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 Gozetotide (first dossier requirement: Detection of PSMA-positive prostate cancer (mCRPC), PSMA-targeted therapy)

of 16 January 2025

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The diagnostic agent Locametz with the active ingredient gozetotide was approved on 19 December 2022 for the detection of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings: Primary staging of patients with high-risk PCa prior to initial curative therapy, suspected PCa recurrence in patients with rising levels of prostate-specific antigen (PSA) in serum after initial curative therapy and identification of patients with PSMA-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) in whom PSMA-targeted therapy is indicated.

With an amendment of the Uniform Value Scale (UVS) with effect from 1 October 2023, gozetotide became reimbursable for the first time as part of a flat-rate fee for material costs, thus falling within the scope of Section 35a paragraph 1 SGB V in analogous application of the regulation in Chapter 5 Section 1, paragraph 2, No. 4 of the Rules of Procedure (VerfO). Accordingly, the pharmaceutical company was requested to submit a dossier. The relevant date for the submission of a dossier was 15 July 2024 in analogous application of the regulation according to Chapter 5 Section 8, paragraph 1, No. 3 of the Rules of Procedure.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 October 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 gozetotide 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. 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 gozetotide.

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 Gozetotide (Locametz) in accordance with the product information

This medicinal product is for diagnostic use only.

Gozetotide, after radiolabelling with gallium-68, is indicated for the detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:

- Primary staging of patients with high-risk PCa prior to primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,
- Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

Therapeutic indication of the resolution (resolution of 16.01.2025):

Gozetotide, after radiolabelling with gallium-68, is indicated for the detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:

- Identification of patients with PSMA-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with progressive metastatic castration-resistant prostate cancer (mCRPC); diagnosis; identification of patients with prostate-specific membrane antigen (PSMA)-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated

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

The appropriate comparator therapy for gozetotide after radiolabelling with gallium-68 for positron emission tomography (PET) possibly followed by PSMA-targeted therapy with lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway:

A patient-individual therapy under selection of:

- abiraterone in combination with prednisone or prednisolone,
- enzalutamide,
- cabazitaxel,
- olaparib,
- best supportive care,

taking into account previous therapies, comorbidity, general condition and BRCA1/2 mutational status.

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

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

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

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

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

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,

2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

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

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

On 1. In addition to gozetotide, there are currently no medicinal products approved for the identification of patients with PSMA-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

On 2. In this therapeutic indication, computed tomography or (skeletal) scintigraphy can generally be used as non-medicinal treatment options. These treatment options are not considered for identifying PSMA-positive lesions.

On 3. No resolutions are available.

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

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The diagnostic agent Locametz with the active ingredient gozetotide is the first approved medicinal product that can be used to identify patients with prostate-specific membrane antigen (PSMA)-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

There are no further or other diagnostic agents with a marketing authorisation to identify patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. A comparison with another diagnostic agent or another diagnostic test is therefore not considered for the determination of the appropriate comparator therapy.

During the assessment of diagnostic tests, it must be taken into account that the health-related benefit (or harm) of diagnostic procedures essentially arises from the fact that the test is followed by therapeutic procedures. Diagnostics should therefore facilitate therapy control.

Diagnostic interventions should be assessed in terms of benefit and harm in a very similar way to therapeutic interventions. Benefit assessments of diagnostic procedures should primarily be carried out on the basis of comparative intervention studies with patient-relevant endpoints. Depending on the diagnostic intervention and medical context, i.e. the research question, different study designs can be considered, whereby

a distinction must be made between strategy design, interaction design and enrichment design.

Based on this, a therapy was determined for the appropriate comparator therapy both on the intervention side and for the comparison as central cornerstones of the research question for the benefit assessment according to Section 35a SGB V.

The active ingredient gozetotide is intended to identify patients with PSMA-positive, progressive mCRPC for whom PSMA-targeted therapy is indicated. After diagnosis with gozetotide, PSMA-positive patients undergo PSMA-targeting therapy, which is therefore the therapy on the intervention side in PSMA-positive patients. There is no change with regard to the subsequent therapy for patients who are ineligible for PSMA-targeted therapy due to a negative test result. This therefore corresponds to the previous standard therapy for PSMA-negative patients or the previous standard therapy independent of PSMA status

In this regard, only the active ingredient lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway is currently approved for the treatment of PSMA-positive mCRPC. In their written statement, the Drugs Commission of the German Medical Association (AkdÄ) recommends lutetium (^{177}Lu) vipivotide tetraxetan for patients with mCRPC. In addition, an indication of a considerable additional benefit was identified for a sub-population in the associated benefit assessment found (resolution of 06.07.2023). According to the marketing authorisation for lutetium (^{177}Lu) vipivotide tetraxetan, PSMA testing is a prerequisite prior to initiation of treatment with the active ingredient. Thus, for the research question of the benefit assessment for the intervention side with regard to PSMA-positive patients, it is established that gozetotide radiolabelled with gallium-68 should be considered for positron emission tomography (PET) followed by PSMA-targeted therapy with lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway.

For the comparator therapy, the standard therapy is determined independently of the PSMA status. In this regard, a patient-individual therapy is determined according to the current state of medical knowledge by selecting abiraterone in combination with prednisone or prednisolone, enzalutamide, cabazitaxel, olaparib and best supportive care, taking into account previous therapies, comorbidity, general condition and BRCA1/2 mutational status.

