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 (New Therapeutic Indication: Metastatic Hormone-sensitive Prostate Cancer (mHSPC))

of 20 August 2020

At its session on 20 August 2020, 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), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. 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 1 August 2019, last amended on 20 February 2020:

Apalutamide

Resolution of: 20 August 2020
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 29 January 2020):

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

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

Adult men with metastatic hormone-sensitive prostate cancer (mHSPC)

Appropriate comparator therapy:

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

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)

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

An additional benefit is not proven.

Study results according to endpoints:[1]

Adult men with metastatic hormone-sensitive prostate cancer (mHSPC)

Adjusted indirect comparison of apalutamide + ADT vs docetaxel + ADT + prednisolone via the bridge comparator ADT (+ placebo)

TITAN study: Apalutamide + ADT **vs** placebo + ADT
STAMPEDE study: Docetaxel + prednisolone + ADT **vs** ADT
Relevant sub-population of the STAMPEDE study: Patients with distant metastases

Mortality

Endpoint	**Apalutamide + ADT or docetaxel + ADT + prednisolone**		**ADT (+ placebo) (bridge comparator)**		**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 (%)*	Hazard Ratio [95% CI] p value
Overall survival					
Apalutamide + ADT vs placebo + ADT					
	525	n.a. 83 (15.8)	527	n.a. 117 (22.2)	0.67 [0.51; 0.89] 0.005
Docetaxel + prednisolone + ADT vs ADT					
	362	59.1 [no data available] 225 (62.2)	724	43.1 [no data available] 494 (68.2)	0.81 [0.69; 0.95] 0.003
Adjusted, indirect comparison[a]: Apalutamide + ADT vs docetaxel + ADT + prednisolone					0.83 [0.60; 1.14] 0.247

[1] Data from the dossier assessment of the IQWiG (A20-20) unless otherwise indicated.

Morbidity

Endpoint	Apalutamide + ADT or docetaxel + ADT + prednisolone		ADT (+ placebo) (bridge comparator)		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 (%)*	Hazard Ratio [95% CI] p value
Time until the 1st skeletal event					
Apalutamide + ADT vs placebo + ADT[b]					
	525	n.a. 53 (10.1)	527	n.a. 64 (12.1)	0.80 [0.56; 1.15] 0.225
Docetaxel + prednisolone + ADT vs ADT[c]					
	362	95.80 [no data available] 132 (36.5)	724	49.68 [no data available] 357 (49.3)	0.63 [0.51; 0.76] no data available
Adjusted, indirect comparison: Apalutamide + ADT vs docetaxel + ADT + prednisolone					-[d]

Health-related quality of life

Endpoint	Apalutamide + ADT or docetaxel + ADT + prednisolone		ADT (+ placebo) (bridge comparator)		Group difference
	N	Values at start of study MV (SD) Change after 12 months MV (SE)	N	Values at start of study MV (SD) Change after 12 months MV (SE)	Mean difference [95% CI] p value Hedges' g [95% CI]
FACT-P total score					
Apalutamide + ADT vs placebo + ADT					
	no data available	112.8 (20.2) no data available	no data available	111.5 (19.4) no data available	0.90 [−1.43; 3.23] 0.449 −0.05 [−0.21; 0.12]
Docetaxel + prednisolone + ADT vs ADT					
no data suitable for indirect comparison available					
Adjusted, indirect comparison: Apalutamide + ADT vs docetaxel + ADT + prednisolone					-[e]

Side effects[f]

