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)
Darolutamide (new therapeutic indication: prostate cancer, metastatic, hormone-sensitive, combination with docetaxel and androgen deprivation therapy)

of 21 September 2023

At its session on 21 September 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Darolutamide in accordance with the resolution of 15 October 2020:

Darolutamide

Resolution of: 21 September 2023
Entry into force on: 21 September 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 27 February 2023):

Nubeqa is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy.

Therapeutic indication of the resolution (resolution of 21 September 2023):

See new therapeutic indication according to marketing authorisation.

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

Adult males with metastatic hormone-sensitive prostate cancer (mHSPC)

Appropriate comparator therapy:

- conventional androgen deprivation in combination with apalutamide

or

- conventional androgen deprivation in combination with enzalutamide

or

- conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed, high-risk prostate cancer)

or

- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone

Extent and likelihood of additional benefit of darolutamide in combination with docetaxel and androgen deprivation therapy compared with conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone:

Indication of a considerable additional benefit.

Study results according to endpoints:[1]

Adult males with metastatic hormone-sensitive prostate cancer (mHSPC)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↑↑	Advantages in the endpoints of symptomatic skeletal events and worst pain.
Health-related quality of life	∅	No data available.
Side effects	↔	Overall, no relevant differences for the benefit assessment . In detail, advantages and disadvantages in each of the specific AEs.

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

ARASENS study:

- Double-blind, randomised controlled trial
- Darolutamide + docetaxel + androgen deprivation therapy (ADT) vs placebo + docetaxel + ADT

Mortality

Endpoint	Darolutamide + docetaxel + ADT		Placebo + docetaxel + ADT		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					
	651	n.r. 229 (35.2)	654	48.9 [44.4; n.c.] 304 (46.5)	0.68 [0.57; 0.80] < 0.001

[1] Data from the dossier assessment of the IQWiG (A23-21) and from the addendum to A23-81, unless otherwise indicated.

Morbidity

Endpoint	Darolutamide + docetaxel + ADT		Placebo + docetaxel + ADT		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]
Symptomatic skeletal events					
	651	n.r. 95 (14.6)	654	n.r. 108 (16.5)	0.71 [0.54; 0.94] 0.016
Endpoint component: external radiotherapy for relief of skeletal symptoms	651	n.r. 60 (9.2)	654	n.r. 89 (13.6)	-[b]
Endpoint component: new symptomatic, pathological bone fractures	651	n.r. 17 (2.6)	654	n.r. 8 (1.2)	-[b]
Endpoint component: Occurrence of spinal cord compression	651	n.r. 14 (2.2)	654	n.r. 9 (1.4)	-[b]
Endpoint component: tumour-related orthopaedic surgical intervention	651	n.r. 4 (0.6)	654	n.r. 2 (0.3)	-[b]
Worst pain (BPI-SF item 3)[c]					
	651	16.6 [13.8; 22.1] 377 (57.9)	654	13.6 [11.0; 16.6] 379 (58.0)	0.85 [0.73; 0.98] 0.022 AD = 3.0 months
Symptomatology (DRS-P subscale of the NFPSI-17)[d]					
	651	13.9 [13.1; 19.3] 386 (59.3)	654	13.8 [11.0; 16.4] 370 (56.6)	0.902 [0.78; 1.04] 0.156

Endpoint	Darolutamide + docetaxel + ADT			Placebo + docetaxel + ADT			Intervention vs control
	N[e]	Value at the start of the study MV (SD)	Value over the course of the study LS MV [95% CI]	N[e]	Value at the start of the study MV (SD)	Value over the course of the study LS MV [95% CI]	MD [95% CI] p value SMD [95% CI]
Impairment due to pain (BPI SF item 9a-g)[e]							
	618	1.5 (2.0)	1.6 [1.4; 1.8]	617	1.4 (1.9)	1.8 [1.6; 1.9]	-0.15 [-0.30; 0.00] 0.044 -0.11 [-0.22; 0.00]
Pain intensity (BPI SF items 3-6c (presented additionally)[f]							
	618	1.5 (1.9)	1.6 [1.4; 1.7]	617	1.4 (1.8)	1.7 [1.5; 1.8]	-0.08 [-0.22; 0.05] 0.231 -0.07 [-0.18; 0.05]
Endpoint	**Darolutamide + docetaxel + ADT**			**Placebo + docetaxel + ADT**			**Intervention vs control**
	N[e]	Value at the start of the study MV (SD)	Change over the course of the study MV (SD)	N[e]	Value at the start of the study MV (SD)	Change over the course of the study MV (SD)	MD [95% CI] p value SMD [95% CI]
Symptomatology (TSE subscale of the NFPSI-17)[g]							
	621	11.6 (2.0)	-0.6 (0.1)	616	11.7 (2.1)	-0.8 (0.1)	0.18 [0.00; 0.36] 0.044 0.11 [0.00; 0.23]

Health-related quality of life

No data on health-related quality of life were collected in the ARASENS study.