This is justified as follows: In the national and international guidelines, the therapy recommendations for adults with progressive mCRPC include treatment with the active ingredients abiraterone acetate, cabazitaxel, enzalutamide and olaparib, as well as radium-223 dichloride and lutetium (^{177}Lu) vipivotide tetraxetan. For the appropriate comparator therapy to be determined here, lutetium (^{177}Lu) vipivotide tetraxetan was ruled out as a comparator therapy.

No clear recommendations can be derived from the guidelines for a preferred sequential therapy after previous treatments with an androgen receptor antagonist and taxane chemotherapy, which is why no uniform treatment standard can be named. Patients who have already received a new hormonal substance (NHA) (abiraterone or enzalutamide) can be offered sequence therapy in the further line, taking into account the previously non-administered active ingredient. According to the guidelines, it cannot be conclusively assessed whether a second androgen receptor-directed treatment (ARDT) after progression under the first-line treatment with the respective other active ingredient may be less effective than renewed chemotherapy. Therefore,

it is important to consider the new hormonal substance used to previously treat the patients. The guidelines also recommend that patients who show progression under a new hormonal substance should be offered a change in the therapy principle. The active ingredients cabazitaxel or olaparib should be considered here in particular. In this regard, a therapy with olaparib is recommended for patients with a BRCA 1/2 mutation.

The present therapeutic indication also includes patients who are ineligible for further NHA and/or taxane-containing therapy, taking into account in particular the general condition or relevant comorbidities, or for whom antineoplastic therapy options are usually no longer available. Thus, best supportive care within the framework of patient-individual therapy represents a further regular therapeutic alternative in the present therapeutic indication. "Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

Within the scope of the benefit assessment according to Section 35a SGB V, the active ingredients abiraterone acetate, cabazitaxel, enzalutamide, olaparib and radium-223-dichloride were assessed. The sometimes different therapeutic indications, which address different treatment settings and sometimes specific characteristics, must be taken into account here. For cabazitaxel, an indication of a minor additional benefit was found compared to best supportive care (resolution of 29.03.2012). In the respective benefit assessments, an indication of a considerable additional benefit could be identified for both abiraterone acetate (resolution of 29.03.2012) and enzalutamide (resolution of 20.02.2014) compared with best supportive care. By resolution of 03.06.2021, a hint for a considerable additional benefit of olaparib over patient-individual therapy, selecting abiraterone, enzalutamide, cabazitaxel and docetaxel was identified.

In the respective benefit assessments on olaparib in combination with abiraterone acetate (resolution of 06.07.2023) and niraparib/ abiraterone acetate (resolution of 02.05.2024), no additional benefit over patient-individual therapy was identified for the group of adults with mCRPC for whom chemotherapy is not clinically indicated and who have already received prior therapy for mCRPC, as no data were available. These two combinations of active ingredients are not determined as appropriate comparator therapies.

Talazoparib in combination with enzalutamide is a new treatment option in the present therapeutic indication. The combination of active ingredients was only recently approved (marketing authorisation on 05.01.2024). In the benefit assessment (resolution of 15.08.2024), a hint for a minor benefit was identified for adults without HRR deficiency and no additional benefit compared with enzalutamide for adults with HRR deficiency. Based on the generally accepted state of medical knowledge, talazoparib in combination with enzalutamide is not determined to be an appropriate comparator therapy here.

No additional benefit was identified for radium-223 dichloride compared to patient-individual therapy with selection of abiraterone, enzalutamide, cabazitaxel and docetaxel or compared to best supportive care (resolution of 17.10.2019). In addition, radium-223 dichloride is specifically indicated for symptomatic bone metastases without known visceral metastases. In the overall assessment, radium-223 dichloride is not determined to be an appropriate comparator therapy.

On this basis, a patient-individual therapy is determined as the appropriate comparator therapy with selection of abiraterone acetate in combination with prednisone or

prednisolone, enzalutamide, cabazitaxel, olaparib and best supportive care, taking into account previous therapies, comorbidity, general condition and BRCA-1/2 mutational status.

For the implementation of patient-individual therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned (multi-comparator study).

Continuation of an existing conventional androgen deprivation (ADT) is assumed. In the context of the present therapeutic indication, conventional androgen deprivation therapy refers to surgical or medicinal castration by therapy with GnRH agonists or GnRH antagonists. Metastatic, castration-resistant prostate cancer is a palliative treatment setting. Therefore, maintaining quality of life and symptom control are of particular importance. Adequate concomitant treatment of bone metastases during the study is assumed (e.g. use of bisphosphonates, denosumab, radiation).

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with progressive metastatic castration-resistant prostate cancer (mCRPC); diagnosis; identification of patients with prostate-specific membrane antigen (PSMA)-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated

   a1) Adults for whom abiraterone in combination with prednisone or prednisolone, enzalutamide, or best supportive care is the appropriate patient-individual therapy

   Indication of a considerable additional benefit

   a2) Adults for whom cabazitaxel or olaparib is the appropriate patient-individual therapy

   An additional benefit is not proven.

Justification:

The medicinal product Locametz with the active ingredient gozetotide, after radiolabelling with gallium-68, is approved for the detection of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adults with prostate cancer (PCa) for the identification of patients with PSMA-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) in whom PSMA-targeted therapy is indicated. It is therefore a medicinal product that is used as a diagnostic agent.

