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)
Lutetium (^{177}Lu) vipivotide tetraxetan (prostate cancer, combination with androgen deprivation therapy, PSMA-positive, metastatic, castration-resistant, progression after inhibition of the AR pathway and taxane-based chemotherapy)

of 6 July 2023

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 Lutetium (^{177}Lu) vipivotide tetraxetan on 21 December 2022 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 20 December 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 April 2023 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 lutetium (^{177}Lu) vipivotide tetraxetan 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 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 lutetium (^{177}Lu) vipivotide tetraxetan.

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 Lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto) according to the product information

Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane-based chemotherapy (see section 5.1) [2]

Therapeutic indication of the resolution (resolution of 06.07.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) <u>Adults with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC), after prior treatment with ARDT (androgen receptor-directed therapy) and taxane-containing chemotherapy</u>

Appropriate comparator therapy for lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy with or without androgen receptor inhibition:

Patient-individual therapy with selection of:

- abiraterone in combination with prednisone or prednisolone,
- enzalutamide,
- cabazitaxel,
- olaparib (only for patients with a BRCA 1/2 mutation),
- Best supportive care

taking into account the previous therapy

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.
2 According to 4.2. of the product information, patients should be identified for treatment by PSMA imaging. On 20.06.2023, the assessment committee communicated a need for adjustment of the EBM with regard to lutetium (^{177}Lu) vipivotide tetraxetan.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO:

on 1. In terms of the authorisation status, the active ingredients bicalutamib, cyproterone acetate, flutamide, degarelix, buserelin, goserelin, leuprorelin, triptorelin, enzalutamide, abiraterone acetate, estramustine, cabazitaxel, docetaxel, mitoxantrone, olaparib as monotherapy and in combination with abiraterone acetate and radium-223-dichloride. Medicinal products with explicit marketing authorisation for hormone-sensitive prostate cancer were not considered.

on 2. Radiotherapy is generally considered as a non-medicinal treatment in the present therapeutic indication.

on 3. For metastatic castration-resistant prostate cancer, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V are available for the active ingredients olaparib, radium-223-dichloride, enzalutamide, abiraterone acetate and cabazitaxel.

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

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

For the present therapeutic indication, a taxane-containing chemotherapy is usually understood as a therapy with docetaxel.

Furthermore, 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.

In the national and international guidelines, the therapy recommendations for the presently specified therapeutic indication include treatment with the active ingredients abiraterone acetate, cabazitaxel, enzalutamide and olaparib.

However, there are no recommendations for a preferred treatment sequence, which is why no uniform treatment standard can be named for the treatment setting according to the present therapeutic indication. Patients who have already received androgen receptor-targeted treatment with abiraterone or enzalutamide as therapy 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 previous androgen receptor-targeted treatment received by the patients. Furthermore, the guidelines recommend that patients with progression on a new hormonal agent should be offered a change in treatment strategy, taking into account cabazitaxel or olaparib for patients with BRCA 1/2 mutation.

The therapeutic indication also includes patients who are ineligible for further ARDT and/or taxane-containing therapy, e.g. due to their disease characteristics, or for whom antineoplastic treatment options are 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.

Within the scope of the benefit assessment according to Section 35a SGB V, the above-mentioned active ingredients abiraterone acetate, cabazitaxel, enzalutamide, olaparib (monotherapy) and radium-223-dichloride were assessed. In this context, it is important to consider the partly different therapeutic indications which address different treatment settings as well as partly certain features, e.g. an asymptomatic or mildly symptomatic course of the disease. For cabazitaxel, an indication of a minor additional benefit was found compared to best supportive care (resolution of 29.03.2012). In the benefit assessment, abiraterone acetate was assessed in comparison to best supportive care with an indication of a considerable additional benefit in a resolution dated 29.03.2012. Enzalutamide showed an indication of considerable additional benefit compared to best supportive care (resolution of 20.02.2014). The additional benefit of radium-223-dichloride was assessed as unproven for 2 patient groups compared with patient-individual treatment, selecting abiraterone, enzalutamide, cabazitaxel, and docetaxel, or compared with best supportive care by resolution dated 17.10.2019. By resolution of 03.06.2021, olaparib as monotherapy was found to present a hint for a considerable additional benefit over patient-individual therapy, selecting abiraterone, enzalutamide, cabazitaxel and docetaxel.

