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

of 16 January 2025

At its session on 16 January 2025, 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 Gozetotide as follows:

Gozetotide

Resolution of: 16 January 2025
Entry into force on: 16 January 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

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

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 January 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.

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

a) <u>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</u>

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.

Extent and probability of the additional benefit of gozetotide compared to 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
- Sub-population, randomised from 05.03.2019

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-76) 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[c]	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 (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					
Radiographic progression-free survival[d]	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
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
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)[e]	No suitable data available.				
Impairment due to pain (BPI SF item 9a-g)[e]	No suitable data available.				
Health status					
EQ-5D-VAS[f]	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	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]
FACT-P[g]					
	No suitable data available.				

Side effects[h]

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]
Total 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[i], 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. *140 (38.3)*	167	n.r. *1 (0,6)*	51,27 [7,17; 366.89]; < 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 months
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] from dossier assessment A23-01
[d] from the dossier for the benefit assessment – Module 4 A
[e] 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).
[f] 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).
[g] 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).
[h] 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.
[i] 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 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

approx. 1,870 - 2,760 patients (PSMA-positive: approx. 1,500 - 2,400; PSMA-negative: approx. 360 - 370)

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
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	€ 1,100.00
Lutetium (^{177}Lu) vipivotide tetraxetan	€ 110,098.80
GnRH analogues	€ 1,283.70 - € 2,337.86
Total: Gozetotide + lutetium (^{177}Lu) vipivotide tetraxetan + GnRH analogues	€ 112,482.50 - € 113,536.66
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 55.85 - € 67.34
Total: Gozetotide + lutetium (^{177}Lu) vipivotide tetraxetan + GnRH analogues + abiraterone acetate + prednisone or prednisolone	€ 113,995.31 - € 115,060.96
Enzalutamide	€ 40,687.07
Total: Gozetotide + lutetium (^{177}Lu) vipivotide tetraxetan + GnRH analogues + enzalutamide	€ 153,169.57 - € 154,223.73
Additionally required SHI services	€ 531.77 - € 674.62
Gozetotide followed by androgen deprivation therapy (ADT) with or without inhibition of the androgen receptor (AR) pathway	

Designation of the therapy	Annual treatment costs/ patient
Gozetotide[3]	€ 1,100.00
GnRH analogues	€ 1,283.70 - € 2,337.86
Total: Gozetotide + GnRH analogues	€ 2,383.70 - € 3,437.86
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 55.85 - € 67.34
Total: Gozetotide + GnRH analogues + abiraterone acetate + prednisone or prednisolone	€ 3,896.51 - € 4,962.16
Enzalutamide	€ 40,687.07
Total: Gozetotide + GnRH analogues + enzalutamide	€ 43,070.77 - € 44,124.93
Additionally required SHI services	€ 531.77 - € 674.62
Appropriate comparator therapy:	
A patient-individual therapy under selection of:	
Abiraterone acetate + prednisone or prednisolone + GnRH analogues	
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 55.85 - € 67.34
GnRH analogues	€ 1,283.70 - € 2,337.86
Total	€ 2,796.51 - € 3,862.16
Cabazitaxel + prednisone or prednisolone + GnRH analogues	
Cabazitaxel	€ 19,021.51
Prednisone or prednisolone	€ 55.85 - € 67.34
GnRH analogues	€ 1,283.70 - € 2,337.86
Total	€ 20,361.06 - € 21,426.71
Enzalutamide + GnRH analogues	
Enzalutamide	€ 40,687.07
GnRH analogues	€ 1,283.70 - € 2,337.86

[3] Since gozetotide is used as a diagnostic agent to identify patients with PSMA-positive mCRPC for whom PSMA-targeted therapy is indicated, the costs for gozetotide are also incurred for those patients who test PSMA-negative in the diagnosis and receive another therapy instead of 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.

Designation of the therapy	Annual treatment costs/ patient
Total	€ 41,970.77 - € 43,024.93
Olaparib as monotherapy + GnRH analogues	
Olaparib	€ 58,564.51
GnRH analogues	€ 1,283.70 - € 2,337.86
Total	€ 59,848.21 - € 60,902.37
Best supportive care	
Best supportive care[4]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 December 2024

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. 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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

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.

[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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 January 2025.

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

Berlin, 16 January 2025

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

Prof. Hecken