Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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, in combination with androgen deprivation therapy, PSMA-positive, metastatic, castration-resistant, progression after AR Pathway inhibition and taxane-based chemotherapy)

of 6 July 2023

At its session on 6 July 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Lutetium (^{177}Lu) vipivotide tetraxetan as follows:

Lutetium (^{177}Lu) vipivotide tetraxetan

Resolution of: 6 July 2023
Entry into force on: 6 July 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 December 2022):

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.

Therapeutic indication of the resolution (resolution of 6 July 2023):

See therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

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

Extent and likelihood of additional benefit of lutetium (^{177}Lu) vipivotide tetraxetan in combination with androgen deprivation therapy with or without androgen receptor inhibition compared with the appropriate comparator therapy:

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.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantage in the endpoint of symptomatic skeletal-related event
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↑	Advantages in SAEs. Advantages and disadvantages in each of the specific AEs, in detail.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

Vision study: Lutetium (^{177}Lu) vipivotide tetraxetan + ADT + patient-individual therapy[2] **vs** ADT + patient-individual therapy[2]

Randomised, controlled, open-label, multicentre phase III study

The results are based on the sub-population of patients randomised from 05.03.2019.

[1] Data from the dossier assessment of the IQWiG (A23-01) and from the addendum (A23-46), unless otherwise indicated.
[2] includes, among others, androgen receptor pathway inhibitors, supportive measures (analgesics, transfusions, etc.), corticosteroids, 5-alpha-reductase inhibitors, denosumab, bisphosphonates and external radiotherapy

Mortality

Endpoint	Lutetium (^{177}Lu) vipivotide tetraxetan + ADT + patient-individual therapy		ADT + patient-individual therapy		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
Overall survival					
Total population[3]	551	15.3 [14.2; 16.9] 343 (62.3)	280	11.3 [9.8; 13.5] 187 (66.8)	0.62 [0.52; 0.74] <0.001 AD: 4.0 months
Sub-population (patients randomised after 05.03.2019)	385	14.6 [13.2; 16.0] 240 (62.3)	196	10.5 [8.5; 13.6] 129 (65.8)	0.63 [0.5; 0.78]; < 0.001 AD: 4.1 months

Morbidity

Endpoint	Lutetium (^{177}Lu) vipivotide tetraxetan + ADT + patient-individual therapy		ADT + patient-individual therapy		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI]; p value[a] Absolute difference (AD)[b]
Progression-free survival[4]					
Radiographic progression-free survival	385	8.7 [8.34; 10.48] 254 (66.0)	196	3.5 [2.43; 3.98] 93 (47.4)	0.42 [0.32; 0.54] < 0.001 AD: 5.2 months

[3] Data from IQWiG's dossier assessment A-23-01; based on the total population of the data cut-off of 27.01.2021
[4] Data from the statement of the pharmaceutical company on lutetium (^{177}Lu) vipivotide tetraxetan from 08.05.2023

Endpoint	Lutetium (^{177}Lu) vipivotide tetraxetan ADT + patient-individual therapy		ADT + patient-individual therapy		Intervention vs control
	N	Median time to event [95% CI] *Patients with event n (%)*	N	Median time to event [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
Symptomatic skeletal-related events					
Symptomatic skeletal-related event	385	n.r. 60 (15.6)	196	n.r. 34 (17.3)	0.36 [0.23; 0.56]; < 0.001
Endpoint component					
New symptomatic pathological bone fracture	385	n.r. 16 (4.2)	196	n.r. 1 (0.5)	4.27 [0.56; 32.72]; 0.129
Spinal cord compression	385	n.r. 7 (1.8)	196	n.r. 12 (6.1)	0.14 [0.05; 0.38]; < 0.001
Tumour-related orthopaedic surgery	385	n.r. 10 (2.6)	196	n.r. 3 (1.5)	0.64 [0.16; 2.47]; 0.509
Need for radiotherapy to relieve bone pain	385	n.r. 54 (14.0)	196	n.r. 31 (15.8)	0.39 [0.25; 0.63]; < 0.001
Pain (BPI-SF)					
Worst pain (BPI-SF item 3)[c]	No suitable data available.				
Impairment due to pain (BPI-SF item 9a-g)[c]	No suitable data available.				
Health status					
EQ-5D-VAS[d]	No suitable data available.				

Health-related quality of life

Endpoint	Lutetium (^{177}Lu) vipivotide tetraxetan + ADT + patient-individual therapy			ADT + patient-individual therapy			Intervention vs control
	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	N	Values at the start of the study MV (SD)	Change at time of evaluation MV (SE)	Mean difference [95% CI] p value Hedges' g
FACT-P[e]							
	No suitable data available.						

Side effects[f]

Endpoint	Lutetium (^{177}Lu) vipivotide tetraxetan + ADT + patient-individual therapy		ADT + patient-individual therapy		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[a] Absolute difference (AD)[b]
Adverse events (presented additionally)					
	366	*0.69 [0.66; 0.76] 361 (98.6)*	*167*	*0.72 [0.53; 0.92] 143 (85.6)*	-
Serious adverse events (SAEs)					
	366	18.20 [n.c.; n.c.] 129 (35.2)	167	13.34 [n.c.; n.c.] 44 (26.3)	0.64 [0.45; 0.91]; 0.013
Severe adverse events (CTCAE grade 3 or 4)					
	366	8.08 [6.77; 11.5] 187 (51.1)	167	6.05 [n.c.; n.c.] 59 (35.3)	0.79 [0.58; 1.07]; 0.121
Therapy discontinuation due to adverse events					
	366	n.r. 63 (17.2)	167	n.r. 14 (8.4)	0.98 [0.54; 1.77]; 0.940
Specific adverse events					
Myelosuppression (SMQ[g], severe AEs)	366	n.r. 88 (24.0)	167	n.r. 10 (6.0)	2.16 [1.11; 4.19]; 0.020

