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 (Reassessment after the Deadline: Non-metastatic Castration-resistant Prostate Cancer)

of 1 October 2020

At its session on 1 October 2020 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 on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII will be amended as follows:

1. The information on apalutamide in accordance with the resolution of 1 August 2019 (Federal Gazette, BAnz AT 27 August 2019 B5) as last amended on 20 February 2020 (Federal Gazette, BAnz AT 19 March 2020 B3) is hereby repealed.

2. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of apalutamide in accordance with the resolution of 20 August 2020:

Apalutamide

Resolution of: 1 October 2020
Entry into force on: 1 October 2020
Federal Gazette, 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 (nmCRPC) 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 (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 apalutamide compared with the wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT):

Indication of a minor additional benefit

Study results according to endpoints[1]:

SPARTAN study: Apalutamide + ADT vs placebo + ADT[2]

Study design: randomised, double-blind, Phase III

Data cut-off: 1 December 2019[3]

Mortality

Endpoint	Apalutamide + 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][a] p value Absolute difference (AD)[b]
Overall survival					
	806	66.10 [61.34; n.c.] *261 (32.4)*	401	58.68 [52.70; n.c.] *149 (37.2)*	0.77 [0.63; 0.94] no data available AD: 7.42 months

Morbidity

Metastasis-free survival (MFS)[c]					
	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] < 0.001 AD: 24.81 months
Time before initiation of cytotoxic chemotherapy[c]					
	806	n.a. [n.a.; n.a.] *149 (18.5)*	401	n.a. [n.a.; n.a.] *100 (24.9)*	0.62 [0.48; 0.80] no data available AD: n.c.
Symptomatic progression					
	806	n.a. *149 (18.5)*	401	n.a. *102 (25.4)*	0.58 [0.45; 0.75] no data available AD: n.c.

(Continuation)

[1] Data from the dossier assessment of the IQWiG (A20-36) unless otherwise indicated.

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

[3] Conditions for a time limit of the G-BA

Endpoint component: skeletal events[d]	806	n.a. *51 (6.3)*	401	n.a. *33 (8.2)*	0.64 [0.41; 0.99] no data available AD: n.c.
Endpoint component: pain progression or deterioration of disease-related symptoms[e]	806	n.a. *77 (9.6)*	401	n.a. *54 (13.5)*	0.60 [0.42; 0.85] no data available AD: n.c.
Endpoint component: clinically significant symptoms because of locoregional tumour progression[f]	806	n.a. *45 (5.6)*	401	n.a. *31 (7.7)*	0.62 [0.39; 0.97] no data available AD: n.c.
Health status (EQ-5D VAS)					
Time until deterioration [g]					
MID 7	806	10.02 [7.43; 15.05] *474 (58.8)*	401	11.30 [6.47; 18.53] *201 (50.1)*	0.95 [0.80; 1.13] no data available
MID 10	806	14.75 [9.96; 25.79] *447 (55.5)*	401	15.70 [9.27; 22.11] *191 (47.6)*	0.93 [0.78; 1.10] no data available

Endpoint	**Apalutamide + ADT**			**Placebo + ADT**[2]			**Intervention vs control**
	N	Values at start of study MV (SD)	Change MV (SD)	N	Values at start of study MV (SD)	Change MV (SD)	Effect [95% CI] p value
Health status (EQ-5D VAS)							
No usable data							

(Continuation)

Health-related quality of life

Endpoint	Apalutamide + 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][a] p value Absolute difference (AD)[b]
FACT-P total score[h]					
	806	6.60 [5.55; 8.28] *544 (67.5)*	401	8.38 [6.47; 12.95] *230 (57.4)*	1.04 [0.89; 1.22] no data available
FACT-P sub-scales (presented additionally)[i]					
Prostate cancer sub-scale (PCS)	806	3.84 [3.71; 4.70] *619 (76.8)*	401	3.78 [2.86; 4.80] *272 (67.8)*	0.97 [0.84; 1.13] no data available
Physical well-being (PWB)	806	6.57 [5.55; 8.38] *530 (65.8)*	401	7.43 [5.59; 11.11] *234 (58.4)*	0.97 [0.83; 1.14] no data available
Familiar/social well-being (SWB)	806	7.49 [5.62; 11.11] *473 (58.7)*	401	4.90 [3.84; 8.38] *223 (55.6)*	0.87 [0.73; 1.02] no data available
Emotional well-being (EWB)	806	14.69 [11.07; 18.63] *459 (56.9)*	401	14.82 [10.61; 32.99] *181 (45.1)*	1.06 [0.89; 1.27] no data available
Functional well-being (FWB)	806	4.63 [3.78; 5.59] *558 (69.2)*	401	6.51 [4.70; 9.27] *229 (57.1)*	1.15 [0.98; 1.35] no data available

