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

of 5 November 2020

On 5 November 2020, the Federal Joint Committee (G-BA) resolved by written statement 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), 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on enzalutamide in accordance with the resolution of 16 May 2019 (Federal Gazette, BAnz AT 31 May 2019 B2) is hereby repealed.

2. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of enzalutamide in accordance with the resolution of 18 June 2015:

Enzalutamide

Resolution of: 5 November 2020
Entry into force on: 5 November 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

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

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

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

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

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 enzalutamide 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]

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

PROSPER study: Enzalutamide + ADT vs placebo + ADT

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

Data cut-offs: 1st data cut-off of 28 June 2017; 3rd data cut-off of 15 October 2019

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 [95% CI] p value Absolute difference (AD)[a]
Overall survival					
3rd data cut-off	933	67.0 [64.0; n.a.] 288 (30.9)	468	56.3 [54.4; 63.0] 178 (38.0)	0.73 [0.61; 0.88] 0.001 AD = 10.7 months

Morbidity

Endpoint	**Enzalutamide + ADT**		**Placebo + 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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Metastasis-free survival (MFS)[2]					
1st data cut-off	933	36.6 [33,1; n.c.] 219 (23.5)	468	14.7 [14.2; 15.6] 228 (48.7)	0.29 [0.24; 0.35] < 0.001 AD = 21.9 months
Time to start of cytotoxic chemotherapy[3]					
3rd data cut-off	933	58.3 [52.6; 66.0] 372 (39.9)	468	41.6 [37.3; 46.4] 242 (51.7)	0.62 [0.52; 0.72] p < 0.0001 AD = 16.7 months
Worst pain (BPI-SF Item 3)[b]					

[1] Data from the dossier assessment of the IQWiG (A20-46) unless otherwise indicated.
[2] Data from the addendum (A19-34) of the IQWiG on the dossier assessment (A18-80)
[3] Data from the dossier on enzalutamide (Module 4A) dated 14 May 2020

Endpoint	Enzalutamide + ADT		Placebo + 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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
1st data cut-off	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
Health status (EQ-5D VAS)[4]					
MID 7 1st data cut-off	836	11.1 [7.8; 11.2] 515 (55.2)	414	7.5 [7.4; 11.0] 250 (53.4)	0.83 [0.71; 0.97] 0.019 AD = 3.6 months
MID 10 1st data cut-off	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

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Values at the start of study MV (SE) Change at week 97 MV (SE)	N	Values at the start of study MV (SE) Change at week 97 MV (SE)	Mean difference [95% CI] p value
Pain intensity (BPI-SF items 3– 6; presented additionally)					
1st data cut-off	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
Impairment due to pain (BPI-SF item 9a–g)					
1st data cut-off	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
Health status (EQ-5D VAS) (presented additionally)					
1st data cut-off	836	no data available −4.57 (0.91)	414	no data available −5.29 (1.47)	0.72 [−2.30; 3.75] 0.639

[4] Data from the addendum (A19-34) of the IQWiG on the dossier assessment (A18-80)

Health-related quality of life

Endpoint	Enzalutamide + ADT		Placebo + 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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
FACT-P total score[c]					
1st data cut-off	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)					
Physical well-being (PWB)[d] 1st data cut-off	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[5]
Social well-being (SWB)[d] 1st data cut-off	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[5]
Emotional well-being (EWB)[d] 1st data cut-off	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[5]
Functional well-being (FWB)[d] 1st data cut-off	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[5]
Prostate cancer sub-scale (PCS)[d] 1st data cut-off	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[5]

[5] Data from the addendum (A19-34) of the IQWiG on the dossier assessment (A18-80)

Side effects

Endpoint	Enzalutamide + ADT		Placebo + 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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (presented additionally)[e]					
3rd data cut-off	930	1.0 [0.9; 1.3] 873 (93.9)	465	2.8 [1.9; 3.5] 379 (81.5)	-
Serious adverse events (SAE) [e]					
3rd data cut-off	930	53.6 [47.5; n.a.] 345 (37.1)	465	n.a. [n.a.; n.a.] 97 (20.9)	0.94 [0.74; 1.19] 0.610
Severe adverse events (CTCAE grade ≥ 3) [e]					
3rd data cut-off	930	40.8 [37.3; 46.9] 424 (45.6)	465	40.5 [31.9; n.a.] 124 (26.7)	1.05 [0.85; 1.29] 0.637
Therapy discontinuations because of adverse events [e]					
3rd data cut-off	930	n.a. [n.a.; n.a.] 133 (14.3)	465	n.a. [n.a.; n.a.] 37 (8.0)	1.01 [0.69; 1.48] 0.946
Specific adverse events [f]					
Psychiatric disorders (SOC, AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 148 (15.9)	465	n.a. [n.a.; n.a.] 26 (5.6)	2.17 [1.42; 3.31] < 0.001
General disorders and administration site conditions (SOC, severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 75 (8.1)	465	n.a. [n.a.; n.a.] 10 (2.2)	2.21 [1.13; 4.32] 0.018
Nervous system disorders (SOC, severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 61 (6.6)	465	n.a. [n.a.; n.a.] 8 (1.7)	2.16 [1.02; 4.59] 0.04
Renal and urinary disorders (SOC, severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 81 (8.7)	465	n.a. [n.a.; n.a.]; 46 (9.9)	0.43 [0.29; 0.63] < 0.001
Hypertension (SMQ[g], severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 54 (5.8)	465	n.a. [n.a.; n.a.] 11 (2.4)	1.99 [1.03; 3.82] 0.036

Endpoint	Enzalutamide + ADT		Placebo + 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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Time to first deterioration by ≥ 2 points
[c] Time to first deterioration by ≥ 10 points
[d] Time to first deterioration by ≥ 3 points
[e] Without events that are considered to be a progression of the underlying disease
[f] 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.
[g] Based on the information provided in Module 4 A, it is assumed that the SMQ hypertension includes PTs of severity CTCAE ≥ 3

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; DC = data cut-off; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; SMQ = standardised MedDRA query; SOC = system organ class; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↔	No difference relevant for the benefit assessment
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. 1090–3800 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 Xtandi (active ingredient: enzalutamide) at the following publicly accessible link (last access: 23 September 2020):

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

Treatment with enzalutamide 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:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Enzalutamide	€ 43,464.98
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Total:	€ 44,711.76 – 45,561.70
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 October 2020

Costs for additionally required SHI services: not applicable

I. 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 5 November 2020.

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

Berlin, 5 November 2020

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

Prof. Hecken