Gemeinsamer Bundesausschuss

Darolutamide

Resolution of: 15 October 2020 Valid until: unlimited
Entry into force on: 15 October 2020
Federal Gazette, BAnz AT 26 11 2020 B4

Therapeutic indication (according to the marketing authorisation of 27 March 2020):

Nubeqa is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nm-CRPC) who are at high risk of developing metastatic disease.

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

Adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease

Appropriate comparator therapy:

A wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT).

Extent and probability of the additional benefit of darolutamide compared with the wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT):

Indication of a considerable additional benefit

Study results according to endpoints[1]:

ARAMIS study: Darolutamide + ADT vs placebo + ADT[2]

Study design: randomised, double-blind, two-armed, Phase III

Data cut-offs: 1st data cut-off of 3 September 2018; 2nd data cut-off of 15 November 2019

Mortality

Endpoint	**Darolutamide + ADT**		**Placebo + ADT[2]**		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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Overall survival					
1st data cut-off	955	n.a. [44,4; n.c.] *78 (8.2)*	554	n.a. *58 (10.5)*	0.71 [0.50; 0.99] 0.045 AD: n.c.
2nd data cut-off	955	n.a. [56,1; n.c.] *148 (15.5)*	554	n.a. [46,9; n.c.] *106 (19.1)*	0.69 [0.53; 0.88]; 0.003 AD: n.c.

Morbidity[b]

Endpoint	**Darolutamide + ADT**		**Placebo + ADT[2]**		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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Metastasis-free survival (MFS)[c]					
	955	40.4 [34.3; n.c.] *221 (23.1)*	554	18.4 [15.5; 22.3] *216 (39.0)*	0.41 [0.34; 0.50] < 0.001 AD: 22.0 months

[1] Data from the dossier assessment of the IQWiG (A20-43) and the addendum (A20-84) unless otherwise indicated.

[2] Sufficient approximation to the appropriate comparator therapy wait-and-see approach while maintaining the existing conventional androgen deprivation (ADT)

Endpoint	Darolutamide + ADT		Placebo + ADT[2]		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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Symptomatic skeletal events					
	955	n.a. *16 (1.7)*	554	n.a. *18 (3.2)*	0.43 [0.22; 0.84] 0.011 AD: n.c.
Endpoint component: external radiotherapy to alleviate skeletal symptoms	955	n.a. *12 (1.3)*	554	n.a. *11 (2.0)*	–[d]
Endpoint component: new symptomatic, pathological bone fractures	955	n.a. *2 (0.2)*	554	n.a. *2 (0.4)*	–[d]
Endpoint component: Occurrence of spinal cord compression	955	n.a. *0 (0)*	554	n.a. *3 (0.5)*	–[d]
Endpoint component: Tumour-related orthopaedic surgery	955	n.a. *2 (0.2)*	554	n.a. *2 (0.4)*	–[d]
Invasive procedures specific to prostate cancer					
	955	n.a. *34 (3.6)*	554	n.a. *44 (7.9)*	0.39 [0.25; 0.61] < 0.001 AD: n.c.
Pain progression					
BPI-SF Item 3[e] or start of opioid therapy	955	40.3 [33.2; 41.2] *251 (26.3)*	554	25.4 [19.1; 29.6] *178 (32.1)*	0.65 [0.53; 0.79] < 0.001 AD: 14.9 months
presented additionally: BPI-SF Item 3[e]	955	n.a. [40,3; n.c.] *238 (24.9)*	554	26.9 [22.1; 31.4] *168 (30.3)*	0.66 [0.54; 0.81] < 0.001 AD: n.c.

Endpoint	Darolutamide + ADT			Placebo + ADT[2]			Intervention vs control
	N[f]	Values at the start of study MV (SD)	Change at the first data cut-off MV [95% CI]	N[f]	Values at the start of study MV (SD)	Change at the first data cut-off MV [95% CI]	Mean difference (MD) [95% CI] p value
Impairment because of pain							
BPI-SF Items 9a–g[g]	no data available	no data available	1.1 [1.0; 1.3]	no data available	no data available	1.3 [1.2; 1.4]	−0.2 [−0.3; −0.1] no data available Hedges' g: −0.12 [no data available]
Pain intensity (presented additionally)							
BPI-SF Items 3–6[g]	no data available	no data available	1.3 [1.1; 1.4]	no data available	no data available	1.4 [1.3; 1.6]	−0.2 [−0.3; −0.1] no data available Hedges' g: –[h]

Endpoint	Darolutamide + ADT		Placebo + ADT[2]		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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Health status (EQ-5D VAS) – time to deterioration					
No usable data					

