Justification

Gemeinsamer Bundesausschuss

to the Resolution 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 Radium-223 dichloride (reassessment due to new scientific knowledge: prostate carcinoma)

of 17 October 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

Radium-233 dichloride as an active ingredient of the medicinal product Xofigo® was first placed on the market on 1 January 2014. The G-BA prompted a new benefit assessment in accordance with Section 35a, paragraph 1 SGB V in conjunction with Section 3, paragraph 1 no. 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and Chapter 5, Section 13 Rules of Procedure (VerfO) of the G-BA for the active ingredient radium-223 dichloride at the request of its members in the resolution of 1 November 2018. The new benefit assessment was initiated based on new scientific findings from the current ERA-223 study and a related change in the approved therapeutic indication of radium-223 dichloride by resolution of the EU Commission dated 28 September 2018.

The relevant date for the first placing on the market of the active ingredient radium-223 dichloride in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is 2 April 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, No. 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, No. 6 VerfO on 1 April 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 July 2019, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of radium-223 dichloride compared with the appropriate comparator therapy could be determined because of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of radium-223 dichloride.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of radium-223 dichloride (Xofigo®) in accordance with the product information

Xofigo monotherapy or in combination with an LHRH luteinising hormone-releasing hormone) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues) or ineligible for any available systemic mCRPC treatment (see Section 4.4).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are in progression after at least two prior lines of systemic therapy for the treatment of mCRPC (other than LHRH analogues)

   Patient-individual therapy taking into account previous therapies and selecting abiraterone, enzalutamide, cabazitaxel, and docetaxel

b) Adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are ineligible for any available systemic mCRPC treatment

   Best supportive care (especially adequate pain therapy, treatment with bisphosphonates, denosumab, and/or radionuclides)

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

- Radiotherapeutics: Strontium-89, samarium-153
- Active ingredients that influence bone structure and mineralisation: zoledronic acid, ibandronic acid, clodronic acid, denosumab
- Endocrine active ingredients: enzalutamide, abiraterone acetate

Other endocrine active ingredients, the marketing authorisation of which does not explicitly cover the castration-resistant or hormone-refractory situation are not considered.

- Cytostatic agents: docetaxel, cabazitaxel, mitoxantrone, estramustine
- Glucocorticoids: prednisone, prednisolone, methylprednisolone, dexamethasone

On 2. Radiotherapy can be considered as a non-medicinal treatment.

On 3. Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V on the treatment of prostate carcinoma:

– Abiraterone acetate – Resolution of 29 March 2012

– Abiraterone acetate – Resolution of 4 July 2013

− Radium-223 dichloride – Resolution of 19 June 2014

− Enzalutamide – Resolution of 20 February 2014

− Enzalutamide – Resolution of 18 June 2015

− Cabazitaxel – Resolution of 29 March 2012

Resolutions on an amendment to the directive Methods of hospital treatment in Annex II (methods for which the evaluation procedures are suspended):

- Proton therapy for prostate carcinoma

On 4. Overall, the evidence for patients who have already received two prior systemic therapies for the treatment of mCRPC is very limited. In the current guidelines, only one guideline[2] refers to a possible further line of therapy following the second one. The selection of the therapy option is determined on the basis of the previously used medicinal products. Within the framework of the written comments procedure, medical

[2] Alberta Provincial Genitourinary Tumour Team. Prostate cancer; Version 6 [online]. 03.2015. Edmonton (CAN): Alberta Health Services; 2015

societies and experts clearly emphasised the clinical significance of an active systemic therapy within the 3rd line of therapy. This is also made possible by the marketing authorisation of new targeted therapy options within the last few years. The selection of the therapy option used is based on the success and tolerability of the respective previous therapies. Thus, for patients with mCRPC and symptomatic bone metastases without known visceral metastases in which the disease progresses after receiving at least two preceding systemic lines of therapy for the treatment of mCRPC (excluding LHRH analogues), a patient-individual therapy taking into account previous therapies and selecting abiraterone, enzalutamide, cabazitaxel, and docetaxel is specified as an appropriate comparator therapy.

For patients for whom no other available systemic therapy is suitable according to the therapeutic indication, by definition only best supportive care (BSC) can be considered as appropriate comparator therapy. Best supportive care is the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve the quality of life. The guidelines provide a strong recommendation for adequate symptomatic treatment (e.g. of bone metastases). Thus BSC (in particular, adequate pain therapy, treatment with bisphosphonates, denosumab, and/or radionuclides) is specified as an appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

Change of the appropriate comparator therapy:

The appropriate comparator therapy was originally determined as follows:

The appropriate comparator therapy for radium-223-dichloride as monotherapy or in combination with an LHRH (luteinising hormone-releasing hormone) analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues) or ineligible for any available systemic mCRPC therapy is suitable is

– Best supportive care (especially adequate pain therapy, treatment with bisphosphonates, denosumab, and/or radionuclides)

The change is made taking into account the importance of a further active, systemic therapy following two previous lines of therapy as stated in the written statements of medical societies and experts in the present procedure.

