Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Appendix XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V Enzalutamide (New Therapeutic Indication: Non-Metastatic Castration-Resistant High-Risk Prostate Cancer)

From 16. May 2019

At its meeting on 16. May 2019, the Federal Joint Committee (G-BA) decided to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008/22 January 2009 (BAnz. No. 49a of 31 March 2009), as last amended on TT. Monat JJJJ (BAnz AT TT.MM.JJJJ BX), as follows:

I. In Appendix XII, the following entries shall be inserted after point 4 to the entries concerning the benefit assessment of enzalutamide, as per the resolution of 18 June 2015:

Enzalutamide

Resolution from: 16. May 2019
Date of entry into force: 16. May 2019
BAnz. AT TT. MM JJJJ Bx

New therapeutic indication (according to the marketing authorisation of 23 October 2018):

Enzalutamide (Xtandi™) is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer (CRPC).

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

Adult men with non-metastatic castration-resistant high-risk prostate cancer (CRPC):

Appropriate comparator:

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

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

No additional benefit has been proven.

Study results according to endpoints:[1]

Adult men with non-metastatic castration-resistant high-risk prostate cancer (CRPC)

PROSPER study: Enzalutimide + ADT vs. placebo + ADT

Mortality

Endpoint	Enzalutamide + 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]
Mortality					
Overall survival					
	933	n.a. [49,9; n.a.] 184 (19.7)	468	n.a. [49,4; n.a.] 104 (22.2)	0.83 [0.65; 1.06] 0.134

Morbidity

Endpoint	Enzalutamide + 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 (%)*	HR [95%-CI] p-value Absolute difference (AD)[a]
Metastasis-free survival (MFS)					
	933	36.6 [33,1; n.a.] 219 (23.5)	468	14.7 [14.2; 15.0] 228 (48.7)	0.29 [0.24; 0.35] < 0.001 AD=21.9 months
Time before commencement of cytotoxic chemotherapy					
	933	38.1 [37,8; n.c.] 157 (16.8)	468	34.0 [30.3; 39.7] 132 (28.2)	0.50 [0.40; 0.64] p < 0.001 AD=4.1 months
Health status (EQ-5D VAS)					
MID 7[b]	836	11.1 [7.8; 11.2]	414	7.5 [7.4; 11.0]	0.83 [0.71; 0.97]

[1] Data from the dossier evaluation by the IQWiG (A18-80) and from the addendum (A19-34), unless otherwise indicated.

Endpoint	Enzalutamide + 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 (%)*	HR [95%-CI] p-value Absolute difference (AD)[a]
		515 (55.2)		250 (53.4)	0.019 AD=3.6 months
MID 10[c]	836	14.6 [11.1; 14.8] 473 (50.7)	414	11.0 [7.5; 11.1] 235 (50.2)	0.79 [0.67; 0.93] 0.004 AD=3.6 months
Worst pain (BPI-SF Item 3)					
	839	18.5 [18.3; 22.1] 390 (41.8)	415	18.5 [14.8; 25.8] 165 (35.3)	0.98 [0.82; 1.18] 0.838

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs. control
	N	Values at commencement of study MV (SD) Change at week 97 MV (SE)	N	Values at commencement of study MV (SD) Change at week 97 MV (SE)	Mean difference [95%-CI] p-value Hedges´ g
Pain interference (BPI-SF item 9 (a–g))					
	839	No data available 0.65 (0.1)	415	No data available 0.85 (0.16)	-0.20 [-0.53; 0.13] No data available
Pain Intensity (BPI-SF items 3–6; presented as a supplement)					
	839	No data available 0.49 (0.1)	415	No data available 0.55 (0.16)	-0.06 [-0.40; 0.29] No data available
Health status (EQ-5D VAS) (presented as a supplement)					
MD	839	No data available -4.57 (0.91)	414	No data available -5.29 (1.47)	0.72 [−2.30; 3.75] 0.639

Health-related quality of life

Endpoint	Enzalutamide + 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 (%)*	HR [95%-CI] p-value Absolute difference (AD)[a]
FACT-P total score[c]					
	839	11.1 [11.0; 14.7] 499 (53.5)	415	11.1 [11.1; 14.7] 226 (48.3)	0.97 [0.82; 1.14] 0.700
FACT-P sub-scales (presented additionally)[e]					
Physical well-being (PWB)	839	7.9 [7.5; 11.1] 538 (57.7)	415	11.5 [11.1; 14.8] 206 (44.0)	1.28 [1.08; 1.50] 0.004
Social well-being (SWB)	839	18.4 [14.8; 22.2] 398 (42.7)	415	14.8 [11.1; 18.6] 187 (40.0)	0.88 [0.73; 1.05] 0.153
Emotional well-being (EWB)	839	25.8 [22.0; 29.4] 359 (38.5)	415	18.4 [14.7; 18.6] 173 (37.0)	0.84 [0.70; 1.01] 0.070
Functional well-being (FWB)	839	11.0 [7.5; 11.1] 534 (57.2)	415	11.1 [10.7; 14.6] 229 (48.9)	1.07 [0.91; 1.25] 0.419
PCS	839	7.8 [7.5; 11.1] 549 (58.8)	415	7.7 [7.4; 11.1] 264 (56.4)	0.85 [0.73; 0.99] 0.036

