Niraparib/ abiraterone acetate (prostate cancer, metastatic, castration-resistant, BRCA 1/2 mutations, chemotherapy not clinically indicated, combination with prednis(ol)one)

Resolution of: 2 May 2024 valid until: unlimited
Entry into force on: 2 May 2024
Federal Gazette, BAnz AT 13 06 2024 B4

Therapeutic indication (according to the marketing authorisation of 19 April 2023):

Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

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

See therapeutic indication according to marketing authorisation.

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

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

Appropriate comparator therapy:

- abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy, in whom chemotherapy is not yet clinically indicated)

  or

- enzalutamide (only for patients whose disease progresses during or after chemotherapy with docetaxel; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated)

  or

- olaparib as monotherapy (only for patients whose disease is progressive after previous treatment that included a new hormonal agent),

  or

- olaparib in combination with abiraterone acetate and prednisone or prednisolone

Extent and probability of the additional benefit of niraparib/ abiraterone acetate in combination with prednisone or prednisolone versus abiraterone acetate in combination with prednisone or prednisolone:

Hint for a considerable additional benefit.

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

Appropriate comparator therapy:

Patient-individual therapy with selection of:

- abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy),
- enzalutamide (only for patients whose disease progresses during or after chemotherapy with docetaxel) and
- olaparib as monotherapy (only for patients whose disease is progressive after previous treatment that included a new hormonal agent),

taking into account the previous therapy/ therapies.

Extent and probability of the additional benefit of niraparib/ abiraterone acetate in combination with prednisone or prednisolone compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

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 progression
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment.
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		

[1] Data from the dossier assessment of the IQWiG (A23-107) and from the addendum (A24-33), unless otherwise indicated.

↑↑: 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

MAGNITUDE study:

- Randomised, controlled, double-blind, multicentre phase III study
- Niraparib/ abiraterone acetate + prednis(ol)one **vs** placebo + abiraterone acetate + prednis(ol)one
- Relevant sub-population: Patients for whom chemotherapy is not clinically indicated

Mortality

Endpoint	**Niraparib/ abiraterone acetate + prednis(ol)one**		**Placebo + abiraterone acetate + prednis(ol)one**		**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 Absolute difference (AD)[a]
Overall survival					
	92	35.9 [29.2; n.c.] 44 (47.8)	88	28.3 [20.8; 32.4] 58 (65.9)	0.62 [0.42; 0.91] 0.015 AD = 7.6 months
Subgroups according to the characteristic "previous taxane-containing chemotherapy"					
yes	26	25.4 [14.9; 41.9] 18 (69.2)	27[b]	31.3 [20.2; n.c.] 15 (55.6)	1.19 [0.59; 2.41] 0.625
no	66	n.r. [30.4; n.c.] 26 (39.4)	61	28.3 [19.5; 33.0] 43 (70.5)	0.46 [0.28; 0.75] 0.001
Interaction					0.029

Morbidity

Endpoint	Niraparib/ abiraterone acetate + prednis(ol)one		Placebo + abiraterone acetate + prednis(ol)one		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 Absolute difference (AD)[a]
Radiographic progression-free survival (rPFS)[2]					
	92	22.14 [18.43; 28.71] 50 (54.3)	88	10.88 [8.31; 13.80] 69 (78.4)	0.48 [0.33; 0.69] < 0.0001 AD = 11.26 months
Symptomatic progression[c]					
	92	n.r. [36.5; n.c.] 25 (27.2[d])	88	28.3 [18.4; n.c.] 41 (46.6[d])	0.48 [0.29; 0.79] 0.004
Endpoint component: Incidence of cancer-related morbidity events[e]	92	n.r. 5 (5.4[d])	88	n.r. 7 (8.0[d])	0.64 [0.20; 2.01] 0.441
Endpoint component: external radiotherapy for skeletal symptoms	92	n.r. 12 (13.0)	88	n.r. 18 (20.5)	0.53 [0.25; 1.10] 0.083
Endpoint component: tumour-related orthopaedic surgical intervention	92	n.r. 0 (0)	88	n.r. 1 (1.1)	n.a. 0.238
Endpoint component: Start of a new systemic cancer therapy due to cancer pain	92	n.r. 9 (9.8)	88	n.r. [35.8; n.c.] 26 (29.5)	0.28 [0.13; 0.59] < 0.001
Endpoint component: Use of other cancer-related interventions	92	n.r. 5 (5.4)	88	n.r. 6 (6.8)	0.76 [0.23; 2.50] 0.652
Symptomatic progression (incl. the component of chronic opioid administration, presented additionally)[e,f,g]					