Side effects[h]

Endpoint	Darolutamide + docetaxel + ADT		Placebo + docetaxel + ADT		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]
Total adverse events (presented additionally)					
	652	0.5 [0.5; 0.6] 649 (99.5)	650	0.5 [0.4; 0.6] 643 (98.9)	-
Serious adverse events (SAE)					
	652	45.6 [34.9; n.c.] 293 (44.9)	650	40.0 [28.8; n.c.] 275 (42.3)	0.94 [0.80; 1.11] 0.464
Severe adverse events (CTCAE grade ≥ 3)					
	652	4.0 [3.1; 6.3] 460 (70.6)	650	3.9 [2.9; 5.7] 439 (67.5)	0.98 [0.86; 1.11] 0.699
Therapy discontinuation due to adverse events[i]					
	652	n.r. 124 (19.0)	650	n.r. 114 (17.5)	0.96 [0.74; 1.24] 0.759
Specific adverse events[j]					
Skin and subcutaneous tissue disorders (SOC, severe AE[k])	652	n.r. 20 (3.1)	650	n.r. 4 (0.6)	4.64 [1.58; 13.62] 0.002
Bone pain (PT, severe AE[k])	652	n.r. 8 (1.2)	650	n.r. 19 (2.9)	0.35 [0.15; 0.80] 0.009
Hypertension (PT, severe AE[k])	652	n.r. 43 (6.6)	650	n.r. 20 (3.1)	1.81 [1.06; 3.09] 0.027

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Since only the 1st event was recorded within the composite endpoint of symptomatic skeletal events, an effect estimate for the individual components of the endpoint cannot be meaningfully interpreted.
[c] Time to first deterioration. An increase by ≥ 2 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 in score by ≥ 6 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 40).

Endpoint	Darolutamide + docetaxel + ADT		Placebo + docetaxel + ADT		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]

[e] Number of adults who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
[f] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range for BPI-SF item 9a-g: 0 to 70, for BPI-SF item 3-6: 0-40).
[g] Higher (increasing) values mean better symptomatology; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0-16).
[h] Results in the side effects category are based on the safety update and also include events that the pharmaceutical company has defined as disease-related.
[i] AEs that led to discontinuation of darolutamide or placebo or docetaxel.
[j] Selection according to the IQWiG methodology; selection using events occurred in the study, based on frequency and differences between treatment arms, and taking into account patient relevance.
[k] Operationalised as CTCAE grade ≥ 3

Abbreviations used:
AD = absolute difference; ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory - Short Form; CTCAE = Common Terminology Criteria for Adverse Events; DRS-P = Disease-Related Symptoms-Physical; HR = hazard ratio; CI = confidence interval; LS = least squares; MD = mean difference; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; NFPSI 17 = National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index - 17 item version; SD = standard deviation; SMD = standardised mean difference; TSE = treatment side effects; vs = versus

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

Adult males with metastatic hormone-sensitive prostate cancer (mHSPC)

approx. 2,590 - 3,640 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 Nubeqa (active ingredient: darolutamide) at the following publicly accessible link (last access: 9 August 2023):

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

Treatment with darolutamide should only be initiated and monitored by specialists in internal medicine, haematology, oncology and urology, and specialists 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:

Adult males with metastatic hormone-sensitive prostate cancer (mHSPC)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Darolutamide in combination with docetaxel and androgen deprivation therapy	
Darolutamide	€ 45,213.72
Docetaxel	€ 2,939.04
if necessary, prednisone or prednisolone	€ 39.30 - € 42.93
GnRH agonist/ GnRH antagonist Orchiectomy	€ 1,283.70 - € 2,459.86 € 4,190.92
Total:	€ 49,436.46 - € 52,386.61
Appropriate comparator therapy:	
Conventional androgen deprivation in combination with apalutamide	
GnRH agonist/ GnRH antagonist Orchiectomy	€ 1,283.70 - € 2,459.86 € 4,190.92
Apalutamide	€ 35,408.65
Total:	€ 36,692.35 - € 39,599.57
Conventional androgen deprivation in combination with enzalutamide	
GnRH agonist/ GnRH antagonist Orchiectomy	€ 1,283.70 - € 2,459.86 € 4,190.92
Enzalutamide	€ 39,933.87
Total	€ 41,217.57 - € 44,124.79
Conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone	
GnRH agonist/ GnRH antagonist Orchiectomy	€ 1,283.70 - € 2,459.86 € 4,190.92
Abiraterone acetate	€ 1,456.96
Prednisone or prednisolone	€ 47.82 - € 52.23
Total:	€ 2,788.47 - € 5,700.11
Conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone	

Designation of the therapy	Annual treatment costs/ patient
GnRH agonist/ GnRH antagonist Orchiectomy	€ 1,283.70 - € 2,459.86 € 4,190.92
Docetaxel	€ 2,939.04
if necessary, prednisone or prednisolone	€ 39.30 - € 42.93
Total:	€ 4,222.74 - € 7,172.89

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2023

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Darolutamide in combination with docetaxel and androgen deprivation therapy					
Docetaxel	Surcharge for production of a parenteral, cytostatic solution	€ 100	1	6	€ 600
Appropriate comparator therapy:					
Conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone					
Docetaxel	Surcharge for production of a parenteral, cytostatic solution	€ 100	1	6	€ 600

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:

Adult males with metastatic hormone-sensitive prostate cancer (mHSPC)

The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA has identified at least considerable additional benefit for the combination with the assessed medicinal product in the present resolution:

Relugolix (Orgovyx).

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 21 September 2023.

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

Berlin, 21 September 2023

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

Prof. Hecken