Side effects

Adverse events (presented additionally)					
	803	0.56 [0.43; 0.70] *781 (97.3)*	398	0.76 [0.53; 0.92] *373 (93.7)*	-
Serious adverse events (SAE)					
	803	35.06 [31.34; 41.92] *295 (36.7)*	398	35.25 [28.19; n.c.] *100 (25.1)*	0.84 [0.67; 1.07] no data available

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Severe adverse events (CTCAE grade ≥ 3)					
	803	21.91 [18.46; 25.92] *450 (56.0)*	398	24.15 [18.53; 29.47] *146 (36.7)*	1.10 [0.91; 1.34] no data available
Therapy discontinuation because of adverse events					
	803	n.a. [54.41; n.c.] *115 (14.3)*	398	n.a. *29 (7.3)*	1.40 [0.92; 2.12] no data available
Specific adverse events[j]					
Arthralgia (PT, AE)	803	57.20 [45.17; n.c.] *158 (19.7)*	398	n.a. *33 (8.3)*	1.74 [1.19; 2.54] no data available AD: n.c.
Skin and subcutaneous tissue disorders (SOC, severe AE CTCAE grade ≥ 3)	803	n.a. *52 (6.5)*	398	n.a. *1 (0.3)*	23.84 [3.29; 172.53] no data available AD: n.c.
Nervous system disorders (SOC, AE)	803	37.16 [30.42; 47.80] *326 (40.6)*	398	n.a. *93 (23.4)*	1.54 [1.22; 1.94] no data available
Renal and urinary disorders (SOC, severe AE CTCAE grade ≥ 3)	803	n.a. [58.91; n.c.] *67 (8.3)*	398	n.a. [35.48; n.c.] *46 (11.6)*	0.38 [0.25; 0.57] no data available AD: n.c.
Hypothyroidism (PT, AE)	803	n.a. *59 (7.3)*	398	n.a. *5 (1.3)*	4.43 [1.77; 11.09] no data available AD: n.c.
Infections and infestations (SOC, SAE)	803	n.a. [53.09; n.c.] *76 (9.5)*	398	n.a. *9 (2.3)*	2.29 [1.13; 4.64] no data available AD: n.c.
Injury, poisoning, and procedural complications (SOC, SAE)	803	n.a. [59.37; n.c.] *60 (7.5)*	398	n.a. *6 (1.5)*	2.82 [1.20; 6.61] no data available AD: n.c.

[a] HR and CI: Cox proportional hazard model with treatment as the only explanatory variable stratified by PSADT (≤ 6 months vs > 6 months), use of bone-preserving substances (yes vs no), presence of locoregional disease (N0 vs N1)

(Continuation)

[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[c] Data from the dossier on apalutamide Module 4A of 30 March 2020
[d] Pathological fractures, compression of the spinal cord, or need for surgical intervention or radiotherapy of the bone.
[e] With need to initiate a new systemic cancer therapy.
[f] With need of surgical intervention or radiotherapy.
[g] Deterioration means reduction of the score by the respective MID
[h] Time to deterioration by ≥ 10 points
[i] Time to deterioration by ≥ 3 points
[j] Selection according to the methodology of the IQWiG; selection using events based on frequency and differences between treatment arms and taking into account patient relevance.

Abbreviations used:
AD = absolute difference; ADT = androgen deprivation therapy; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life Questionnaire – 5 Dimensions; FACT-P = Functional Assessment of Cancer Therapy – Prostate; CI = confidence interval; MID = minimal important Difference; MV = mean value; 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; SOC = system organ class; PSA: prostate-specific antigen; PSADT: PSA doubling time; PT = preferred term; 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	↑	Advantage in symptomatic progression
Health-related quality of life	↔	No difference relevant for the benefit assessment
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 Erleada® (active ingredient: apalutamide) at the following publicly accessible link (last access: 16 September 2020):

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

Treatment with apalutamide 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.

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:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Apalutamide	€ 38,663.80
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Total:	€ 39,910.58 – 40,760.52
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

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 1 October 2020.

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

Berlin, 1 October 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken