Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Elacestrant (breast cancer, ER+, HER2-, with ESR1 mutation, after at least 1 prior therapy)

of 2 May 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

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

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

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

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

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient elacestrant on 2 November 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 31 October 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 February 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of elacestrant compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of elacestrant.

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

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

2.1.1 Approved therapeutic indication of Elacestrant (Orserdu) in accordance with the product information

ORSERDU monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Therapeutic indication of the resolution (resolution of 2 May 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Appropriate comparator therapy for elacestrant as monotherapy:

Therapy according to doctor's instructions, taking into account a change of endocrine therapy to

- tamoxifen
- anastrozole
- fulvestrant as monotherapy
- letrozole

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

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

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Appropriate comparator therapy for elacestrant as monotherapy:

Therapy according to doctor's instructions, taking into account a change of endocrine therapy to

- tamoxifen,
- aromatase inhibitor in combination with a GnRH analogue,
- fulvestrant

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

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

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the

appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

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

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

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

on 1. In addition to elacestrant, the anti-estrogens tamoxifen, toremifene, fulvestrant; the non-steroidal aromatase inhibitors anastrozole and letrozole; the steroidal aromatase inhibitor exemestane; the progestogens megestrol acetate and medroxyprogesterone acetate, the gonadotropin-releasing hormone analogues leuprorelin and goserelin; the protein kinase inhibitors everolimus, palbociclib, ribociclib and abemaciclib as well as the PARP inhibitors olaparib and talazoparib and the PI3K inhibitor alpelisib are approved for the present therapeutic indication.

on 2. Both surgical resection and/or radiotherapy as well as ovariectomy for the cessation of ovarian function are generally considered as non-medicinal therapies for the treatment of breast carcinoma. For the present therapeutic indication, it is assumed that radiotherapy and/or (secondary) resection with a curative objective is not indicated. The (secondary) resection and/or radiotherapy were therefore not included in the appropriate comparator therapy.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Abemaciclib: Resolutions of 02.05.2019, 03.09.2020 and 19.05.2022
- Alpelisib: Resolution of 18 February 2021
- Olaparib: Resolution of 16 January 2020
- Palbociclib: Resolutions of 18.05.2017, 22.03.2019 and 15.12.2022
- Ribociclib: Resolutions of 04.07.2019 and 20.08.2020
- 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 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").

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

When determining the appropriate comparator therapy, it was assumed that re-therapy with a CDK4/6 inhibitor is not an option according to the available evidence. Therefore, CDK4/6 inhibitors were not considered as an appropriate comparator therapy for patients who have already received treatment with a CDK4/6 inhibitor.

For the present therapeutic indication, it is also assumed that an additional endocrine therapy is indicated for the patients and in particular that there is no indication for chemotherapy for achieving a necessary, quick remission. Furthermore, it is assumed that there is no indication for (secondary) resection or radiotherapy with a curative objective.

It is also assumed that a change of treatment takes place with regard to the active ingredients used in the previous endocrine therapy.

It is also assumed that treatment with elacestrant is not indicated for patients with a genomic BRCA1/2 mutation for whom BRCA-specific therapy is an option.

The present therapeutic indication includes both women and men, which is why a differentiation by sex (women/men) is made in the patient populations when determining the appropriate comparator therapy:

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

In the treatment setting of disease progression in postmenopausal patients on previous endocrine therapy, national and international guidelines unanimously recommend further endocrine therapy, using an alternative agent, if there is no indication for chemotherapy. Patients who have already received prior chemotherapy can also be offered endocrine therapy in accordance with the guidelines. Overall, anti-estrogens, estrogen receptor antagonists, aromatase inhibitors and the mTOR inhibitor everolimus are mentioned as possible treatment options in the event of disease progression following endocrine therapy. 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 restriction to patients without symptomatic visceral metastasis followed by progression after a non-steroidal aromatase inhibitor for everolimus in combination with exemestane reflects the authorisation status.

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

The available guidelines[2,3] show that a change of the substance class used is recommended as an essential part of the therapy algorithm in the context of endocrine therapy of advanced HR-positive breast cancer. Against this background, when determining the appropriate comparator therapy, the G-BA specifically focussed on a change in endocrine therapy, naming the corresponding active ingredients.

In the case of prior therapy with an aromatase inhibitor, the guidelines[2,3] recommend switching to treatment with an anti-oestrogen or an oestrogen receptor antagonist. In this regard, the available guidelines specifically state that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors. This fact was also presented in the statements submitted by medical experts in the benefit assessment procedures of the G-BA already carried out in this therapeutic indication.

