Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

Enzalutamide (new therapeutic indication: prostate cancer, metastatic, hormone-sensitive, combination with androgen deprivation therapy)

of 19 November 2021

At its session on 19 November 2021, 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 by the publication of the resolution of D. month YYYY (BAnz AT TT.MM.JJJJ BX), as follows:

I. 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 5 November 2020:

Enzalutamide

Resolution of: 19 November 2021
Entry into force on: 19 November 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 30 April 2021):

Xtandi is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.

Therapeutic indication of the resolution (resolution from 19 November 2021):

See new therapeutic indication according to marketing authorisation

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

Adult men with metastatic hormone-sensitive prostate cancer

Appropriate comparator therapy:

- conventional androgen deprivation in combination with docetaxel with or without prednisone or prednisolone (only for patients with remote metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70 % according to Karnofsky index))

or

- conventional androgen deprivation in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed, high-risk, metastatic, hormone-sensitive prostate cancer)

or

- conventional androgen deprivation in combination with apalutamide (only for patients with good general condition (0 to 1 according to ECOG / WHO))

Extent and probability of the additional benefit of enzalutamide in combination with androgen deprivation therapy (ADT) versus docetaxel in combination with prednisolone and ADT (for patients with remote metastases (M1 stage) and good general condition (0 to 1 according to ECOG / WHO or ≥ 70 % according to Karnofsky index)):

An additional benefit is not proven.

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	Advantage in the serious AE endpoint.
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		

Indirect comparison: Enzalutamide in combination with ADT (ARCHES study) versus docetaxel in combination with prednisolone and ADT (STAMPEDE study) via the bridge comparator ADT (+ placebo)

ARCHES study:

- multi-national, double-blind RCT in phase III
- Enzalutamide + ADT *versus* placebo + ADT

STAMPEDE study:

- randomised, open-label, multi-arm, multi-stage platform study with a total of 12 arms for comparing different active ingredients in advanced or metastatic prostate cancer
- Docetaxel + prednisolone + ADT *versus* ADT

[1] Data from the dossier assessment of the IQWiG (A21-77) and from the addendum (A21-132), unless otherwise indicated.

Mortality

Endpoint	**Enzalutamide + ADT or docetaxel + prednisolone + ADT**		**(Placebo +) ADT**		Group difference
	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
Overall survival					
Enzalutamide + ADT versus placebo + ADT (ARCHES)	536	n.a. *148 (27.6)*	531	n.a. [47.7; n.a.] *199 (37.5)*	0.62 [0.50; 0.77]; < 0.001
Docetaxel + prednisolone + ADT vs ADT	362	59.1 [51.1; 69.8] *225 (62.2)*	724	43.1 [41.0; 47.4] *494 (68.2)*	0.81 [0.69; 0.95]; 0.008
Indirect comparison via bridge comparators[a]: Enzalutamide + ADT vs docetaxel + prednisolone + ADT					-[e]

Morbidity

Symptomatic skeletal events	no indirect comparison because of insufficient similarity
Symptomatology	no (usable) data for indirect comparison[c]
Health status (EQ-5D VAS)	no (usable) data for indirect comparison[d]

Health-related quality of life

	no (usable) data for indirect comparison[c]