Dry mouth (PT, AEs)	366	n.r. 142 (38.8)	167	n.r. 2 (1.2)	26.06 [6.45; 105.33]; < 0.001
Acute kidney failure (SMQ, SAEs)	366	n.r. 4 (1.1)	167	n.r. 5 (3.0)	0.18 [0.05; 0.74]; 0.009
Gastrointestinal disorders (SOC, AEs)	366	1.97 [1.71; 2.56] 277 (75.7)	167	6.47 [n.c.; n.c.] 59 (35.3)	2.04 [1.54; 2.70]; < 0.001 AD: 4.5
Urinary tract infection (PT, AEs)	366	n.r. 45 (12.3)	167	n.r. 1 (0.6)	11.53 [1.58; 84.10]; 0.002

[a] Effect and CI: Cox proportional hazards model; p value: log-rank test. Each stratified by LDH level at the start of the study (≤ 260 IU/l vs > 260 IU/l), presence of liver metastases at the start of the study (yes vs no), ECOG-PS at the start of the study (0 or 1 vs 2) and androgen receptor pathway inhibitor as part of study medication at the start of the study (yes vs no). Unstratified for side effects endpoints.
[b] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[c] Time to first deterioration. An increase by ≥ 1.5 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 10).
[d] Time to first deterioration. A decrease by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[e] Time to first deterioration. An increase by ≥ 23.4 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 156).
[f] According to study protocol version 3.0, events due to progression of the underlying disease should not be reported as AEs. However, 10 (2.7%) vs 2 (1.2%) patients with event for SOC "Benign, malignant and non-specific neoplasms (including cysts and polyps)" were documented among AEs.
[g] SMQ "Haematopoietic cytopenias".

Abbreviations used:
AD = absolute difference; BPI-SF = Brief Pain Inventory - Short Form; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS = Eastern Cooperative Oncology Group-Performance Status; FACT-P = Functional Assessment of Cancer Therapy - Prostate; HR = hazard ratio; CI = confidence interval; LDH = lactate dehydrogenase; N = number of patients evaluated; n.c. = not calculable; n.r. = not reached; PT = preferred term; SMQ = Standardised MedDRA Query; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 1,500 to 2,400 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lutetium (^{177}Lu) vipivotide tetraxetan[5]	€ 157,080.00
Medicinal androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway	
Medicinal androgen deprivation therapy (ADT): GnRH agonist/ GnRH antagonist	€ 1,283.62 - € 2,139.00
Total in combination with GnRH agonist/ GnRH antagonist:	€ 158,363.62 - € 159,219.00
Androgen receptor inhibition: Enzalutamide	
Enzalutamide	€ 39,933.35
Total in combination with GnRH agonist/ GnRH antagonist and enzalutamide:	€ 198,296.97 - € 199,152.35
Androgen receptor inhibition: Abiraterone + prednisone or prednisolone	
Abiraterone	€ 1,456.59
Prednisone	€ 67.20
Prednisolone	€ 55.74
Total in combination with GnRH agonist/ GnRH antagonist and abiraterone + prednisone or prednisolone:	€ 159,875.95 - € 160,742.79
Appropriate comparator therapy:	
Abiraterone in combination with prednisone or prednisolone + medicinal androgen deprivation therapy (ADT)	
Abiraterone	€ 1,456.59
Prednisone	€ 67.20
Prednisolone	€ 55.74

[5] It concerns only the cost of the medicinal product Pluvicto®.

Designation of the therapy	Annual treatment costs/ patient
Medicinal androgen deprivation therapy (ADT): GnRH agonist/ GnRH antagonist	€ 1,283.62 - € 2,139.00
Total:	€ 2,795.95 - € 3,662.79
Enzalutamide + medicinal androgen deprivation therapy (ADT)	
Enzalutamide	€ 39,933.35
Medicinal androgen deprivation therapy (ADT): GnRH agonist/ GnRH antagonist	€ 1,283.62 - € 2,139.00
Total:	€ 41,216.97 - € 42,072.35
Cabazitaxel + prednisone or prednisolone + medicinal androgen deprivation therapy (ADT)	
Cabazitaxel	€ 19,020.98
Prednisone	€ 67.20
Prednisolone	€ 55.74
Medicinal androgen deprivation therapy (ADT): GnRH agonist/ GnRH antagonist	€ 1,283.62 - € 2,139.00
Total:	€ 20,360.34 - € 21,227.18
Olaparib (only for patients with a BRCA 1/2 mutation) + medicinal androgen deprivation therapy (ADT)	
Olaparib	€ 58,205.77
Medicinal androgen deprivation therapy (ADT): GnRH agonist/ GnRH antagonist	€ 1,283.62 - € 2,139.00
Total:	€ 59,489.39 - € 60,344.77
Best supportive care (BSC)	
Best supportive care[6]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2023

Costs for additionally required SHI services: not applicable

[6] 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.

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Cabazitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

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

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with lutetium (^{177}Lu) vipivotide tetraxetan for the treatment of progressive prostate-specific membrane antigen (PSMA)-positive, metastatic castration-resistant prostate cancer (mCRPC), after prior treatment with ARDT (androgen receptor-directed therapy) and taxane-based chemotherapy.

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

A designation of the concomitant active ingredients shall be made in a further resolution. The adoption of the resolution will be preceded by a written and oral written statement procedure pursuant to Chapter 5, Section 19 of the Regulation, in the course of which the pharmaceutical companies concerned will be given the opportunity to comment on the planned designation.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 July 2023.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 6 July 2023

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

Prof. Hecken