According to the legal grounds pursuant to Section 35a paragraph 1 SGB V, the G-BA assesses the benefit of all reimbursable medicinal products with new active ingredients. The active ingredient gozetotide is a medicinal product within the meaning of Section 2 paragraph 1 Medicinal Products Act with a new active ingredient within the meaning of Chapter 5 Section

2, paragraph 1 Rules of Procedure (VerfO), thus generally being subject to the scope of the benefit assessment according to Section 35a paragraph 1 SGB V. Accordingly, the differentiated requirements for the benefit assessment according to Section 35a SGB V in the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and the G-BA's Rules of Procedure are to be applied.

Gozetotide is the first approved medicinal product that can be used to identify patients with prostate-specific membrane antigen (PSMA)-positive, progressive, metastatic castration-resistant prostate cancer for whom PSMA-targeted therapy is indicated. There is no other diagnostic agent with a marketing authorisation in this therapeutic indication. A comparison with another diagnostic agent is not considered for the benefit assessment.

Depending on the diagnostic intervention and medical context, i.e. the research question, different RCT study designs can be considered for the assessment of diagnostic agents, whereby a distinction must be made between strategy design, interaction design and enrichment design. The aim of the diagnosis here is to identify patients with PSMA-positive mCRPC in whom PSMA-targeted therapy is indicated. The additional benefit of the diagnostic agent gozetotide for the detection of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) was therefore assessed. Due to the explicit substantial link between the use of the active ingredient gozetotide in the context of performing a PSMA-PET for the specific indication of a therapy with lutetium (^{177}Lu) vipivotide tetraxetan, there was a special feature in the research question for the present procedure.

For the benefit assessment, the pharmaceutical company presented the VISION study, which follows the enrichment design. In this design, only some of the patients (in this case, the patients with PSMA-positive lesions) are randomised to the intervention or comparator arm on the basis of the diagnostic agent or diagnostic test to be reviewed. The use of the enrichment design to answer the specific research question here was assessed by IQWiG as appropriate, taking into account the medical context described above. This is based on the assumption that PSMA-negative patients do not benefit from PSMA-targeted therapy.

In the oral hearing in the present procedure, the clinical assessment experts confirmed that PSMA-negative patients should not be intended for study designs with PSMA-targeted therapy. However, there is no specific data available for PSMA-negative patients to support this assumption on the basis of evidence.

Furthermore, it can be assumed that gozetotide does not cause direct (side) effects to a relevant extent. Therefore, the requirements for the use of the VISION study for the assessment of the diagnostic agent gozetotide for the present benefit assessment procedure are considered to be fulfilled overall. The VISION study is therefore used for the benefit assessment of the diagnostic agent gozetotide.

Nevertheless, it should be emphasised that only the effect of gozetotide in combination with the subsequent therapy can be assessed, based on the VISION study. In addition, only those patients who were classified as PSMA-positive by performing a diagnosis with gozetotide were enrolled in the VISION study. However, no data are available for PSMA-negative patients in whom a diagnosis with gozetotide is also performed in medical treatment practice to rule out targeted therapy with lutetium (^{177}Lu) vipivotide tetraxetan.

About the VISION study

The pharmaceutical company presented the results of the VISION study for proving an additional benefit of gozetotide for the detection of prostate-specific membrane antigen (PSMA)-positive lesions in patients with PSMA-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) in whom PSMA-targeted therapy is indicated.

The VISION study is an open-label, randomised, controlled phase III study comparing PSMA-positive patients post-diagnosis with gozetotide with lutetium (^{177}Lu) vipivotide tetraxetan with continuation of existing androgen deprivation therapy (ADT) and patient-individual therapy versus continuation of existing ADT and patient-individual therapy alone.

The study was conducted from May 2018 to December 2023 in 86 study sites, particularly in Europe and North America, with a total of 831 patients.

The study enrolled adult males with progressive mCRPC and a general condition according to Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) ≤ 2. Patients had to have already been treated with at least 1 androgen receptor pathway inhibitor and 1 to 2 taxane-based chemotherapies.

In the screening phase prior to enrolment in the study and randomisation, 1,003 patients were examined with gozetotide for the presence of PSMA-positive lesions. 172 (17.1%) patients were not randomised because the majority of them were PSMA negative and therefore did not meet the inclusion criteria regarding PSMA status. 831 (82.9%) patients were randomised in a 2:1 ratio into the intervention arm (N = 551) or the comparator arm (N = 280).

Patients who had received 1 taxane-based chemotherapy in the prior therapy were only enrolled in the study if, according to the principal investigator's assessment, further taxane-based chemotherapy was not an option for them, e.g. due to geriatric or health-related frailty or intolerance. Furthermore, prior to version 3.0 of the study protocol (01.04.2019), patients with 1 prior taxane-based chemotherapy could participate in the study if they declined treatment with another taxane-based chemotherapy.

Treatment with lutetium (^{177}Lu) vipivotidte traxetan was carried out for up to 6 cycles according to the product information. An existing ADT had to be continued during the study. Patient-individual therapy was determined for each patient at the doctor’s discretion prior to randomisation and could be adjusted in both treatment arms during the study. Cytotoxic chemotherapy (e.g. taxane-based chemotherapies), systemic therapies with other radioisotopes (e.g. radium-223) and other test preparations (e.g. olaparib, which was not approved for the treatment of mCRPC at the start of the VISION study) were not allowed in the VISION study. After discontinuation of the study medication, patients could participate in up to 2 years of long-term follow-up until the end of the study.