Side effects

Endpoint	Enzalutamide + ADT or docetaxel + prednisolone + ADT		(Placebo +) ADT		Group difference
	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
AE (presented additionally)					
Enzalutamide + ADT versus placebo + ADT (ARCHES)	534	1.0 [1.0; 1.4] *457 (85.6)*	530	1.6 [1.1; 2.1] *457 (86.2)*	-
Docetaxel + prednisolone + ADT vs ADT (STAMPEDE)	335	0.8 [0.7; 1.1] *327 (97.6)*	724	1.5 [1.5; 1.5] *693 (95.7)*	-
SAE					
Enzalutamide + ADT versus placebo + ADT (ARCHES)	534	33.7 [29.9; 36.4] *189 (35.4)*	530	29.5 [25.6; 34.2] *143 (27.0)*	0.81 [0.64; 1.01]; 0.062
Docetaxel + prednisolone + ADT vs ADT (STAMPEDE)	335	n.a. *96 (28.7)*	724	n.a. [109.1; n.a.] *80 (11.0)*	9.04 [5.92; 13.79]; < 0.001
Indirect comparison via bridge comparators[a]: Enzalutamide + ADT vs docetaxel + prednisolone + ADT					0.09 [0.06; 0.14]; < 0.001
Severe AE					
Enzalutamide + ADT versus placebo + ADT (ARCHES)	534	29.2 [26.2; 33.7] *221 (41.4)*	530	25.6 [24.4; 28.6] *184 (34.7)*	0.84 [0.69; 1.03]; 0.093
Docetaxel + prednisolone + ADT vs ADT (STAMPEDE)	335	n.a. *108 (32.2)*	724	n.a. [102.8; n.c.] *219 (30.2)*	2.39 [1.84; 3.11]; < 0.001
Indirect comparison via bridge comparators[a]: Enzalutamide + ADT vs docetaxel + prednisolone + ADT					-[e]
Discontinuation due to AE	no (usable) data for indirect comparison[d]				

a. Indirect comparison according to Bucher[2]
b. IQWiG calculations
c. Indirect comparison is not possible since usable data are available from a maximum of 1 study for all instruments used in this category to assess the endpoints.
d. The endpoint was only collected in the ARCHES study, but the company does not provide data on the endpoint in module 4.

[2]Bucher HC, Guyatt GH, Griffith LE et al. The results of direct and indirect treatment comparisons in meta-analysis of randomised controlled trials. J Clin Epidemiol 1997; 50(6): 683-691. https://dx.doi.org/10.1016/S0895-4356(97)00049-8.

e. No indirect comparison is calculated as the requirement for the certainty of results to perform an adjusted indirect comparison is not met.

Abbreviations used:
ADT: Androgen Deprivation Therapy; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: EuroQoL 5 Dimensions; HR: Hazard Ratio; CI: Confidence Interval; N: Number of patients evaluated; n: Number of patients with (at least 1) event; n.c.: not calculable; n.a.: not achieved; RCT: Randomised Controlled Trial; SAE: Serious Adverse Event; AE: Adverse Event; VAS: Visual Analogue Scale

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

approx. 2,590 to 3,640 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: 19 August 2021):

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

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

Medicinal castration with a GnRH agonist or antagonist 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:	
Enzalutamide	€ 45,028.23
GnRH agonist/ GnRH antagonist orchiectomy	€ 1,283.62 - € 2,164.84 € 3,852.53
Total	€ 46,311.85 - € 48,880.76

Appropriate comparator therapy:	
Androgen deprivation therapy in combination with apalutamide	
Apalutamide	€ 36,882.99
GnRH agonist/ GnRH antagonist orchiectomy	€ 1,283.62 - € 2,164.84 € 3,852.53
Total	€ 38,166.61 - € 40,735.52
Androgen deprivation therapy in combination with docetaxel and, if applicable, prednis(ol)one	
Docetaxel	€ 7,320.90
GnRH agonist/ GnRH antagonist orchiectomy	€ 1,283.62 - € 2,164.84 € 3,852.53
prednis(ol)one, if applicable	€ 39.18 - € 42.81
Total	€ 8,604.52 - € 11,216.24
Androgen deprivation therapy in combination with abiraterone acetate and prednis(ol)one	
Abiraterone acetate	€ 45,842.70
Prednis(ol)one	€ 47.67- € 52.09
GnRH agonist/ GnRH antagonist orchiectomy	€ 1,283.62 - € 2,164.84 € 3,852.53
Total	€ 47,173.99 - € 49,747.32

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 November 2021)

Costs for additionally required SHI services:

not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	6	€ 486

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 November 2021.

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

Berlin, 19 November 2021

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

Prof. Hecken