 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:

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

a1) Women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

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:					
Imlunestrant	400 mg	400 mg	2 x 200 mg	365.0	730 x 200 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					
Tamoxifen (only suitable for premenopausal patients who have not received tamoxifen during prior (neo-)adjuvant endocrine therapy; only suitable for postmenopausal patients if aromatase inhibitors are unsuitable)					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Letrozole					
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Exemestane (only suitable for patients with disease progression following anti-oestrogen treatment)					
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg
Anastrozole					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Fulvestrant					
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Everolimus in combination with exemestane (only suitable for patients without symptomatic visceral metastasis who have disease progression following a non-steroidal aromatase inhibitor)					
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Anastrozole	1 mg	1 mg	1 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	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
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

a2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following (neo-)adjuvant endocrine therapy; no prior treatment at the locally advanced or metastatic stage

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:					
Imlunestrant	400 mg	400 mg	2 x 200 mg	365.0	730 x 200 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
Appropriate comparator therapy					
Tamoxifen					
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 ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

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:					
Imlunestrant	400 mg	400 mg	2 x 200 mg	365.0	730 x 200 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Individualised therapy, taking into account a change of endocrine therapy to					
Tamoxifen					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Letrozole					
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365 x 2.5 mg
Exemestane					
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365 x 25 mg
Anastrozole					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 mg
Fulvestrant					
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 mg
Everolimus in combination with exemestane (only suitable for patients without symptomatic visceral metastasis who have disease progression following a non-steroidal aromatase inhibitor)					
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
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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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
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

b2) Men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1-mutation, who have disease progression following prior treatment with an endocrine based regimen, which was given at the locally advanced or metastatic stage

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:					
Imlunestrant	400 mg	400 mg	2 x 200 mg	365.0	730 x 200 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
Appropriate comparator therapy					
Individualised therapy, taking into account a change of endocrine therapy to					
Tamoxifen					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Aromatase inhibitor in combination with a GnRH analogue					
Aromatase inhibitor:					
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365 x 1 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
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
GnRH analogues:					
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
Fulvestrant					
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26 x 250 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:					
Imlunestrant 200 mg	56 FCT	€ 18,502.76	€ 1.77	€ 1,053.36	€ 17,447.63
Goserelin 3.6 mg	3 IMP	€ 700.76	€ 1.77	€ 38.16	€ 660.83
Leuprorelin 11.25 mg	2 SRM	€ 1,011.32	€ 1.77	€ 55.32	€ 954.23
Appropriate comparator therapy:					
Abemaciclib 150 mg	168 FCT	€ 6,069.07	€ 1.77	€ 343.27	€ 5,724.03
Anastrozole 1 mg ⁷	100 FCT	€ 44.46	€ 1.77	€ 2.56	€ 40.13
Everolimus 10 mg	90 TAB	€ 1,000.49	€ 1.77	€ 46.91	€ 951.81
Exemestane 25 mg ⁷	100 FCT	€ 128.31	€ 1.77	€ 9.19	€ 117.35
Fulvestrant 250 mg ⁷	1 IPFS	€ 88.54	€ 1.77	€ 6.05	€ 80.72
Goserelin 3.6 mg	3 IMP	€ 700.76	€ 1.77	€ 38.16	€ 660.83
Letrozole 2.5 mg ⁷	120 FCT	€ 62.45	€ 1.77	€ 3.98	€ 56.70
Leuprorelin 11.25 mg	2 SRM	€ 1,011.32	€ 1.77	€ 55.32	€ 954.23
Palbociclib 125 mg	21 FCT	€ 1,620.82	€ 1.77	€ 89.23	€ 1,529.82
Ribociclib 200 mg	189 FCT	€ 6,846.91	€ 1.77	€ 0.00	€ 6,845.14
Tamoxifen 20 mg ⁷	100 TAB	€ 28.82	€ 1.77	€ 1.32	€ 25.73
Abbreviations: FCT = film-coated tablets; IPFS = solution for injection in a pre-filled syringe; IMP = implant; SRM = sustained-release microcapsules and suspending agents; TAB = tablets					

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Costs for additionally required SHI services:

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

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

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

⁷ Fixed reimbursement rate

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 11 June 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 March 2026, the pharmaceutical company submitted a dossier for the benefit assessment of imlunestrant to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 13 March 2026 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 imlunestrant.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 June 2026, and the written statement procedure was initiated with publication on the G-BA website on 15 June 2026. The deadline for submitting written statements was 6 July 2026.

The oral hearing was held on 27 July 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 were discussed at the Subcommittee's session on 25 August 2026, and deliberation of the draft resolution was concluded.

At their session on 3 September 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	4 February 2026	Determination of the appropriate comparator therapy
Working group Section 35a	14 July 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 July 2026	Conduct of the oral hearing
Working group Section 35a	4 August 2026 18 August 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 August 2026	Concluding discussion of the draft resolution
Plenum	3 September 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 September 2026

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

Dr Optendrenk