In addition to the primary endpoints of radiologically confirmed progression-free survival (rPFS) and overall survival, endpoints in the categories of morbidity, health-related quality of life and side effects were also collected.

For the present benefit assessment, the 1st data cut-off of the VISION study from 27.01.2021 is used.

Analysis population used

For the benefit assessment, the pharmaceutical company presented, among others, data based on the total population, i.e. on all randomised patients (551 patients in the intervention arm and 280 patients in the comparator arm). The evaluations for the endpoints of side effects are based on the patients who received at least 1 dose of the study medication (529 patients in the intervention arm vs 205 patients in the comparator arm).

In the VISION study, an increased frequency of withdrawn consent forms was observed in the comparator arm after the start of the study. A total of 79 patients (28.2%) in the comparator arm and 18 patients (3.3%) in the intervention arm did not receive any study medication. The differential percentage of patients who did not receive study medication is > 15 percentage points between the treatment arms. Therefore, with the exception of the evaluation on

overall survival, the evaluations on the total population are not used for the present benefit assessment.

In contrast to the other endpoints, overall survival was assessed until the end of the study. Those patients who withdrew their consent to treatment but agreed to participate in the long-term follow-up of the study are also included in the evaluation.

Due to the increased frequency of withdrawn consents, the pharmaceutical company has adapted the study protocol. Patients who had received 1 taxane-based chemotherapy in pretreatment were only enrolled in the study if the principal investigator determined that they were ineligible for further taxane-based chemotherapy. The protocol amendment (version 3.0, 01.04.2019; for all patients randomised from 05.03.2019) results in a further analysis population in addition to the total population. This includes all patients randomised under version 3.0 of the study protocol from 05.03.2019. For these patients last mentioned, the differential percentage of patients who did not receive study medication between treatment arms was 12.1 percentage points (16 [4.2%] vs 32 [16.3%] patients), thus being lower than in the total population. The evaluations for this sub-population are suitable for the benefit assessment and will be used for it.

However, it should also be noted that the treatment setting for mCRPC has changed since the start of the study. It can be assumed that the VISION study also enrolled patients with the breast cancer susceptibility gene (BRCA) mutation. For these patients, monotherapy with olaparib would have been the appropriate therapeutic alternative according to the generally accepted state of medical knowledge.

Extent and probability of the additional benefit

About the derivation of the additional benefit for sub-populations

In IQWiG's dossier assessment, the additional benefit was assessed separately. It was divided into patients for whom abiraterone, enzalutamide or best supportive care and patients for whom cabazitaxel or olaparib is the appropriate patient-individual therapy.

In the VISION study, treatment with the active ingredients cabazitaxel and olaparib was not permitted. Thus, the therapy options used in the VISION study do not cover all active ingredients of the appropriate comparator therapy. Accordingly, it is not possible to make any statements on the additional benefit for patients for whom cabazitaxel or olaparib is the most appropriate patient-individual therapy.

In the written statement procedure on the benefit assessment of lutetium (^{177}Lu) vipivotide tetraxetan, the scientific-medical societies designate the subgroup of patients, for whom cabazitaxel or olaparib is the appropriate patient-individual therapeutic alternative, as a biologically and clinically distinct patient population compared with patients for whom enzalutamide, abiraterone and BSC is the appropriate patient-individual therapy.

The G-BA therefore considers it appropriate to divide the patient population into: patients for whom enzalutamide, abiraterone and BSC represent the appropriate patient-individual therapy (patient group a1)) and patients for whom cabazitaxel or olaparib represents the appropriate patient-individual therapy (patient group a2)).

a1) Adults for whom abiraterone in combination with prednisone or prednisolone, enzalutamide, or best supportive care is the appropriate patient-individual therapy

Mortality

In the VISION study, overall survival was defined as the time (in months) between randomisation and death from any cause. It was the only endpoint collected until the end of the study.

For the endpoint of overall survival, there was a statistically significant survival benefit in favour of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post PSMA-diagnosis with gozetotide regarding the total population as well as the sub-population of patients randomised from 05.03.2019.

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival

In the VISION study, radiological progression-free survival (rPFS) was defined as the time (in months) between randomisation and radiological disease progression based on blinded, independent and central assessment according to PCWG3 criteria or death from any cause. Under lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy, rPFS is statistically significantly prolonged in the total population compared to ADT in combination with patient-individual therapy.

The present rPFS is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component of “disease progression” is assessed according to PCWG3 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 rPFS endpoint. The overall statement on the additional benefit remains unaffected.

Symptomatic skeletal-related events (SSRE)

The composite endpoint of symptomatic skeletal-related events was defined in the VISION study as the time (in months) between randomisation and one of the following events:

- New symptomatic pathological bone fracture
- Spinal cord compression
- Tumour-related orthopaedic surgery
- Need for radiotherapy to relieve bone pain

The results of the composite endpoint based on those patients who were randomised from 05.03.2019 are used for this benefit assessment. Furthermore, only the evaluations of the pharmaceutical company which do not take deaths into account are used in each case.

For the individual components of spinal cord compression and need for radiotherapy to relieve bone pain , there was a statistically significant advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide.

For the individual components of *new symptomatic pathological bone fracture* and *tumour-related orthopaedic surgery*, there was no statistically significant difference between the treatment groups.

For the present assessment, the result for the composite endpoint is used, which shows a clear advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide.