Endpoint	Darolutamide + ADT			Placebo + ADT[2]			Intervention vs control
	N[f]	Values at the start of study MV (SD)	Values at Week 16 MV (SD)	N[f]	Values at the start of study MV (SD)	Values at Week 16 MV (SD)	Mean difference (MD) [95% CI] p value
Health status (EQ-5D VAS)[i]							
	868	70.3 (21.4)	74.9 (17.3)	489	71.5 (17.0)	72.7 (18.3)	2.2 [0.2; 4.2] 0.028 Hedges' g: 0.12 [0.01; 0.24]

Health-related quality of life

Endpoint	Darolutamide + ADT		Placebo + ADT[2]		Intervention vs control
	N[j]	Patients with event at Week 16 n (%)	N[j]	Patients with event at Week 16 n (%)	relative risk (RR) [95% CI] p value Absolute difference (AD)[a]
FACT-P Total score – deterioration[k] by ≥ 10 points					
	848	167 (19.7)	478	117 (24.5)	0.80 [0.65; 0.99] 0.041 AD: 4.8%
FACT-P sub-scales – deterioration[k] by ≥ 3 points (presented additionally)					
Physical well-being	863	138 (16.0)	483	101 (20.9)	0.76 [0.61; 0.96]
Social/familiar well-being	862	193 (22.4)	484	133 (27.5)	0.81 [0.67; 0.99]
Emotional well-being	857	142 (16.6)	484	108 (22.3)	0.74 [0.59; 0.93]
Functional well-being	857	183 (21.4)	483	126 (26.1)	0.82 [0.67; 1.00]
Prostate cancer sub-scale	882	219 (24.8)	501	154 (30.7)	0.81 [0.68; 0.96]

Side effects[b]

Endpoint	Darolutamide + ADT		Placebo + ADT[2]		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]
Adverse events in total (presented additionally)					
	954	3.9 [3.2; 4.2] *794 (83.2)*	554	4.3 [3.8; 4.6] *426 (76.9)*	–
Serious adverse events (SAE)					
	954	44.4 [44.4; n.c.] *237 (24.8)*	554	n.a. *111 (20.0)*	1.14 [0.91; 1.43] 0.263
Severe adverse events (CTCAE grade ≥ 3)[l]					
	954	38.5 [34.1; n.c.] *280 (29.4)*	554	n.a. *137 (24.7)*	1.11 [0.91; 1.36] 0.311
Therapy discontinuation because of adverse events					
	954	n.a. *86 (9.0)*	554	n.a. *48 (8.7)*	0.95 [0.67; 1.36] 0.791
Specific adverse events					
Renal and urinary disorders (SOC, SAE)	954	n.a. *45 (4.7)*	554	n.a. *40 (7.2)*	0.58 [0.38; 0.89] 0.012 AD: n.c.
General disorders and administration site conditions (SOC, SAE)	954	n.a. *17 (1.8)*	554	n.a. *1 (0.2)*	9.12 [1.21; 68.56] 0.032 AD: n.c.

[a] AD given only in the case of a statistically significant difference; own calculation
[b] 1st data cut-off of 3 September 2018 (unless otherwise stated)
[c] Data from the dossier on darolutamide Module 4A of 1 May 2020
[d] Because only the first result within the combined endpoint symptomatic skeletal events was recorded, an effect estimate cannot be interpreted meaningfully.
[e] Time to first deterioration by ≥ 2 points compared with the start of study
[f] Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study can be based on other patient numbers.
[g] A positive change means a deterioration; a negative effect estimate means an advantage for the intervention.
[h] Calculation of the IQWiG not possible because of lack of data; because of the rather small differences in mean values, no relevant effect can be assumed
[i] Higher values compared with the start of study mean an improvement; a positive effect estimate means an advantage for the intervention.

[j] Patients who have received a questionnaire
[k] Deterioration means a decrease of the score
[l] In addition to AE that occurred under the treatment, AE that occurred from the signing of the consent form to randomisation are also included.

Abbreviations used:
AD = absolute difference; ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life Questionnaire – 5 Dimensions; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HR = hazard ratio; CI = confidence interval; MD = mean difference; MID = minimal important difference MFS = metastasis-free survival; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; RR = relative risk; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

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 symptomatic skeletal events, invasive procedures specific to prostate cancer, and pain progression
Health-related quality of life	↑	Advantage in disease-specific quality of life
Side effects	↔	No difference relevant for the benefit assessment; advantage and disadvantage in individual specific AE

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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

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

approx. 1,090–3,800 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: 31 August 2020):

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

Treatment with darolutamide should be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in urology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with prostate cancer.

Medicinal castration with a luteinising hormone releasing hormone (LHRH) analogue should be continued during the treatment of patients who have not been surgically castrated.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Darolutamide	€ 57,743.52
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Total:	€ 58,990.30 – 59,840.24
Appropriate comparator therapy:	
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services: not applicable