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

For the indication area following prior therapy with a non-steroidal aromatase inhibitor, monotherapy with the steroidal aromatase inhibitor exemestane is therefore adequate in view of the guideline recommendations[2]. A corresponding implementation would also not be fully possible with the approved therapy option everolimus in combination with exemestane, as this is again only indicated for a limited patient population according to the marketing authorisation.

It should also be taken into account that the use of a (renewed) therapy with a non-steroidal aromatase inhibitor after a possible previous therapy with a non-steroidal aromatase inhibitor in combination with a CDK4/6 inhibitor is considered implausible in the sense of the standard case according to the current state of medical knowledge. This also applies to the indication area after previous therapy with a steroidal aromatase inhibitor in combination with a CDK4/6 inhibitor with regard to (renewed) therapy with the steroidal aromatase inhibitor exemestane.

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2 Oncology guideline programme, German Cancer Society (DKG), German Cancer Aid (DKH), Association of the Scientific-Medical Societies in Germany (AWMF). Early detection, diagnosis, therapy and follow-up of breast cancer, interdisciplinary S3 guideline, long version 4.4 [online]. AWMF register 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.

Overall, for the patient group of postmenopausal women, the use of fulvestrant, letrozole and exemestane for the indication area after prior therapy with an endocrine therapy other than anti-oestrogens, in particular after prior therapy with aromatase inhibitors, is generally preferable 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 medicinal products also in the off-label use for this indication area as the appropriate comparator therapy.

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

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. 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.

The active ingredients tamoxifen, fulvestrant and aromatase inhibitors + GnRH analogue are recommended in the guidelines[2,3,4] for the patient group of men. However, aromatase inhibitors and fulvestrant are only approved for use in women. Accordingly, the use of aromatase inhibitors and fulvestrant in the patient group of men represents an off-label use.

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

The available guidelines also indicate that a change of substance class is recommended as an essential part of the treatment algorithm for endocrine therapy of advanced HR-positive breast cancer.

Based on the available evidence, it can also be assumed that renewed treatment with a CDK4/6 inhibitor is not an option.

Thus, the use of fulvestrant and aromatase inhibitors + GnRH analogue is generally preferable to tamoxifen for the patient group of men in the described indication area, in accordance with Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV. It is therefore appropriate to determine the off-label use of the above-mentioned medicinal products as appropriate comparator therapy.

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

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

   a1) Postmenopausal women with 1 prior line of endocrine therapy

      An additional benefit is not proven.

   a2) Postmenopausal women with 2 prior lines of endocrine therapy

      Hint for a considerable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company submits results of the EMERALD study. In the ongoing open-label phase III EMERALD study, elacestrant is being compared with a therapy according to doctor's instructions with selection of fulvestrant, anastrozole, letrozole and exemestane. The study has been conducted in 150 study sites in Australia, Asia, Europe and USA since May 2019.

The study enrolled postmenopausal women and men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease had progressed after 1 or 2 lines of endocrine therapy, including a CDK 4/6 inhibitor. For these patients, endocrine therapy still had to be indicated and they were allowed to have received a maximum of 1 chemotherapy line in the advanced/ metastatic stage. Further requirements were an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1 and the absence of symptomatic visceral metastases.

In accordance with the inclusion criteria of the EMERALD study, patients with bilateral ovariectomy were also enrolled in the study. The ESR1-mut population includes 46 patients (20.2%) who were enrolled as postmenopausal due to bilateral ovariectomy.

An existing activating ESR1 mutation was determined as part of the screening. Patients with and without an ESR1 mutation in the tumour tissue were enrolled.

Overall, 478 patients were randomised in a 1:1 ratio to treatment with elacestrant (N = 239) or to therapy according to doctor's instructions (N = 239) and enrolled. Elacestrant is only approved for patients with an activating ESR1 mutation.

The dossier presented a post hoc sub-population of the ESR1-mut population excluding approx. 13% of the patients. Data on the complete ESR1-mut population were subsequently submitted as part of the written statement procedure and are used for the present assessment.

The ESR1-mut sub-population of the EMERALD study comprises a total of 228 patients, 115 in the intervention arm and 113 in the comparator arm. Stratification was based on ESR1 mutational status (ESR1-mut [mutated] vs ESR1-mut-nd [not detected or indeterminable]), pretreatment with fulvestrant (yes vs no) and the presence of visceral metastases (yes vs no).

