Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Apalutamide

of 1 August 2019

At its session on 1 August 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. no. 49a of 31 March 2009), last changed on DD Month YYY (BAnz AT DD MM YYY BX), to be amended as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient apalutamide as follows:

Apalutamide

Resolution of: 1 August 2019
Entry into force on: 1 August 2019
BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 January 2019):

Erleada is indicated in adult men for the treatment of 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 carcinoma (nm-CRPC) who are at high risk of developing metastases:

Appropriate comparator therapy:

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

The extent and probability of the additional benefit of apalutamide over the monitoring wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT):

Hint for a minor additional benefit.

Study results according to endpoints:[1]

Adult men with non-metastatic castration-resistant prostate carcinoma (nm-CRPC) who are at high risk of developing metastases:

SPARTAN study: Apalutamide + ADT vs placebo + ADT

Mortality

Endpoint	Apalutamide + ADT		Placebo + 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 (%)*	Hazard ratio (HR) [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	806	n.a. 62 (7.7)	401	39.03 [39.03; n.c.] 42 (10.5)	0.70 [0.47; 1.04] 0.076

Morbidity

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Metastasis-free survival (MFS)[2]					
	806	40.51 [29.70; 40.51] 209 (25.9)	401	15.70 [14.55; 18.40] 210 (52.4)	0.30 [0.24; 0.36] < 0.0001 AD=24.81 months
Time before initiation of cytotoxic chemotherapy[2]					
	806	n.a. [n.a.; n.a.] 46 (5.7)	401	n.a. [n.a.; n.a.] 44 (11.0)	0.44 [0.29; 0.66] < 0.0001
Symptomatic progression					
	806	n.a. 64 (7.9)	401	n.a. [36.83; n.c.] 63 (15.7)	0.45 [0.32; 0.63] < 0.001

[1] Data from the dossier evaluation of the IQWiG (A19-09) and from the addendum (A19-51), unless otherwise indicated.

[2] Dossier apalutamide Module 4A of 21 January 2019

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Endpoint component: skeletal events[b]	806	n.a. 25 (3.1)	401	n.a. 18 (4.5)	0.62 [0.34; 1.14] 0.127
Endpoint component Pain progression or deterioration of disease-related symptoms[c]	806	n.a. 35 (4.3)	401	n.a. [36.83; n.c.] 28 (7.0)	0.56 [0.34; 0.92] 0.022
Endpoint component Clinically significant symptoms because of locoregional tumour progression[d]	806	n.a. 18 (2.2)	401	n.a. 24 (6.0)	0.34 [0.18; 0.62] < 0.001
Health status (EQ-5D VAS)					
MID 7[e]	806	10.02 [7.43; 14.85] 432 (53.6)	401	11.30 [6.47; 18.50] 198 (49.4)	0.96 [0.81; 1.14] 0.618
MID 10[f]	806	14.69 [9.96; 23.95] 408 (50.6)	401	14.85 [9.27; 18.60] 188 (46.9)	0.93 [0.78; 1.11] 0.428

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Values at start of study MV (SD) Change to Cycle 13 MV (SE)	N	Values at start of study MV (SD) Change to Cycle 13 MV (SE)	Mean difference [95% CI] p value Hedges´ g
Health status (EQ-5D VAS) (presented as a supplement)					
	no data available	76.17 (17.31) 0.44 (0.55)	no data available	76.81 (16.88) −0.60 (0.88)	1.04 [no data available] 0.315

Health-related quality of life

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
FACT-P total score[f]					
	806	6.60 [5.55; 7.92] 498 (61.8)	401	8.38 [6.47; 12.91] 222 (55.4)	1.06 [0.90; 1.25] 0.465
FACT-P sub-scales (presented additionally)[g]					
Prostate cancer sub-scale (PCS)	806	3.84 [3.71; 4.70] 575 (71.3)	401	3.78 [2.86; 4.80] 266 (66.3)	0.98 [0.84; 1.14]
Physical well-being (PWB)	806	6.57 [5.55; 8.38] 488 (60.5)	401	7.43 [5.59; 11.10] 222 (55.4)	1.02 [0.87; 1.20]
Familiar/social well-being (SWB)	806	7.46 [5.59; 11.07] 437 (54.2)	401	4.90 [3.84; 8.38] 218 (54.4)	0.88 [0.75; 1.04]
Emotional well-being (EWB)	806	12.98 [10.87; 18.43] 411 (51.0)	401	14.75 [10.61; n.c.] 176 (43.9)	1.08 [0.90; 1.29]
Functional well-being (FWB)	806	4.63 [3.78; 5.59] 522 (64.8)	401	6.51 [4.70; 9.26] 224 (55.9)	1.17 [1.00; 1.37]