Olaparib in combination with abiraterone acetate and predniso(lo)ne is a new treatment option in this therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 16.12.2022). Based on the generally accepted state of medical knowledge, olaparib in combination with abiraterone acetate and predniso(lo)ne is not identified to be an appropriate comparator therapy for the present resolution.

In particular, due to the open question on the therapy sequence and the significance of the previous therapy for the subsequent treatment decision, a patient-individual

therapy, taking into account the previous therapies, is identified to be the appropriate comparator therapy, which is to be carried out by selecting abiraterone acetate, enzalutamide, cabazitaxel, olaparib and best supportive care.

"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.

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 lutetium (^{177}Lu) vipivotide tetraxetan is assessed as follows:

a) Adults with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC), after prior treatment with ARDT (androgen receptor-directed therapy) and taxane-containing chemotherapy

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:

To demonstrate an additional benefit of lutetium (^{177}Lu) vipivotide tetraxetan for the treatment of men with castration-resistant metastatic prostate cancer (mCRPC) after prior treatment with ARDT and taxane-containing chemotherapy, the pharmaceutical company presents the dossier with the results of the VISION study (data cut-off of 27.01.2021), which has been conducted since May 2018 in 86 study sites, particularly in Europe and North America, with a total of 831 patients.

The VISION study is an open-label, randomised, controlled phase III study comparing 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 enrolled men with progressive mCRPC and a general condition according to Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of ≤ 2 who had already been

treated with at least 1 androgen receptor pathway inhibitor and 1 to 2 taxane-based chemotherapies. Randomisation was 2:1 into either 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 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.

Primary endpoints of the study were radiologically confirmed progression-free survival (rPFS) and overall survival. In addition, patient-relevant endpoints on morbidity, health-related quality of life and side effects were assessed.

Increased frequency of withdrawn consent forms

In the VISION study, an increased frequency of withdrawn consent forms was observed in the comparator arm after the start of the study. However, participation in the long-term follow-up was possible for patients with withdrawn consent.

Evaluation populations

In the dossier for the benefit assessment, the pharmaceutical company presents evaluations based on all randomised patients (551 patients in the intervention arm vs 280 patients in the comparator arm). The evaluations for the endpoints of side effects are based on those 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 comparator arm, a total of 79 (28.2%) patients did not receive study medication; in the intervention arm, significantly fewer patients (18 (3.3%)) did not receive study medication. The differential percentage of patients who did not receive study medication is > 15 percentage points between the treatment arms. 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. Therefore, the evaluations presented in the dossier for the benefit assessment, with the exception of the evaluation on overall survival, are unsuitable for the present benefit assessment.

To address the circumstance of increased frequency of withdrawn consents, the study protocol was adapted so that patients who had received 1 taxane-based chemotherapy in pretreatment were only enrolled in the study if the principal investigator determined a lack of treatment eligibility for further taxane-based chemotherapy. This protocol amendment (version 3.0, 01.04.2019; for all patients randomised from 05.03.2019) results in a further evaluation population in addition to the overall population (all randomised patients), which includes patients randomised from 05.03.2019 under version 3.0 of the study protocol. For

this latter sub-population of 385 patients in the intervention arm and 196 patients in the comparator arm, the pharmaceutical company submits complete data and evaluations in the written statement procedure. 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), which is lower than in the overall population.

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

Implementation of the appropriate comparator therapy

In IQWiG's dossier assessment, a separate assessment of the additional benefit was made for patients for whom enzalutamide, abiraterone or BSC is the appropriate or inappropriate patient-individual therapy. This was done against the background that, in addition to enzalutamide, abiraterone and BSC, other treatment options are included in the appropriate comparator therapy (patient-individual therapy, taking into account previous therapy) - such as cabazitaxel and olaparib. According to IQWiG's dossier assessment, however, the VISION study does not allow any conclusions to be drawn about the additional benefit for patients for whom cabazitaxel or olaparib is the appropriate patient-individual therapy.