Endpoint	Apalutamide + ADT or docetaxel + ADT + prednisolone		ADT (+ placebo) (bridge comparator)		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 (%)*	Hazard Ratio [95% CI] p value
Adverse events in total (presented additionally)					
Apalutamide + ADT vs placebo + ADT					
	524	0.95 [0.95; 1.25] 507 (96.8)	527	1.71 [1.38; 1.87] 509 (96.6)	-
Docetaxel + prednisolone + ADT vs ADT					
	335	0.82 [no data available] 327 (97.6)	724	1.48 [no data available] 693 (95.7)	-
Serious adverse events (SAE)					
Apalutamide + ADT vs placebo + ADT					
	524	n.a. 104 (19.8)	527	n.a. 107 (20.3)	0.91 [0.70; 1.20] 0.516
Docetaxel + prednisolone + ADT vs ADT					
	335	n.a. 96 (28.7)	724	n.a. 80 (11.0)	9.04 [5,92; 13,79] no data available
Adjusted, indirect comparison[a]: Apalutamide + ADT vs docetaxel + ADT + prednisolone					0.10 [0.06; 0.17] < 0.001
Severe adverse events (CTCAE grade ≥ 3)					
Apalutamide + ADT vs placebo + ADT					
	524	n.a. [23.5; n.a.] 223 (42.6)	527	n.a. [20.3; n.a.] 222 (42.1)	0.99 [0.83; 1.20] 0.961
Docetaxel + prednisolone + ADT vs ADT					
	335	n.a. 108 (32.2)	724	n.a. 219 (30.2)	2.39 [1,84; 3,11] no data available
Adjusted, indirect comparison: Apalutamide + ADT vs docetaxel + ADT + prednisolone					-[g]
Therapy discontinuation because of adverse events					

Endpoint	Apalutamide + ADT or docetaxel + ADT + prednisolone		ADT (+ placebo) (bridge comparator)		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 (%)*	Hazard Ratio [95% CI] p value
Apalutamide + ADT vs placebo + ADT					
	524	n.a. 42 (8.0)	527	n.a. 28 (5.3)	1.41 [0.87; 2.27] 0.162
Docetaxel + prednisolone + ADT vs ADT					
	no data available				
Adjusted, indirect comparison: Apalutamide + ADT vs docetaxel + ADT + prednisolone					-

[a] Adjusted indirect comparison according to Bucher.
[b] Defined as the occurrence of a symptomatic pathological fracture, spinal cord compression, bone irradiation, or bone surgery
[c] Defined as the occurrence of pathological fractures, spinal cord compression, the need for palliative bone irradiation (for pain or fracture prevention), or bone surgery (preventive or for treatment of a fracture)
[d] Because of insufficient similarity, the IQWiG did not perform an indirect comparison for the endpoint in the present assessment
[e] In the STAMPEDE study, the health-related quality of life was assessed using EORTC QLQ-C30. In accordance with the IQWiG, an indirect comparison is not possible.
[f] For both studies, the information on AE includes events that can also be attributed to symptomatology. These are, for example, spinal cord compression or urinary retention. However, these occur in only a few patients and therefore have no relevant effect on the overall rates of the side effects endpoints
[g] Because the requirement for certainty of results for carrying out an adjusted indirect comparison is not fulfilled, the IQWiG did not calculate an indirect comparison

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; 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; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment.
Morbidity	n.a.	No data suitable for the benefit assessment.
Health-related quality of life	n.a.	No data suitable for the benefit assessment.
Side effects	↔	Advantage in the endpoint serious 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. 2,590–3,640 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 Erleada® (active ingredient: apalutamide) at the following publicly accessible link (last access: 23 June 2020):

https://www.ema.europa.eu/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	€ 49,591.12
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Orchiectomy	€ 3,293.26
Total:	€ 50,837.90 – 52,884.38
Appropriate comparator therapy:	
ADT in combination with docetaxel and prednis(ol)one	
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Orchiectomy	€ 3,293.26
Docetaxel	€ 7,109.52
Possibly prednis(ol)one	€ 38.04 – 41.55
Total	€ 8,356.30 – 10,444.33
ADT in combination with abiraterone acetate and prednis(ol)one	
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Orchiectomy	€ 3,293.26
Abiraterone acetate	€ 44,686.43
Prednis(ol)one	€ 46.28 – 50.55
Total	€ 45,979.49 – 48,030.24

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2020

Other services covered by SHI funds:

Designation of the 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	€ 486.00

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 20 August 2020.

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

Berlin, 20 August 2020

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

Prof. Hecken