In both study arms, the treatment of the patients was in accordance with the requirements in the respective product information. Treatment switching from the intervention to the comparator therapy or vice versa was not permitted. The study protocol does not include any specifications with regard to the use of possible follow-up treatments.

The primary endpoint of the EMERALD study is progression-free survival (PFS) according to the blinded, independent review committee (IRC). Results are also available for other endpoints in the categories of mortality, morbidity, health-related quality of life and side effects.

Three data cut-offs have been carried out so far. The data cut-off from 06.09.2021 is the final PFS data cut-off. An FDA safety data cut-off was carried out on 08.07.2022. The data cut-off from 02.09.2022 was the final data cut-off on overall survival. The data cut-offs from 08.07.2022 and 02.09.2022 are used for the present assessment.

Extent and probability of the additional benefit

Analysis across endpoints

In the subgroup analyses for the characteristic "number of previous lines of endocrine therapy in the advanced/ metastatic stage" (1 vs 2) showed a significantly different effect for the overall survival endpoint depending on the number of previous lines of therapy.

As part of the written statement procedure, the clinical experts discussed this difference in effect in connection with increasing resistance to conventional endocrine therapy.

The G-BA considers it appropriate to conduct a separate assessment of the additional benefit for patients with 2 previous lines of endocrine therapy and with 1 previous line of endocrine therapy based on the effect modification with regard to the characteristic "number of previous lines of endocrine therapy".

Mortality

The overall survival was operationalised in the EMERALD study as the time from randomisation to death from any cause.

For this endpoint, there was no statistically significant difference between the study arms in the total population.

The subgroup analysis showed a statistically significant difference in overall survival in favour of elacestrant compared to therapy according to doctor's instructions for patients with 2 previous lines of endocrine therapy. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

For patients with 1 previous line of endocrine therapy, there was no statistically significant difference between the treatment arms.

Morbidity

Progression-free survival (PFS)

Progression-free survival (PFS) is defined in the study as the time from randomisation to the earlier date of subsequent events: Documented progression of disease (RECIST version 1.1) according to the assessment by a blinded IRC or death from any cause.

For the PFS, there was a statistically significant difference to the advantage of elacestrant compared to therapy according to doctor's instructions.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component of mortality is already assessed via the endpoint of overall survival 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.

Irrespective of this, the overall statement on the extent of additional benefit would remain unchanged even if the present result on PFS were taken into account.

Symptomatology (EORTC QLQ-C30)

The symptomatology of the EMERALD study patients was collected using the symptom scales of the EORTC QLQ-C30 questionnaire.

For the endpoint of appetite loss, there was a statistically significant difference to the disadvantage of elacestrant compared to therapy according to doctor's instructions.

For the endpoint of insomnia, there was no statistically significant difference between the treatment groups. There is an effect modification by the characteristic of number of previous lines of endocrine therapy. For patients with 1 previous line of endocrine therapy, there was a statistically significant difference between the treatment arms to the advantage of elacestrant. For patients with 2 previous lines of endocrine therapy, there was no statistically significant difference between the treatment groups.

There was no statistically significant difference between the treatment groups for the endpoints of fatigue, nausea/ vomiting, pain, dyspnoea, constipation and diarrhoea.

Health status (EQ-5D VAS)

For the endpoint of health status, assessed by EQ-5D VAS, there is no statistically significant difference between the treatment arms.

In the overall analysis of the results, neither an advantage nor a disadvantage was found with regard to morbidity.

Health-related quality of life

The quality of life of the EMERALD study patients is assessed using the functional scales of the EORTC QLQ-C30 questionnaire.

There was no statistically significant difference between the treatment groups for the endpoints of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning.

With regard to health-related quality of life, there is no statistically significant difference between the treatment arms.

Side effects

Adverse events in total

In the EMERALD study, AEs occurred in both treatment arms in almost all study participants. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and discontinuation due to AEs

There were no statistically significant differences between the treatment groups for each of the endpoints of SAEs, severe AEs and discontinuation due to AEs.

Specific AEs

"Gastrointestinal disorders" and "Musculoskeletal and connective tissue disorders"

For the endpoints "gastrointestinal disorders" (SOC, AEs) and "musculoskeletal and connective tissue disorders" (SOC, severe AEs), there was a statistically significant difference to the disadvantage of elacestrant in the total population.