In addition, in the present written statement procedure, 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.

Therefore, the G-BA 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 represent 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

Overall survival was defined in the VISION study as the time (in months) between randomisation and death from any cause and was the only endpoint collected until the end of the study. For this endpoint, there is a statistically significant survival benefit to the advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy in both the overall population and 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

Radiological progression-free survival (rPFS) was defined in the VISION study 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 overall population compared to ADT in combination with patient-individual therapy.

The present rPFS endpoint is a combined endpoint composed of endpoints of 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 endpoint PFS. The overall statement on the additional benefit remains unaffected.

Symptomatic skeletal-related events (SSRE)

The combined 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 combined endpoint of symptomatic skeletal-related events based on those patients who were randomised from 05.03.2019 onwards may be used. In contrast to the total population, the differential percentage of patients not included in the assessment is < 15 percentage points for these patients. 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 is a statistically significant difference in each case to the advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy. For the individual components of new symptomatic fracture and tumour-related orthopaedic surgery, there is no statistically significant difference between the treatment groups.

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

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

For the endpoints of worst pain, assessed using BPI-SF item 3, impairment due to pain, assessed using BPI-SF item 9a-g, and health status, assessed using the EQ-5D visual analogue scale (VAS), the evaluations are unsuitable for the present benefit assessment. The differential percentage of patients not included in the evaluation between treatment arms is > 15 percentage points for both the sub-population (patients randomised from 05.03.2019) and the overall population (all randomised patients). Thus, no suitable data are available.

In the overall analysis, there are clear advantages in terms of morbidity for lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy compared with ADT in combination with patient-individual therapy in the sub-population of patients randomised from 05.03.2019.

Quality of life

FACT-P

For the endpoint of health-related quality of life, assessed using the FACT-P, the differential percentage of patients not included in the evaluation between the treatment arms is > 15 percentage points for both the sub-population (patients randomised from 05.03.2019) and the total population (all randomised patients). Thus, no suitable data are available.

Side effects

In the data submitted in the pharmaceutical company's statement on the side effects endpoints of severe AEs, serious AEs (SAEs), discontinuation due to AEs, myelosuppression, dry mouth, acute kidney failure, gastrointestinal disorders and urinary tract infection, which are based on the results of patients randomised from 05.03.2019, the differential percentage of patients not included in the evaluations for this sub-population is < 15 percentage points, thus allowing its use.

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.

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

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

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 with regard to myelosuppression (severe AEs), dry mouth (AEs), gastrointestinal disorders (AEs) and urinary tract infection (AE). In detail, there is a statistically significant difference to the advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy with regard to acute kidney failure (SAEs).

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

Overall assessment

For the assessment of the additional benefit of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy in patients with metastatic castration-resistant prostate cancer after at least 2 prior treatments, results on mortality, morbidity, health-related quality of life and side effects are available from the open-label, randomised, controlled phase III VISION study. 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.

With the data submitted subsequently in the written statement procedure on patients randomised from 05.03.2019, there is a sub-population that can be evaluated in large parts in addition to the overall population, as the differential percentage of patients who did not receive study medication is < 15 percentage points between the treatment arms.

For the endpoint of overall survival, both the overall population (all randomised patients) and the sub-population (patients randomised from 05.03.2019) show a clear advantage to the advantage of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy.

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

No suitable data are available for health-related quality of life (assessed by 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 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 with regard to 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 patients 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 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.

Based on the data submitted by the pharmaceutical company in the written statement procedure on this sub-population, the risk of bias across endpoints of the VISION study was rated as low.

For the endpoint of overall survival, the risk of bias is classified as low due to the censoring information subsequently submitted by the pharmaceutical company in the written statement procedure.

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.

In the endpoint category of side effects, the risk of bias is classified as high, in particular due to large differences between the treatment groups in patients not included 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 to be 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.

Justification:

The available data do not allow any statements on the additional benefit for patients for whom cabazitaxel or olaparib is the appropriate patient-individual therapy. For the treatment of men with metastatic castration-resistant prostate cancer after previous treatment with ARDT and taxane-containing chemotherapy, for which cabazitaxel or olaparib is the appropriate patient-individual therapy, an additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment for the active ingredient lutetium (^{177}Lu) vipivotide tetraxetan:

"Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane-based chemotherapy."