[2] Data from Module 4 A of the dossier of the pharmaceutical company from 07.11.2023

Endpoint	Niraparib/ abiraterone acetate + prednis(ol)one		Placebo + abiraterone acetate + prednis(ol)one		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 Absolute difference (AD)[a]
	92	n.r. [36.2; n.c.] 28 (30.4[d])	88	21.7 [17.3; 35.8] 46 (52.3[d])	0.46 [0.29; 0.75] 0.002
Endpoint component: chronic opioid administration	92	n.r. 6 (6.5)	88	n.r. 7 (8.0)	0.72 [0.24; 2.15] 0.555
Worst pain (BPI-SF item 3)[h]					
	92	11.3 [8.3; 20.1] 61 (66.3)	88	8.4 [6.4; 13.0] 65 (73.9)	0.75 [0.52; 1.07] 0.110
Pain intensity (BPI SF items 3-6) (presented additionally)[h]					
	92	16.6 [12.8; 33.2] 46 (50)	88	14.9 [9.2; 18.5] 50 (56.8)	0.66 [0.44; 0.99] 0.044 AD = 1.7 months
Impairment due to pain (BPI-SF item 9a-g)[h]					
	92	22.1 [16.6; 35.1] 41 (44.6)	88	22.1 [13.0; 30.4] 44 (50)	0.79 [0.52; 1.21] 0.283
Health status (EQ-5D VAS)[i]					
	92	18.4 [8.3; 35.1] 45 (48.9)	88	14.1 [6.0; 16.9] 51 (58.0)	0.85 [0.57; 1.27] 0.417

Health-related quality of life

Endpoint	Niraparib/ abiraterone acetate + prednis(ol)one		Placebo + abiraterone acetate + prednis(ol)one		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 Absolute difference (AD)[a]
FACT-P total score[j]					
	92	22.1 [14.8; 33.2] 35 (38.0)	88	16.5 [11.1; 17.5] 41 (46.6)	0.64 [0.41; 1.01] 0.056
FACT-P sub-scales (presented additionally)					
Physical well-being[k]	92	3.8 [2.8; 7.5] 50 (54.3)	88	12.8 [6.0; 16.6] 47 (53.4)	1.29 [0.87; 1.93]
Social/ family well-being[k]	92	4.7 [2.8; 14.8] 34 (37.0)	88	4.2 [2.8; 10.9] 34 (38.6)	0.94 [0.58; 1.53]
Emotional well-being[l]	92	4.8 [2.8; 7.5] 47 (51.1)	88	5.1 [2.8; 9.3] 45 (51.1)	0.90 [0.60; 1.36]
Functional well-being[k]	92	3.8 [2.8; 7.4] 47 (51.1)	88	4.9 [2.8; 7.5] 52 (59.1)	0.82 [0.55; 1.22]
Prostate cancer-specific sub-scale[m]	92	21.4 [10.6; 26.8] 43 (46.7)	88	16.5 [13.0; 18.5] 44 (50.0)	0.86 [0.56; 1.31]

Side effects

Endpoint	Niraparib/ abiraterone acetate + prednis(ol)one		Placebo + abiraterone acetate + prednis(ol)one		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	92	0.5 [0.3; 0.5]	88	0.6 [0.5; 1.4]	-

Endpoint	Niraparib/ abiraterone acetate + prednis(ol)one		Placebo + abiraterone acetate + prednis(ol)one		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
		92 (100.0)		87 (98.9)	
Serious adverse events (SAE)					
	92	30.1 [21.7; n.c.] 39 (42.4)	88	33.4 [21.5; n.c.] 26 (29.5)	1.19 [0.72; 1.96] 0.494
Severe adverse events (CTCAE grade ≥ 3)					
	92	4.5 [2.7; 12.4] 65 (70.7)	88	10.3 [5.9; 16.7] 53 (60.2)	1.22 [0.85; 1.76] 0.281
Therapy discontinuation due to adverse events[n]					
	92	n.r. [38.2; n.c.] 15 (16.3)	88	n.r. 7 (8.0)	1.69 [0.68; 4.18] 0.256
Specific adverse events					
MDS (SMQ, AEs)[o]	92	n.r. 0 (0)	88	n.r. 0 (0)	-
AML (PT, AEs)[p]	92	0 (0)	88	1 (1.1)	n.a. [n.c.; n.c.] 0.9975
Anaemia (PT, severe AEs)	92	n.r. [34.3; n.c.] 25 (27.2)	88	n.r. 7 (8.0)	3.77 [1.63; 8.72] 0.002