This change in the appropriate comparator therapy does not make it necessary to repeat the benefit assessment because the pharmaceutical company also included the appropriate comparator therapy established by this resolution in the dossier for the present benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of radium-223 dichloride is assessed as follows:

a) Adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are in progression after at least two prior lines of systemic therapy for the treatment of mCRPC (other than LHRH analogues)

For adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), an additional benefit is not proven.

Justification:

To derive the additional benefit, the pharmaceutical company presented a retrospective comparative data analysis of the Flatiron Health database. Data on overall survival under radium-223 dichloride therapy were considered in comparison to abiraterone, cabazitaxel, docetaxel, and enzalutamide. Furthermore, the pharmaceutical company presented data on further endpoints of the 1-arm PARABO and REASSURE studies as well as the ALSYMPCA registration study.

The ALSYMPCA directly comparative pivotal study compares radium-223 dichloride therapy with best supportive care. The appropriate comparator therapy is thus not implemented. Furthermore, the patient population included in the study does not correspond to the patient population covered by the therapeutic indication, which has received at least two prior therapies. The data of the 1-arm PARABO and REASSURE studies as well as the retrospective data analysis of the Flatiron Health database are also not suitable for deriving an additional benefit.

In the dossier, the pharmaceutical company shall therefore not present any results from directly comparative studies compared with the appropriate comparator therapy or studies suitable for an adjusted indirect comparison. It is not possible to assess the additional benefit on the basis of the data provided.

The additional benefit for radium-223-dichloride as monotherapy or in combination with an LHRH (luteinising hormone-releasing hormone) analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues) is thus not proven.

b) Adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are ineligible for any available systemic mCRPC treatment

   For adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are ineligible for any available systemic mCRPC treatment, an additional benefit is not proven.

Justification:

To derive the additional benefit, the pharmaceutical company presented the results of the ALSYMPCA study, which already formed the basis of the resolution of the first benefit assessment procedure for radium-223 dichloride (resolution of 19 June 2014). The ALSYMPCA study is a double-blind, randomised, controlled Phase III study in which radium-223 dichloride + BSC is compared with placebo + BSC. Patients who had already been treated with docetaxel or for whom therapy with docetaxel was not indicated or refused were included. The marketing authorisation of new active ingredients (abiraterone, cabazitaxel, enzalutamide) has fundamentally changed the therapy situation. Thus, patients in the ALSYMPCA study would now have additional therapy options available in the previous therapy. The results of the ALSYMPCA study cannot be applied to the current therapy situation. Thus, the pharmaceutical company does not present any data in the dossier that would allow an assessment of the additional benefit.

The pharmaceutical company was commissioned by the EMA to conduct a randomised, double-blind, multi-centre Phase IV study in the authorised indication. According to information provided by the pharmaceutical company, this study is currently being planned or coordinated with the EMA.

The additional benefit for radium-223-dichloride as monotherapy or in combination with an LHRH (luteinising hormone-releasing hormone) analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are ineligible for any available systemic mCRPC treatment is thus not proven.

2.1.4 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient radium-223 dichloride on the basis of an application based on new scientific findings according to Section 13 (Chapter 5, Section 13, paragraph 1, sentence 1 VerfO) after restriction of the marketing authorisation.

The new therapeutic indication following the restriction on authorisation of 28 September 2018 is as follows:

Xofigo monotherapy or in combination with an LHRH analogue (LHRH: luteinising hormone-releasing hormone) is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues) or or ineligible for any available systemic mCRPC treatment.

In the benefit assessment, two patient groups were distinguished:

a) Adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are in progression after at least two prior lines of systemic therapy for the treatment of mCRPC (other than LHRH analogues)

b) Adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases who are ineligible for any available systemic mCRPC treatment

About patient group a)

The appropriate comparator therapy was determined by the G-BA as follows:

– Patient-individual therapy taking into account previous therapies and selecting abiraterone, enzalutamide, cabazitaxel, and docetaxel

The pharmaceutical company presented a retrospective comparative data analysis of the Flatiron Health database as well as data from the 1-arm PARABO and REASSURE studies as well as the ALSYMPCA registration study. There are no results from directly comparative studies compared with the appropriate comparator therapy or studies suitable for an adjusted indirect comparison.

The additional benefit cannot be assessed based on the evidence provided. Thus, an additional benefit is not proven.

About patient group b)

The appropriate comparator therapy was determined by the G-BA as follows:

– Best supportive care (especially adequate pain therapy, treatment with bisphosphonates, denosumab, and/or radionuclides)

The pharmaceutical company presented the results of the ALSYMPCA randomised controlled study in which radium-223 dichloride + BSC was compared with placebo + BSC. This was already the basis for the first benefit assessment.

The availability of new medicinal products for the treatment of castration-resistant prostate carcinoma has fundamentally changed the therapy situation. As a result, patients enrolled in the ALSYMPCA study now have additional treatment options in the previous therapy. Thus, the results of the ALSYMPCA study are not transferable to the current therapy situation.