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

a) Adults with prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC), after prior treatment with ARDT (androgen receptor-directed therapy) and taxane-containing chemotherapy

   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 therapy.

For the benefit assessment, the pharmaceutical company submitted data from the VISION study. In this randomised, controlled, open-label phase III study, patients with pretreated mCRPC were randomised in a 2:1 ratio 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).

The study enrolled a total of 831 adult patients with mCRPC who had already received androgen receptor-directed therapy (ARDT) and a taxane at this stage of the disease and had a general condition according to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of ≤ 2. With the exception of overall survival, the data submitted in the dossier for the benefit assessment could not be evaluated due to the increased frequency of withdrawn

consent forms. In the context of the written statement procedure, the pharmaceutical company submitted suitable data on patients randomised from 05.03.2019 for the endpoints of mortality, morbidity and side effects.

On a1)

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

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

The results on side effects show an overall advantage.

As a result, the G-BA identifies a considerable additional benefit of lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and patient-individual therapy compared to ADT in combination with patient-individual therapy for patients with pretreated mCRPC.

Despite reliable uncertainty in the endpoints of morbidity and side effects, the low risk of bias in overall survival results in an indication of an additional benefit with regard to the significance of the evidence.

On a2)

For the sub-population of adult patients with PSMA-positive, metastatic castration-resistant prostate cancer 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 lutetium (^{177}Lu) vipivotide tetraxetan in combination with ADT and a patient-individual therapy is therefore unproven for the sub-population a2).

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 information from the dossier of the pharmaceutical company. This information is subject to uncertainties, which are explained below with the main reasons.

The presentation of the specific application periods of medicinal product prescriptions for the estimation of patient numbers in 2020 as well as the extrapolation of percentages concerning male SHI insurants are not completely comprehensible, which means that, on the one hand, an underestimation of patient numbers cannot be ruled out due to the ambiguities regarding the application periods and, on the other, a slightly higher patient number results due to the uncertainties in the extrapolation to the SHI insured.

In addition, there are uncertainties in the transferability of the percentage to the present target population of patients with metastatic castration-resistant prostate cancer, which result from the fact that the sources used by the pharmaceutical company and the percentage values based on them are based on patients with non-metastatic prostate cancer.

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 Pluvicto (active ingredient: lutetium (^{177}Lu) vipivotide tetraxetan) at the following publicly accessible link (last access: 22 June 2023):

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

Treatment with lutetium (^{177}Lu) vipivotide tetraxetan should only be initiated and monitored by specialists in internal medicine, haematology and oncology, as well as specialists in urology and doctors from other professional groups participating in the Oncology Agreement who are experienced in the treatment of patients with prostate cancer.

The medicinal product may only be used by persons authorised to handle radioactive medicinal products in a designated clinical area.

The regulations of the Radiation Protection Ordinance must be observed.

Medicinal castration with a GnRH agonist or antagonist should be continued during the treatment of patients who have not been surgically castrated.

Patients should be identified for treatment with lutetium (^{177}Lu) vipivotide tetraxetan by PSMA imaging.

2.4 Treatment costs

The treatment costs are based on the contents of the product information, the information listed in the LAUER-TAXE® (last revised: 15 June 2023) and on the information provided by the pharmaceutical company (as of: 20 December 2022).

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

Lutetium (^{177}Lu) vipivotide tetraxetan is not listed in the LAUER-TAXE®. The price of the medicinal product is therefore taken from the information provided by the pharmaceutical company in the benefit assessment dossier. In Module 3 of its dossier, the pharmaceutical company states a manufacturer sales price of € 26,180.00, including 19% value added tax.