In the overall analysis of the results regarding side effects, neither an advantage nor a disadvantage was found for treatment with elacestrant in comparison to therapy according to doctor's instructions. In detail, there were disadvantages in the specific AEs "gastrointestinal disorders" and "musculoskeletal and connective tissue disorders".

Overall assessment/ conclusion

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

For the assessment of the additional benefit of elacestrant in patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation; with disease progression after at least one line of endocrine therapy including a CDK4/6 inhibitor, results on mortality, morbidity, health-related quality of life and side effects from the randomised, open-label, multicentre, controlled EMERALD study are available. In the EMERALD study, elacestrant was compared with a therapy according to doctor's instructions with a choice of fulvestrant, anastrozole, letrozole and exemestane.

The assessment is based on the data cut-offs from 08.07.2022 and 02.09.2022.

In the subgroup analyses on the characteristic "number of previous lines of endocrine therapy in the advanced/ metastatic stage" (1 vs 2), a significantly different effect was shown for the endpoint "overall survival" depending on the number of previous lines of therapy.

Due to this effect modification, a separate assessment of the additional benefit is performed for patients with 1 previous line of endocrine therapy and with 2 previous lines of endocrine therapy.

a1) Postmenopausal women with 1 prior line of endocrine therapy

For patients with a previous line of endocrine therapy, there was no statistically significant difference between the treatment arms in the endpoint category of overall survival.

In the morbidity category, there was neither an overall advantage nor a disadvantage of treatment with elacestrant. In detail, there is a disadvantage for the total population in the endpoint "appetite loss" (collected using the EORTC QLQ-C30) and an advantage for patients with 1 previous line of endocrine therapy for the endpoint "insomnia" (collected using the EORTC QLQ-C30).

For health-related quality of life, there was neither an advantage nor a disadvantage of treatment with elacestrant.

For the endpoint category of side effects, there was neither an advantage nor a disadvantage of elacestrant compared to therapy according to doctor's instructions. In detail, the total population showed disadvantages for specific AEs.

In the overall analysis of the results, there were neither advantages nor disadvantages in all endpoint categories. For patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation and 1 previous line of therapy, an additional benefit of elacestrant compared to therapy according to doctor's instructions is therefore not proven.

a2) Postmenopausal women with 2 prior lines of endocrine therapy

For patients with 2 previous lines of endocrine therapy, there was a statistically significant difference to the advantage of elacestrant in the endpoint category of overall survival. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

In the morbidity category, there was neither an overall advantage nor a disadvantage of treatment with elacestrant. In detail, there was a disadvantage for the total population in the endpoint "appetite loss" (collected using the EORTC QLQ-C30).

For health-related quality of life, there was neither an advantage nor a disadvantage of treatment with elacestrant.

For the endpoint category of side effects, there was neither an advantage nor a disadvantage of elacestrant compared to therapy according to doctor's instructions. In detail, the total population showed disadvantages for specific AEs.

In the overall assessment, there was an advantage in mortality. Overall, there were neither advantages nor disadvantages in the other endpoint categories. The overall assessment found a considerable additional benefit of elacestrant compared with therapy according to doctor's instructions for patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation and 2 prior lines of therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, phase III EMERALD study.

Due to the relevant difference between the treatment arms in patients not included in the evaluation, there is a high risk of bias across endpoints in relation to the overall study population. However, the present data basis shows that only one patient was not included in the evaluation for the subgroup of patients with two previous lines of endocrine therapy. This means that there is a low risk of bias in the results for the endpoint of overall survival for this subgroup.

A relevant limitation arises due to the low patient number in this subgroup of patients with 2 previous lines of endocrine therapy.

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

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

An additional benefit is not proven.

Justification:

No men are enrolled in the label-enabling sub-population from the EMERALD study (ESR1-mut sub-population).

Overall, there are therefore no data for the assessment of the additional benefit of elacestrant compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Orserdu with the active ingredient elacestrant.

The active ingredient elacestrant is approved for the treatment of postmenopausal women and men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor.

In the therapeutic indication under consideration, 2 patient groups were distinguished and the appropriate comparator therapy was determined as follows:

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an

activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

On a)

The appropriate comparator therapy is a therapy according to doctor's instructions, taking into account a change of endocrine therapy to tamoxifen, anastrozole, fulvestrant as monotherapy, letrozole, exemestane and everolimus.

The pharmaceutical company submits data from the EMERALD study for the benefit assessment. The patient population relevant for the assessment is made up of ESR1-mutated patients.