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Discrepancy in the information on patient characteristics in Module 4 A, according to which 29 patients have previously received taxane-containing chemotherapy. According to the pharmaceutical company's statement,
no prior chemotherapy was administered to two patients,
although these patients were surveyed in the stratum of "prior taxane-containing chemotherapy".
[c] Number of patients with qualifying event for the composite endpoint of symptomatic progression (intervention vs control arm):

- Component "incidence of cancer-related morbidity events": 4 (4%) vs 6 (7%)
- Component "external radiotherapy for skeletal symptoms": 10 (11%) vs 16 (18%)
- Component "tumour-related orthopaedic surgical intervention": 0 vs 0
- Component "start of a new systemic cancer therapy due to cancer pain": 7 (8%) vs 17 (19%)
- Component "use of other cancer-related interventions": 4 (4%) vs 3 (3%)

[d] IQWiG calculation

Endpoint	Niraparib/ abiraterone acetate + prednis(ol)one		Placebo + abiraterone acetate + prednis(ol)one		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]

[e] Only the following cancer-related morbidity events are included in the evaluations subsequently submitted by the pharmaceutical company with the statement: spinal cord compression and fractures (symptomatic and/or pathological).
[f] Sensitivity analysis with addition of the component time to chronic opioid administration (defined by the pharmaceutical company as oral opioid consumption over ≥ 3 weeks; parenteral opioid consumption over ≥ 7 days) within the endpoint time to symptomatic progression
[g] Information on the number of patients with a qualifying event is missing
[h] 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)
[i] Time to first deterioration. A decrease by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0–100).
[j] Time to first deterioration. A decrease by ≥ 23.4 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0–156).
[k] Time to first deterioration. A decrease by ≥ 4.2 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0–28).
[l] Time to first deterioration. A decrease by ≥ 3.6 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0–24).
[m] Time to first deterioration. A decrease by ≥ 7.2 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0–48).
[n] Premature discontinuation of at least one therapy component
[o] AESI defined by the pharmaceutical company.
[p] Data from Module 4 A of the dossier of the pharmaceutical company from 07.11.2023

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; vs = versus

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

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 metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

and

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

approx. 1,030 - 2,200 patients in total

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 Akeega (active ingredient: niraparib/ abiraterone acetate) at the following publicly accessible link (last access: 20 March 2024):

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

Treatment with niraparib/ abiraterone acetate should only be initiated and monitored by specialists in internal medicine, haematology, and oncology as well as specialists in urology and further doctors from other professional groups participating in the Oncology Agreement who are experienced in the treatment of patients with prostate cancer.

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

4. Treatment costs

Annual treatment costs:

a) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Niraparib/ abiraterone acetate + prednisone or prednisolone + GnRH analogues	
Niraparib/ abiraterone acetate	€ 81,099.35
Prednisone or prednisolone	€ 55.85 - € 70.19
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 82,438.90 - € 83,400.50
Appropriate comparator therapy:	
Abiraterone acetate + prednisone or prednisolone + GnRH analogues	
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 55.85 - € 70.19
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 2,796.51 - € 3,758.11
Enzalutamide + GnRH analogues	
Enzalutamide	€ 40,687.07
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 41,970.77 - € 42,918.03
Olaparib as monotherapy + GnRH analogues	
Olaparib	€ 60,805.74
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 62,089.44 - € 63,036.70
Olaparib + abiraterone acetate + prednisone or prednisolone + GnRH analogues	
Olaparib	€ 60,805.74
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 55.85 - € 70.19
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 63,602.25 - € 64,563.85

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

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Niraparib/ abiraterone acetate + prednisone or prednisolone + GnRH analogues	
Niraparib/ abiraterone acetate	€ 81,099.35
Prednisone or prednisolone	€ 55.85 - € 70.19
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 82,438.90 - € 83,400.50
Appropriate comparator therapy:	
Abiraterone acetate + prednisone or prednisolone + GnRH analogues	
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 55.85 - € 70.19
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 2,796.51 - € 3,758.11
Enzalutamide + GnRH analogues	
Enzalutamide	€ 40,687.07
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 41,970.77 - € 42,918.03
Olaparib as monotherapy + GnRH analogues	
Olaparib	€ 60,805.74
GnRH analogues	€ 1,283.70 - € 2,230.96
Total	€ 62,089.44 - € 63,036.70

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

Costs for additionally required SHI services: not applicable

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 metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have not received prior therapy for mCRPC

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Adults with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated and who have already received a prior therapy for mCRPC

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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.