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lutetium (^{177}Lu) vipivotide tetraxetan[3]	1 x every 6 weeks	6.0	1	6.0
Medicinal androgen deprivation therapy (ADT)				
Degarelix	Continuously, 1 x month	12.0	1	12.0
Buserelin	Continuously, every 3 months	4.0	1	4.0
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
Androgen receptor inhibition: Enzalutamide				
Enzalutamide	Continuously, 1 x daily	365.0	1	365.0
Androgen receptor inhibition: Abiraterone + prednisone or prednisolone				
Abiraterone	Continuously, 1 x daily	365.0	1	365.0
Prednisone	Continuously, 1 x daily	365.0	1	365.0
Prednisolone	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Abiraterone in combination with prednisone or prednisolone + medicinal androgen deprivation therapy (ADT)				
Degarelix	Continuously, 1 x month	12.0	1	12.0
Buserelin	Continuously, every 3 months	4.0	1	4.0
Goserelin	Continuously, every 3 months	4.0	1	4.0
Leuprorelin	Continuously, every 3 months	4.0	1	4.0

[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
Triptorelin	Continuously, every 6 months	2.0	1	2.0
Abiraterone	Continuously, 1 x daily	365.0	1	365.0
Prednisone	Continuously, 1 x daily	365.0	1	365.0
Prednisolone	Continuously, 1 x daily	365.0	1	365.0
Enzalutamide + medicinal androgen deprivation therapy (ADT)				
Enzalutamide	Continuously, 1 x daily	365.0	1	365.0
Degarelix	Continuously, 1 x month	12.0	1	12.0
Buserelin	Continuously, every 3 months	4.0	1	4.0
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
Cabazitaxel + prednisone or prednisolone + medicinal androgen deprivation therapy (ADT)				
Cabazitaxel	1 x every 3 weeks	17.4	1	17.4
Prednisolone or prednisone	Continuously, 1 x daily	365.0	1	365.0
Degarelix	Continuously, 1 x month	12.0	1	12.0
Buserelin	Continuously, every 3 months	4.0	1	4.0
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
Olaparib (only for patients with a BRCA 1/2 mutation) + medicinal androgen deprivation therapy (ADT)				
Olaparib	Continuously, 2 x daily	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Degarelix	Continuously, 1 x month	12.0	1	12.0
Buserelin	Continuously, every 3 months	4.0	1	4.0
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 (BSC)				
Best supportive care[4]	Different from patient to patient			

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.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

The average body measurements of adult males were applied for dosages depending on body weight or body surface area (average body height: 1.79 m; average body weight: 85 kg).[4] This results in a body surface area of 2.04 m² (calculated according to Du Bois 1916)[5].

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					
Lutetium (^{177}Lu) vipivotide tetraxetan	7,400 MBq	7,400 MBq	1 x 7,400 MBq	6.0	6 x 7,400 MBq
Medicinal androgen deprivation therapy (ADT)					
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg

[4] When comparing lutetium (^{177}Lu) vipivotide tetraxetan versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product assessed.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Androgen receptor inhibition: Enzalutamide					
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460.0 x 40 mg
Androgen receptor inhibition: Abiraterone + prednisone or prednisolone					
Abiraterone	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460.0 x 250 mg
Prednisolone or prednisone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Appropriate comparator therapy					
Abiraterone in combination with prednisone or prednisolone + medicinal androgen deprivation therapy (ADT)					
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Abiraterone	1,000 mg	1,000 mg	4 x 250 mg	365.0	1,460.0 x 250 mg
Prednisolone or prednisone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Enzalutamide + medicinal androgen deprivation therapy (ADT)					
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Enzalutamide	160 mg	160 mg	4 x 40 mg	365.0	1,460.0 x 40 mg
Cabazitaxel + prednisone or prednisolone + medicinal androgen deprivation therapy (ADT)					
Cabazitaxel	25 mg/m² BW = 51 mg	51 mg	1 x 60 mg	17.4	17.4 x 60 mg
Prednisolone or prednisone	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 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
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Olaparib (only for patients with a BRCA 1/2 mutation) + medicinal androgen deprivation therapy (ADT)					
Olaparib	300 mg	600 mg	4 x 150 mg	365.0	1,460 x 150 mg
Degarelix	80 mg	80 mg	1 x 80 mg	12.0	12.0 x 80 mg
Buserelin	9.45 mg	9.45 mg	1 x 9.45 mg	4.0	4.0 x 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 x 10.8 mg	4.0	4.0 x 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 x 11.25 mg	4.0	4.0 x 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 x 22.5 mg	2.0	2.0 x 22.5 mg
Best supportive care (BSC)					
Best supportive care[4]	Different from patient to patient				

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.