Worst pain (BPI-SF item 3), impairment due to pain (BPI-SF item 9a-g) and health status (EQ-5D VAS)

The endpoint of worst pain was assessed using BPI-SF item 3 and the endpoint of impairment due to pain was assessed using BPI-SF items 9a-g. The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

The pharmaceutical company submitted evaluations for those patients who were randomised from 05.03.2019. The evaluation is unsuitable for the present benefit assessment, particularly due to the sharp decline in the percentage of patients with a survey during the course of the study and a high differential percentage of patients between the treatment groups who were not included in the evaluations. Thus, no suitable data are available.

The overall analysis of the results show clear advantages in terms of morbidity for lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post PSMA diagnosis with gozetotide compared with ADT in combination with patient-individual therapy in the sub-population of patients randomised from 05.03.2019.

Quality of life

The endpoint of health-related quality of life was assessed using the FACT-P.

The evaluations on quality of life are not used for the present benefit assessment due to the high differential percentage of patients not included in the evaluations between the treatment groups in the sub-population (patients randomised from 05.03.2019) and in the total population. Thus, no suitable data are available.

Side effects

In the VISION study, adverse events under gozetotide were assessed separately. However, the study lacked a comparator group without PSMA diagnosis with gozetotide.

However, it is not assumed that there are any relevant direct side effects of gozetotide that would call into question the results of the VISION study comparing lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy.

Adverse events (AEs)

In the control arm, an adverse event occurred in 86% of patients and in the intervention arm, an adverse event was observed in 99% of patients.

Serious AEs (SAEs)

For the endpoint of serious adverse events, there is a statistically significant difference to the advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide.

Severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

For the endpoints of severe adverse events (CTCAE grade ≥ 3) and therapy discontinuation due to AEs, there was no statistically significant difference between the treatment arms.

Specific AEs

In detail, the specific adverse events show statistically significant differences to the disadvantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide with regard to myelosuppression (severe AEs), dry mouth (AEs), gastrointestinal disorders (AEs) and urinary tract infection (AE).

There were statistically significant advantages for lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide with regard to the specific AE of acute renal failure (SAEs).

The overall assessment shows an advantage for the SAEs, and in detail, both advantages and disadvantages for some specific AEs.

Overall assessment

For the benefit assessment of gozetotide, which is indicated after radiolabelling with gallium-68 for the detection of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adults with prostate cancer (PCa) to identify patients with PSMA-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) in whom PSMA-targeted therapy is indicated, results on mortality, morbidity, health-related quality of life and side effects from the open-label, randomised, controlled phase III VISION study are available. The VISION study compared lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy versus ADT in combination with patient-individual therapy. Based on the VISION study, only the effect of gozetotide in combination with the subsequent therapy can be assessed.

The total population and a sub-population consisting of patients randomised from 05.03.2019 are used for the assessment.

For overall survival, there is a clear advantage in favour of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide in both the total population and the sub-population.

In the morbidity category, the composite endpoint of symptomatic skeletal-related events (SSRE) showed clear advantages for patients in the sub-population for treatment with lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post-PSMA diagnosis with gozetotide. No suitable data are available for the endpoints of pain (BPI-SF) and health status (EQ-5D VAS).

No suitable data are available for health-related quality of life, assessed using FACT-P.

For the endpoint category of side effects, an overall advantage can be observed for lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post PSMA diagnosis with gozetotide compared to ADT in combination with patient-individual therapy in the sub-population due to the avoidance of SAEs. In detail, both advantages and disadvantages are evident for each of the specific AEs.

In the overall assessment, positive effects are shown in the endpoint categories of mortality and morbidity. No suitable data are available for the endpoint category of health-related quality of life. An overall advantage can also be identified in the endpoint category of side effects. In conclusion, for adults with metastatic castration-resistant prostate cancer after pretreatment, for whom enzalutamide, abiraterone or BSC is the appropriate patient-individual therapy, the G-BA identifies a considerable additional benefit of gozetotide (if applicable, followed by lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy) compared to the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

This benefit assessment is based on the results of the VISION study for the relevant sub-population of patients randomised from 05.03.2019.

The cross-endpoint risk of bias of the VISION study was rated to be low.

For the endpoint of overall survival, the risk of bias is rated to be low.

For the combined morbidity endpoint of symptomatic skeletal-related events, the risk of bias is considered high, taking into account uncertainties regarding follow-up of patients who did not receive study medication.

The risk of bias of the endpoint category of side effects is classified as high, in particular due to large differences between the treatment arms in patients not considered in the evaluation. For the endpoint of discontinuation due to AEs, the open-label study design and the resulting lack of blinding are included in the assessment of the risk of bias.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment. In particular, the risk of bias of the endpoint of overall survival is rated as low. Thus, the reliability of data for the additional benefit determined is classified in the category "indication".

a2) Adults for whom cabazitaxel or olaparib is the appropriate patient-individual therapy

An additional benefit is not proven.

The VISION study compared PSMA-positive patients post-diagnosis with gozetotide with lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy versus ADT in combination with patient-individual therapy. Based on the VISION study, only the effect of gozetotide in combination with the subsequent therapy can be assessed.

The available data do not allow any statements on the additional benefit for adults for whom cabazitaxel or olaparib is the appropriate patient-individual therapy, as neither cabazitaxel nor olaparib was used as part of patient-individual therapy. An additional benefit of gozetotide (if applicable, followed by lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and a patient-individual therapy) is therefore not proven for patients for whom cabazitaxel or olaparib is the appropriate patient-individual therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Locametz with the active ingredient gozetotide.