Side effects

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	803	0.56 [0.46; 0.72] 775 (96.5)	398	0.76 [0.53; 0.92] 371 (93.2)	-
Serious adverse events (SAE)					
	803	n.a. 204 (25.4)	398	35.25 [25.96; n.c.] 93 (23.4)	0.80 [0.62; 1.03] 0.081

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Severe adverse events (CTCAE grade ≥ 3)					
	803	22.44 [17.68; 26.18] 366 (45.6)	398	24.15 [18.53; 30.00] 137 (34.4)	1.13 [0.92; 1.37] 0.246
Therapy discontinuation because of adverse events					
	803	n.a. 85 (10.6)	398	36.83 [36.83; n.c.] 28 (7.0)	1.33 [0.87; 2.04] 0.193
Specific adverse events[h]					
Arthralgia (PT, AE)	803	n.a. 126 (15.7)[i]	398	n.a. 30 (7.5)	1.80 [1.21; 2.69] 0.004
Skin and subcutaneous tissue disorders (SOC, severe AE)	803	n.a. 50 (6.2)	398	n.a. 1 (0.3)	23.48 [3.24; 170.03] 0.002
Nervous system disorders (SOC AE)	803	n.a. 288 (35.9)	398	n.a. [26.28; n.c.] 90 (22.6)	1.53 [1.21; 1.94] < 0.001
Renal and urinary disorders (SOC, severe AE)	803	n.a. 38 (4.7)	398	n.a. 39 (9.8)	0.37 [0.23; 0.58] < 0.001
Hypothyroidism (PT, AE)	803	n.a. 49 (6.1)	398	n.a. 5 (1.3)	4.09 [1.63; 10.30] 0.003
General disorders and administration site conditions (SOC, severe AE)	803	n.a. 18 (2.2)	398	n.a. 1 (0.3)	7.79 [1.04; 58.49] 0.046
Injury, poisoning, and procedural complications (SOC, SAE)	803	n.a. 41 (5.1)	398	n.a. 5 (1.3)	3.05 [1.20; 7.75] 0.019

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone
[c] With need to initiate a new systemic cancer therapy
[d] With need of surgical intervention or radiotherapy
[e] Time to deterioration by ≥ 7 points
[f] Time to deterioration by ≥ 10 points

Endpoint	Apalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]

[g] Time to deterioration by ≥ 3 points
[i] Selection in accordance with IQWiG methodology; selection based on those identified in the study
Events based on frequency and differences between treatment arms and taking into account patient relevance.
[i] According to the study report, 128 (15.9%) of the patients in the apalutamide arm had at least one event.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; MID = minimal important difference; MD = mean difference; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; SD = standard deviation; vs = versus; VAS = visual analogue scale

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

Adult men with non-metastatic castration-resistant prostate carcinoma (nm-CRPC) who are at high risk of developing metastases;

approx. 810–1180 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 Erleada® (active ingredient: apalutamide) at the following publicly accessible link (last access: 10 May 2019):

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

Only specialists in internal medicine, haematology and oncology with experience treating patients with prostate cancer, and specialists in urology and other doctors from other specialisms participating in the oncology agreement may initiate and monitor treatment with apalutamide.

Patients who have not undergone surgical castration should continue receiving chemical castration with GnRH agonists or antagonists during treatment.

4. Treatment costs

Annual treatment costs:

Adult men with non-metastatic castration-resistant prostate carcinoma (nm-CRPC) who are at high risk of developing metastases:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Apalutamide	€ 50,952.18
GnRH agonist/GnRH antagonist	€ 1,283.50–2,124.88
Total:	€ 52,235.68–53,077.06
Appropriate comparator therapy:	
GnRH agonist/GnRH antagonist	€ 1,283.50–2,124.88

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2019)

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the Internet on the website of the G-BA on 1 August 2019.**

2. **The period of validity of the resolution is limited to 15 May 2020.**

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

Berlin, 1 August 2019

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

Prof Hecken