Costs of the medicinal products:

Medicinal product to be assessed					
Designation of the therapy	Packaging size	Cost (manufacturer sales price)	Value added tax (19%)		Costs of the medicinal product
Lutetium (^{177}Lu) vipivotide tetraxetan 7,400 MBq [5]	1 SFI/ INF	€ 22,000.00	€ 4,180.00		€ 26,180.00
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 androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) signalling pathway					
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Buserelin 9.45 mg 3-month implant	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Goserelin 10.8 mg 3-month depot implant	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Enzalutamide 40 mg	112 FCT	€ 3,193.29	€ 2.00	€ 127.91	€ 3,063.38
Abiraterone 250 mg	120 TAB	€ 137.72	€ 2.00	€ 16.00	€ 119.72
Prednisolone 10 mg[6]	100 TAB	€ 17.78	€ 2.00	€ 0.51	€ 15.27
Prednisone 10 mg[6]	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Appropriate comparator therapy					
Degarelix 80 mg	3 PSS	€ 591.85	€ 2.00	€ 55.10	€ 534.75
Buserelin 9.45 mg 3-month implant	2 PS	€ 1,028.11	€ 2.00	€ 96.51	€ 929.60
Goserelin 10.8 mg 3-month depot implant	2 IMP	€ 1,013.52	€ 2.00	€ 95.13	€ 916.39
Leuprorelin 11.25 mg	2 IMP	€ 730.74	€ 2.00	€ 86.93	€ 641.81
Triptorelin 22.5 mg	1 DSS	€ 1,006.38	€ 2.00	€ 94.45	€ 909.93
Abiraterone 250 mg	120 TAB	€ 137.72	€ 2.00	€ 16.00	€ 119.72
Olaparib 150 mg	112 FCT	€ 4,945.66	€ 2.00	€ 478.56	€ 4,465.10
Enzalutamide 40 mg	112 FCT	€ 3,193.29	€ 2.00	€ 127.91	€ 3,063.38
Cabazitaxel 60 mg	1 CIS	€ 1,149.16	€ 2.00	€ 54.00	€ 1,093.16
Prednisolone 10 mg[6]	100 TAB	€ 17.78	€ 2.00	€ 0.51	€ 15.27
Prednisone 10 mg[6]	100 TAB	€ 21.19	€ 2.00	€ 0.78	€ 18.41

[5] There is no pharmacy sales price for lutetium (^{177}Lu) vipivotide tetraxetan; instead, the price of the clinic pack plus 19% value added tax is used here. The price of the medicinal product is based on the information provided by the pharmaceutical company as of 20.12.2022.

[6] Fixed reimbursement rate

Best supportive care[4]	Different from patient to patient
Abbreviations: PSS = powder and solvent for solution for injection, PS = pre-filled syringes, IMP = implant, DSS = dry substance with solvent, FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution, SFI = solution for injection, INF = infusion solution	

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Costs for additionally required SHI services:

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

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

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

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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 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 Lutetium (^{177}Lu) vipivotide tetraxetan

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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 10 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 20 December 2022, the pharmaceutical company submitted a dossier for the benefit assessment of lutetium (^{177}Lu) vipivotide tetraxetan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 9 January 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 lutetium (^{177}Lu) vipivotide tetraxetan.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 April 2023, and the written statement procedure was initiated with publication on the G-BA website on 17 April 2023. The deadline for submitting statements was 8 May 2023.

The oral hearing was held on 22 May 2023.

By letter dated 23 May 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 16 June 2023.

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 27 June 2023, and the proposed resolution was approved.

At its session on 6 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 August 2021	Determination of the appropriate comparator therapy
Working group Section 35a	16 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 May 2023 23 May 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 May 2023 20 June 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	27 June 2023	Concluding discussion of the draft resolution
Plenum	6 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 July 2023

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

Prof. Hecken