The therapeutic indication assessed here is as follows: Gozetotide, after radiolabelling with gallium-68, is indicated for the detection of prostate-specific membrane antigen (PSMA)-positive lesions by positron emission tomography (PET) in adults with prostate cancer (PCa); for the identification of patients with PSMA-positive, progressive, metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated.

Due to the explicit substantial link between the use of gozetotide in the context of performing a PSMA-PET for the indication of a therapy with lutetium (^{177}Lu) vipivotide tetraxetan, there was a special feature in the research question for the present procedure.

Based on the available evidence, the G-BA considers it appropriate to form the following patient groups according to their patient-individual suitability for the following therapy options:

a) Adults with progressive metastatic castration-resistant prostate cancer (mCRPC); diagnosis; identification of patients with prostate-specific membrane antigen (PSMA)-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated

   a1) Adults for whom abiraterone in combination with prednisone or prednisolone, enzalutamide or best supportive care is the appropriate patient-individual therapy

   a2) Adults for whom cabazitaxel or olaparib is the appropriate patient-individual therapy

The appropriate comparator therapy comprises patient-individual therapy, selecting abiraterone in combination with predniso(lo)ne, enzalutamide, cabazitaxel, olaparib and best supportive care (BSC), taking into account prior therapies, comorbidity, the general condition and BRCA1/2 mutational status.

For the benefit assessment, the pharmaceutical company submitted data from the VISION study. In this randomised, controlled, open-label phase III study, PSMA-positive patients with pretreated mCRPC were randomised post PSMA-diagnosis with gozetotide to the treatment arm [lutetium (^{177}Lu) vipivotide tetraxetan with continuation of existing androgen deprivation therapy (ADT) and patient-individual therapy] and the control arm [continuation of existing ADT and patient-individual therapy alone]. Based on the VISION study, only the effect of gozetotide in combination with the subsequent therapy can be assessed.

No data are available for PSMA-negative patients in whom a diagnosis with gozetotide is also performed to rule out therapy with lutetium (^{177}Lu) vipivotide tetraxetan.

With the exception of the endpoint of overall survival, the data for the total population were not used due to the increased frequency of withdrawn consent forms. For the endpoint categories of mortality, morbidity and side effects, a sub-population of patients randomised from 05.03.2019 onwards was taken into account.

On a1)

The endpoint categories of mortality and morbidity show clear advantages in favour of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy post PSMA-diagnosis with gozetotide.

No usable data are available for the endpoint category of health-related quality of life.

Overall, there is an advantage regarding the side effects.

In the overall assessment, there is an indication of a considerable additional benefit of gozetotide (if applicable, followed by lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy).

On a2)

For the sub-population of adults with PSMA-positive mCRPC after previous treatment with ARDT and taxane-containing chemotherapy, for whom cabazitaxel or olaparib is the appropriate patient-individual therapy, no statements on the additional benefit can be made on the basis of the VISION study, as neither cabazitaxel nor olaparib was used as part of the patient-individual therapy.

An additional benefit of gozetotide (if applicable, followed by lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy) is therefore not proven.

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

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. In determining the patient numbers in the SHI target population, the pharmaceutical company relies on the G-BA's resolution on lutetium (^{177}Lu) vipivotide tetraxetan from 2023. The pharmaceutical company states that the percentage of PSMA-positive lesions is approximately 80.2% to 87% and uses this as the basis for calculating the total population. The pharmaceutical company's approach of additionally considering patients with PSMA-negative mCRPC when deriving the patient numbers in the SHI target population is comprehensible.

Due to the special feature of the specific research question at hand, the effect of gozetotide in combination with the subsequent therapy was considered in the benefit assessment. As the subsequent therapy differs between test-positive and test-negative patients, the percentage of test-positive and test-negative patients is also shown.

Overall, these patient numbers are subject to uncertainty. Thus, there is an incompletely comprehensible presentation of the specific periods of pharmaceutical prescriptions used for the estimation of patient numbers in 2020. Furthermore, uncertainty exists due to an incomprehensible extrapolation of percentage values to male SHI-insured persons.

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 Locametz (active ingredient: gozetotide) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 11 October 2024):

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

The medicinal product should only be administered by trained medical professionals with technical expertise in the use and handling of nuclear medicine diagnostics and only in a specialised nuclear medicine facility.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients.

2.4 Treatment costs

These also belong to the assessed therapeutic indication since gozetotide is also approved for patients who only subsequently prove to be test-negative at the beginning of the diagnostic therapeutic chain (ex ante) according to the therapeutic indication of the resolution. These are patients with prostate cancer in whom gozetotide can be used to detect potential PSMA lesions. At the cost level, however, assuming a diagnostic-therapeutic chain, it is not the ex ante perspective that is required, but an ex post consideration of the therapy that actually follows the diagnosis. Lutetium (^{177}Lu) vipivotide tetraxetan cannot be listed in the treatment costs of test-negative patients, as it cannot be used due to the limitation of the marketing

authorisation to the treatment of test-positive patients. As the benchmark for the assessment of treatment costs in accordance with Section 35a, paragraph 1, sentence 3 No. 5 SGB V are the treatment costs for the statutory health insurance, not only the treatment costs of test-positive patients with lutetium (^{177}Lu) vipivotide tetraxetan, but also the treatment costs of test-negative patients with androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway must be presented from an ex post perspective.