For the endpoint of overall survival, there was an effect modification due to the characteristic "number of previous lines of endocrine therapy in the advanced/ metastatic stage". A separate assessment of the additional benefit was conducted for patients with 1 previous line of endocrine therapy and patients with 2 previous lines of endocrine therapy.

On a1)

For patients with a previous line of endocrine therapy, there was no statistically significant difference between the treatment arms in the endpoint categories of mortality and health-related quality of life.

In the categories of morbidity and side effects, there was neither an overall advantage nor a disadvantage of treatment with elacestrant.

The conclusion is that there is no evidence of an additional benefit of elacestrant compared with therapy according to doctor's instructions for patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation and 1 previous line of endocrine therapy.

On a2)

For patients with 2 previous lines of endocrine therapy, there was a clear advantage of elacestrant in the mortality endpoint category.

In the category of morbidity and side effects, there was neither an overall advantage nor a disadvantage of treatment with elacestrant.

For health-related quality of life, there was no statistically significant difference between the treatment arms.

The G-BA concluded that elacestrant has a considerable additional benefit compared with therapy according to doctor's instructions for patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation and 2 previous lines of endocrine therapy.

A relevant limitation arises due to the low patient number in this subgroup of patients with 2 previous lines of endocrine therapy.

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

On b)

The appropriate comparator therapy is a therapy according to doctor's instructions, taking into account a change of endocrine therapy to tamoxifen, aromatase inhibitors in combination with a GnRH analogue and fulvestrant.

No men are enrolled in the label-enabling sub-population from the EMERALD study (ESR1-mut sub-population).

There are therefore no data for the assessment of the additional benefit of elacestrant compared to the appropriate comparator therapy. Therefore, an additional benefit is not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of abemaciclib (resolution of 19 May 2022) for women and to the benefit assessment of alpelisib (resolution of 18 February 2021) for men.

With regard to the presentation of patient numbers as a function of the number of previous therapies, the following percentages were estimated for the patient groups of women: 60.61% for patients with 1 previous line of endocrine therapy in the advanced/ metastatic stage and 39.39% for patients with 2 previous lines of endocrine therapy in the advanced/ metastatic stage. Thus, compared to the benefit assessment of abemaciclib, there are further deviations in the patient numbers by adjusting the percentage of prior therapies.

As treatment with elacestrant is restricted to patients with an ESR1 mutation, the target population was further narrowed down using a range.

Furthermore, the use of more up-to-date data on the incidence and prevalence of breast cancer in Germany and the consideration of the current 87.7% patients in the SHI target population result in further minor deviations.

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Orserdu (active ingredient: elacestrant) at the following publicly accessible link (last access: 22 January 2024):

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

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

Patients should be selected for treatment with ORSERDU based on the presence of an activating ESR1 mutation in plasma specimens, using a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating ESR1 mutation in plasma specimens should be assessed by an alternative validated test.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

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

Treatment period:

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

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Elacestrant	Continuously, 1 x daily	365	1.0	365
Appropriate comparator therapy				
Tamoxifen	Continuously, 1 x daily	365	1.0	365
Anastrozole	Continuously, 1 x daily	365	1.0	365
Fulvestrant	Continuously, Cycle 1: 1 x on day 1 and 15; From cycle 2 onwards: 1 x monthly	13	1.0	13
Letrozole	Continuously, 1 x daily	365	1.0	365
Exemestane	Continuously, 1 x daily	365	1.0	365
Everolimus	Continuously, 1 x daily	365	1.0	365

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Elacestrant	Continuously, 1 x daily	365	1.0	365
Appropriate comparator therapy				
Tamoxifen	Continuously, 1 x daily	365	1.0	365
Fulvestrant[5]	Continuously, Cycle 1: 1 x on day 1 and 15; From cycle 2 onwards: 1 x monthly	13	1.0	13
Aromatase inhibitors in combination with a GnRH analogue[6]				
Anastrozole[6]	Continuously, 1 x daily	365	1.0	365
Letrozole[6]	Continuously, 1 x daily	365	1.0	365
Exemestane[6]	Continuously, 1 x daily	365	1.0	365
Leuprorelin[6]	1 x every 28 days	13.0	1.0	13.0
Goserelin[6]	1 x every 28 days	13.0	1.0	13.0

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.