Side effects

Endpoint	Enzalutamide + 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 (%)*	HR [95%-CI] p-value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	930	1.0 [0.9; 1.4] 806 (86.7)	465	2.9 [1.9; 3.6] 359 (77.2)	-
Serious adverse events (SAE)					
	930	n.a. [38,4; n.a.] 206 (22.2)	465	n.a. [32.9; n.a.] 82 (17.6)	0.90 [0.70; 1] 17 0.444
Severe adverse events (CTCAE grade ≥3)					
	930	n.a. [34,1; n.a.] 280 (30.1)	465	33.1 [26,9; n.a.] 107 (23.0)	1.06 [0.85; 1.33] 0.614
Termination of therapy due to adverse events					
	930	n.a. [n.a.; n.a.] 80 (8.6)	465	n.a. [n.a.; n.a.] 31 (6.7)	1.00 [0.66; 1.52] 0.998
Specific adverse events[f]					
Renal and urinary disorders (SOC, SAEs)	930	n.a. [n.a.; n.a.] 46 (4.9)	465	n.a. [36,8; n.a.] 36 (7.7)	0.44 [0.28; 0.69] < 0.001
Nervous system disorders (SOC, SAEs)	930	n.a. [n.a.; n.a.] 37 (4.0)	465	n.a. [n.a.; n.a.] 6 (1.3)	2.40 [1.01; 5.71] 0.041
Fatigue (PT, SAEs)	930	n.a. [n.a.; n.a.] 27 (2.9)	465	n.a. [n.a.; n.a.] 3 (0.6)	3.75 [1.13; 12.42] 0.020
Reduction in appetite (PT, AEs)	930	n.a. [n.a.; n.a.] 89 (9.6)	465	n.a. [n.a.; n.a.] 18 (3.9)	2.21 [1.33; 3.67] 0.002
Vascular disorders (SOC, AEs)	930	n.a. [n.a.; n.a.] 244 (26.2)	465	n.a. [n.a.; n.a.] 71 (15.3)	1.59 [1.22; 2.07] < 0.001
Urinary tract infection (PT, AEs)	930	n.a. [n.a.; n.a.] 38 (4.1)	465	n.a. [n.a.; n.a.] 30 (6.5)	0.46 [0.28; 0.74] 0.001

Endpoint	Enzalutamide + 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 (%)*	HR [95%-CI] p-value Absolute difference (AD)[a]
Fall (PT, AEs)	930	n.a. [n.a.; n.a.] 106 (11.4)	465	n.a. [36,8; n.a.] 19 (4.1)	2.01 [1.23; 3.28] 0.005

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Time to first deterioration by ≥ 7 points
[b] Time to first deterioration by ≥ 10 points
[b] Time to first deterioration by ≥ 2 points
[b] Time to first deterioration by ≥ 3 points
[f] 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.

Abbreviations employed:
AD = absolute difference; CTCAE = common terminology criteria for adverse events; HR = hazard ratio; No data available [German: k.A.]; 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; SOC = serious organ class; vs. = versus

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

Approx. 810–1180 patients

3. Requirements for quality-assured application

The guidelines in the product information must be observed. The European Medicines Agency (EMA) has made the contents of the technical information on Xtandi® (active ingredient: Enzalutamide) freely available under the following link (last accessed: 28. Februar 2019):

https://www.ema.europa.eu/documents/product-information/xtandi-epar-product-information_en.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 enzalutamide.

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:	
Enzalutamide	€ 45,603.10
GnRH agonist/GnRH antagonist	€ 1,283.50–2,094.00
Total:	€ 46,886.60–47,697.10
Appropriate comparator:	
GnRH agonist/GnRH antagonist	€ 1,283.50–2,094.00

Pharmaceutical retail price (LAUER-TAXE®) as last revised after discounts: 15. April 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 websites of the Federal Joint Committee on 16 May 2019.**
2. **The resolution will expire on 15 May 2020.**

The justification to this resolution is published on the website of the Federal Joint Committee at www.g-ba.de.

Berlin, 16. May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof. Hecken