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

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 for the maximum treatment duration, if specified in the product information.

The fee structure item (FSI) from the UVS is used to calculate the annual treatment costs for gozetotide.

Lutetium (^{177}Lu) vipivotide tetraxetan is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung), and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

The use of lutetium (^{177}Lu) vipivotide tetraxetan is limited to a maximum of 6 administrations/doses.

For dosages depending on body weight (bw) or body surface area (BSA), the average body measurements of adult males from the official representative statistics “Microcensus 2021 – body measurements of the population” were applied (average body height: 1.79 m; average body weight: 85.8 kg). This results in a body surface area of 2.05 m² (calculated according to Du Bois 1916)[2].

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Gozetotide followed by lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway				
Gozetotide				
Gozetotide	Single dose	1	1	1

[2] Federal Health Reporting. Average body measurements of the population (2021, male, 15 years and older), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lutetium (^{177}Lu) vipivotide tetraxetan				
Lutetium (^{177}Lu) vipivotide tetraxetan[3]	1 x every 6 weeks	6.0	1	6.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4.0	1	4.0
Degarelix	Continuously, 1 x monthly	12.0	1	12.0
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0
Triptorelin	Continuously, every 6 months	2.0	1	2.0
Enzalutamide				
Enzalutamide	Continuously, 1 x daily	365.0	1	365.0
Abiraterone acetate + prednisone or prednisolone				
Abiraterone acetate	Continuously, 1 x daily	365.0	1	365.0
Prednisone or prednisolone	Continuously, 1 x daily	365	1	365.0
Gozetotide followed by androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway				
Gozetotide				
Gozetotide	Single dose	1	1	1
GnRH analogues				
Buserelin	Continuously, every 3 months	4.0	1	4.0
Degarelix	Continuously, 1 x monthly	12.0	1	12.0

[3] Lutetium (^{177}Lu) vipivotide tetraxetan is given up to 6 doses in total, according to the product information

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0
Triptorelin	Continuously, every 6 months	2.0	1	2.0
Enzalutamide				
Enzalutamide	Continuously, 1 x daily	365.0	1	365.0
Abiraterone acetate + prednisone or prednisolone				
Abiraterone acetate	Continuously, 1 x daily	365.0	1	365.0
Prednisone or prednisolone	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
A patient-individual therapy under selection of:				
Abiraterone acetate + prednisone or prednisolone + GnRH analogues				
Abiraterone acetate	Continuously, 1 x daily	365.0	1	365.0
Prednisone or prednisolone	Continuously, 1 x daily	365.0	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4.0	1	4.0
Degarelix	Continuously, 1 x monthly	12.0	1	12.0
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0
Triptorelin	Continuously, every 6 months	2.0	1	2.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cabazitaxel + prednisone or prednisolone + GnRH analogues				
Cabazitaxel	Continuously, 1 x every 21 days	17.4	1	17.4
Prednisone or prednisolone	Continuously, 1 x daily	365.0	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4.0	1	4.0
Degarelix	Continuously, 1 x monthly	12.0	1	12.0
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0
Triptorelin	Continuously, every 6 months	2.0	1	2.0
Enzalutamide + GnRH analogues				
Enzalutamide	Continuously, 1 x daily	365.0	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4.0	1	4.0
Degarelix	Continuously, 1 x monthly	12.0	1	12.0
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0
Triptorelin	Continuously, every 6 months	2.0	1	2.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Olaparib as monotherapy + GnRH analogues				
Olaparib	Continuously, 2 x daily	365	1	365.0
GnRH analogues				
Buserelin	Continuously, every 3 months	4.0	1	4.0
Degarelix	Continuously, 1 x monthly	12.0	1	12.0
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0
Triptorelin	Continuously, every 6 months	2.0	1	2.0
Best supportive care				
Best supportive care[4]	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Gozetotide followed by lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway					
Gozetotide					
Gozetotide	1.8 – 2.2 MBq/kg BW = 154.4 – 188.8 MBq	154.4 MBq – 188.8 MBq	1 x 25 µg kit (≙ max. 1,369 MBq)	1	1 x 25 µg kit (≙ max. 1,369 MBq)

[4] When comparing with best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product to be assessed.

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Lutetium (^{177}Lu) vipivotide tetraxetan					
Lutetium (^{177}Lu) vipivotide tetraxetan	7,400 MBq	7,400 MBq	1 x 7,400 MBq	6	6 x 7,400 MBq
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Enzalutamide					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460 x 40 mg
Abiraterone acetate + prednisone or prednisolone					
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg
Prednisone or prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Gozetotide followed by androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway					
Gozetotide	1.8 – 2.2 MBq/kg BW = 154.4 – 188.8 MBq	154.4 MBq – 188.8 MBq	1 x 25 µg kit (≙ max. 1,369 MBq)	1	1 x 25 µg kit (≙ max. 1,369 MBq)
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Enzalutamide					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460 x 40 mg
Abiraterone acetate + prednisone or prednisolone					
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Prednisone or prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Appropriate comparator therapy					
A patient-individual therapy under selection of:					
Abiraterone acetate + prednisone or prednisolone + GnRH analogues					
Abiraterone acetate	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460 x 250 mg
Prednisone or prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Cabazitaxel + prednisone or prednisolone + GnRH analogues					
Cabazitaxel	25 mg/m^2 BSA = 51.3 mg	51.3 mg	1 x 60 mg	17.4	17.4 x 60 mg
Prednisone or prednisolone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Enzalutamide + GnRH analogues					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460 x 40 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Olaparib as monotherapy + GnRH analogues					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
GnRH analogues					
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4 x 9.45 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2 x 22.5 mg
Best supportive care					
Best supportive care[4]	Different from patient to patient				

Costs:

FSI 40585 is used to calculate the annual treatment costs for gozetotide in accordance with the UVS. This includes a flat-rate fee for the material costs in connection with the performance of PSMA positron emission tomography (PET) of the trunk with technical image fusion of diagnostic computed tomography (CT) to determine the indication for treatment with lutetium (^{177}Lu) vipivotide tetraxetan (services corresponding to fee structure items 34720 and 34721) when using a Ga-68-PSMA ligand. All costs, including transport costs, are included in the flat-rate fee 40585.

Medicinal product to be assessed				
Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Gozetotide	(FSI: 40585)	1	€ 1,100.00	€ 1,100.00

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

Costs of the medicinal products:

Medicinal product to be assessed				
Designation of the therapy	Packaging size	Costs (clinic purchase)	Value added tax (19%)	Costs of the medicinal product
Lutetium (^{177}Lu) vipivotide tetraxetan 7,400 MBq	1 IIS	€ 15,420.00	€ 2,929.80	€ 18,349.80

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
Abiraterone acetate 250 mg	120 TAB	€ 137.75	€ 2.00	€ 16.00	€ 119.75
Prednisone 10 mg[5]	100 TAB	€ 21.23	€ 2.00	€ 0.78	€ 18.45
Prednisolone 10 mg[5]	100 TAB	€ 17.81	€ 2.00	€ 0.51	€ 15.30
Enzalutamide 40 mg	112 FCT	€ 3,123.20	€ 2.00	€ 0.00	€ 3,121.20
Buserelin 9.45 mg	2 PS	€ 1,238.90	€ 2.00	€ 67.97	€ 1,168.93
Degarelix 80 mg	3 PSI	€ 591.88	€ 2.00	€ 32.14	€ 557.74
Goserelin 10.8 mg	2 IMP	€ 1,174.45	€ 2.00	€ 64.40	€ 1,108.05
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin 22.5 mg	1 DSS	€ 1,137.88	€ 2.00	€ 62.37	€ 1,073.51
Appropriate comparator therapy					
Abiraterone acetate 250 mg	120 TAB	€ 137.75	€ 2.00	€ 16.00	€ 119.75
Prednisone 10 mg[5]	100 TAB	€ 21.23	€ 2.00	€ 0.78	€ 18.45
Prednisolone 10 mg[5]	100 TAB	€ 17.81	€ 2.00	€ 0.51	€ 15.30
Cabazitaxel 60 mg	1 CIS	€ 1,149.19	€ 2.00	€ 54.00	€ 1,093.19
Enzalutamide 40 mg	112 FCT	€ 3,123.20	€ 2.00	€ 0.00	€ 3,121.20
Buserelin 9.45 mg	2 PS	€ 1,238.90	€ 2.00	€ 67.97	€ 1,168.93
Degarelix 80 mg	3 PSI	€ 591.88	€ 2.00	€ 32.14	€ 557.74
Goserelin 10.8 mg	2 IMP	€ 1,174.45	€ 2.00	€ 64.40	€ 1,108.05
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Triptorelin 22.5 mg	1 DSS	€ 1,137.88	€ 2.00	€ 62.37	€ 1,073.51
Olaparib 150 mg	112 FCT	€ 4,763.36	€ 2.00	€ 268.74	€ 4,492.62
Best supportive care[4]	Different from patient to patient				
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; IIS = solution for injection/ infusion; IMP = implant; PSI = powder and solvent for solution for injection; TAB = tablets; DSS = dry substance with solvent					

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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.

[5] Fixed reimbursement rate

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.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed:				
PSMA-PET of the trunk to determine the indication for treatment with lutetium (^{177}Lu) vipivotide tetraxetan	PSMA-PET without CT (FSI: 34720)	1	€ 531.77	€ 531.77
	PSMA-PET with CT (FSI: 34721)	1	€ 674.62	€ 674.62

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 1 October 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 agents 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 are not added to the pharmacy sales price but rather follow the rules for calculating in the 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 requirements in the product information of the assessed medicinal product.

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

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

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

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

Designation

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

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

Exception to the designation

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

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit

had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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

Justification for the findings on designation in the present resolution:

a) Adults with progressive metastatic castration-resistant prostate cancer (mCRPC); diagnosis; identification of patients with prostate-specific membrane antigen (PSMA)-positive progressive metastatic castration-resistant prostate cancer (mCRPC) for whom PSMA-targeted therapy is indicated

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 28 May 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 15 July 2025, the pharmaceutical company submitted a dossier for the benefit assessment of gozetotide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 3 VerfO.

By letter dated 15 July 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient gozetotide.

The dossier assessment by the IQWiG was submitted to the G-BA on 10 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 October 2024. The deadline for submitting written statements was 5 November 2024.

The oral hearing was held on 25 November 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 7 January 2025, and the proposed draft resolution was approved.

At its session on 16 January 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 May 2024	Determination of the appropriate comparator therapy
Working group Section 35a	19 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 November 2024	Conduct of the oral hearing
Working group Section 35a	3 December 2024 17 December 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 January 2025	Concluding discussion of the draft resolution
Plenum	16 January 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 January 2025

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

Prof. Hecken