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

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					
Elacestrant	345 mg	345 mg	1 x 345 mg	365.0	365.0 x 345 mg
Appropriate comparator therapy					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365.0 x 20 mg
Anastrozole	1 mg	1 mg	1 x 1 mg	365.0	365.0 x 1 mg
Fulvestrant	500 mg	500 mg	2 x 250 mg	13.0	26.0 x 250 mg
Letrozole	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365.0 x 2.5 mg
Exemestane	25 mg	25 mg	1 x 25 mg	365.0	365.0 x 25 mg
Everolimus	10 mg	10 mg	1 x 10 mg	365.0	365.0 x 10 mg

b) Men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

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					
Elacestrant	345 mg	345 mg	1 x 345 mg	365.0	365.0 x 345 mg
Appropriate comparator therapy					
Tamoxifen	20 mg	20 mg	1 x 20 mg	365.0	365.0 x 20 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[5]	250 mg	Cycle 1: 500 mg initial dose on day 1 and 250 mg on day 15; From cycle 2 onwards: 1 x monthly 250 mg	Initial dose on day 1: 2 x 250 mg; all other days: 1 x 250 mg	13.0	14.0 x 250 mg
Aromatase inhibitor in combination with a GnRH analogue[6]					
Anastrozole[6]	1 mg	1 mg	1 x 1 mg	365.0	365.0 x 1 mg
Letrozole[6]	2.5 mg	2.5 mg	1 x 2.5 mg	365.0	365.0 x 2.5 mg
Exemestane[6]	25 mg	25 mg	1 x 25 mg	365.0	365.0 x 25 mg
Leuprorelin[6]	3.75 mg	3.75 mg	3.75 mg	13.0	13.0 x 3.75 mg
Goserelin[6]	3.6 mg	3.6 mg	3.6 mg	13.0	13.0 x 3.6 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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

5 Zagouri F, Sergentanis TN, Chrysikos D, Zografos E, Rudas M, Steger G, Zografos G, Bartsch R. Fulvestrant and male breast cancer: a case series. Ann Oncol. 2013 Jan;24(1):265-6

6 Di Lauro L, Pizzuti L, Barba M, Sergi D, Sperduti I, Mottolese M, Amoreo CA, Belli F, Vici P, Speirs V, Santini D, De Maria R, Maugeri-Saccà M. Role of gonadotropin-releasing hormone analogues in metastatic male breast cancer: results from a pooled analysis. J Hematol Oncol. 2015 May 17;8:53

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						
Elacestrant 345 mg	28	FCT	€ 10,476.11	€ 2.00	€ 595.00	€ 9,879.11
Appropriate comparator therapy						
Tamoxifen 20 mg	100	TAB	€ 22.47	€ 2.00	€ 0.88	€ 19.59
Anastrozole 1 mg	120	FCT	€ 48.87	€ 2.00	€ 2.97	€ 43.90
Fulvestrant 250 mg	2	SFI	€ 370.14	€ 2.00	€ 28.38	€ 339.76
Letrozole 2.5 mg	120	FCT	€ 61.68	€ 2.00	€ 3.98	€ 55.70
Exemestane 25 mg	100	FCT	€ 127.53	€ 2.00	€ 9.19	€ 116.34
Everolimus 10 mg	30	TAB	€ 499.35	€ 2.00	€ 23.16	€ 474.19
Leuprorelin 3.75 mg	3	SRM	€ 501.87	€ 2.00	€ 27.16	€ 472.71
Goserelin 3.6 mg	3	IMP	€ 632.16	€ 2.00	€ 34.37	€ 595.79
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; IMP = implant; SRM = sustained-release microcapsules and suspending agents; TAB = tablets						

LAUER-TAXE® last revised: 15 April 2024

Costs for additionally required SHI services:

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

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

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations

containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

Basic principles of the assessed medicinal product

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

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

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

designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

Concomitant active ingredient

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

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

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

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

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as

part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical

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

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

Justification for the findings on designation in the present resolution:

a) Postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

   No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Patient group - men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor

   No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 its session on 8 June 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 5 October 2023.

On 31 October 2023, the pharmaceutical company submitted a dossier for the benefit assessment of elacestrant to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1 VerfO.

By letter dated 31 October 2023 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 elacestrant.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 January 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 February 2024. The deadline for submitting statements was 22 February 2024.

The oral hearing was held on 11 March 2024.

By letter dated 12 March 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 12 April 2024.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 June 2022	Implementation of the appropriate comparator therapy
Plenum	5 October 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	6 March 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 March 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 March 2024 4 April 2024 16 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

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

Prof. Hecken