The additional benefit cannot be assessed based on the evidence provided. Thus, an additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution will be based on the information from the dossier of the pharmaceutical company. However, the calculation is subject to significant uncertainties. On one hand, only patients from the 3rd line of therapy onwards were considered. Thus, patients in the therapeutic indication of radium-223-dichloride for whom no other available systemic therapy is suitable are not considered. Further uncertainties exist with regard to the underlying base population as well as the evaluations of the commercial database. Similarly, no restriction was performed on patients with visceral metastases.

2.3 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 Xofigo® (active ingredient: radium-223 dichloride) at the following publicly accessible link (last access: 26 August 2019):

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

Treatment with radium-223 dichloride should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in urology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with prostate carcinoma.

The medicinal product may only be used by persons authorised to handle radioactive medicinal products in a designated clinical area.

The regulations of the Radiation Protection Ordinance must be observed.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2019).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Radium-223 dichloride	1 × every 4 weeks	6 cycles	1	6
LHRH analogue				
Buserelin	continuous,	4	1	4

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/ patient/ year
	every 3 months			
Goserelin	continuous, every 3 months	4	1	4
Leuprorelin	continuous, every 3 months	4	1	4
Triptorelin	continuous, every 6 months	2	1	2
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Patient population a)				
Abiraterone acetate + prednisone or prednisolone + LHRH analogue				
Abiraterone acetate	continuous, 1 × daily	365	1	365
Prednisolone or prednisone	continuous, 1 × daily	365	1	365
LHRH analogue				
Buserelin	continuous, every 3 months	4	1	4
Goserelin	continuous, every 3 months	4	1	4
Leuprorelin	continuous, every 3 months	4	1	4
Triptorelin	continuous, every 6 months	2	1	2
Enzalutamide + LHRH analogue				
Enzalutamide	continuous, 1 × daily	365	1	365
LHRH analogue				
Buserelin	continuous, every 3 months	4	1	4
Goserelin	continuous, every 3 months	4	1	4
Leuprorelin	continuous, every 3 months	4	1	4
Triptorelin	continuous, every 6 months	2	1	2
Cabazitaxel + prednisone or prednisolone				
Cabazitaxel	1 × every 3	17	1	17

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/ patient/ year
	weeks			
Prednisolone or prednisone	continuous, 1 × daily	365	1	365
Docetaxel + prednisone or prednisolone				
Docetaxel	1 × every 3 weeks	17	1	17
Prednisolone or prednisone	continuous, 2 × daily	365	1	365
Patient population b)				
Best supportive care	different for each individual patient			

Usage and consumption:

For dosages depending on body weight (BW) or body surface, the average body measurements of an adult male were used as a basis (average body size: 1.79 m, average body weight: 85 kg). From this, a body surface area of 2.04 m² is calculated (calculation according to Du Bois 1916)[3].

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Radium-223 dichloride	55 kBq/kg BW	4.675 kBq	1 ILO with 6.600 kBq	6	6 ILO with 6.600 kBq
LHRH analogue					
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 × 10.8 mg	4	4 × 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 × 22.5 mg	2	2 × 22.5 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					

[3] Statistisches Bundesamt [German Federal Office for Statistics]: Mikrozensus – Fragen zur Gesundheit; Körpermaße der Bevölkerung [Microcensus – Questions about health; body measurements of the population], Wiesbaden 2018. https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/koerpermasse-5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Patient population a)					
Abiraterone acetate + prednisone or prednisolone + LHRH analogue					
Abiraterone acetate	1,000 mg	1,000 mg	2 × 500 mg	365	730 × 500 mg
Prednisolone or prednisone	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
LHRH analogue					
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 × 10.8 mg	4	4 × 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 × 22.5 mg	2	2 × 22.5 mg
Enzalutamide + LHRH analogue					
Enzalutamide	160 mg	160 mg	4 × 40 mg	365	1,460 × 40 mg
LHRH analogue					
Buserelin	9.45 mg	9.45 mg	1 × 9.45 mg	4	4 × 9.45 mg
Goserelin	10.8 mg	10.8 mg	1 × 10.8 mg	4	4 × 10.8 mg
Leuprorelin	11.25 mg	11.25 mg	1 × 11.25 mg	4	4 × 11.25 mg
Triptorelin	22.5 mg	22.5 mg	1 × 22.5 mg	2	2 × 22.5 mg
Cabazitaxel + prednisone or prednisolone					
Cabazitaxel	51 mg	25 mg/m² BW = 51 mg	1 × 60 mg	17	17 × 60 mg
Prednisolone or prednisone	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
Docetaxel + prednisone or prednisolone					
Docetaxel	153 mg	75 mg/m² BW = 153 mg	1 × 160 mg	17	17 × 160 mg
Prednisolone or prednisone	5 mg	5 mg	2 × 5 mg	365	730 × 5 mg
Patient population b)					
Best supportive care	different for each individual patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Radium-223 dichloride is listed in the LAUER-TAXE® but is only sold as a hospital pack. The active ingredient is therefore currently not subject to the Pharmaceutical Price Ordinance, and there are no rebates according to Section 130 or Section 130a SGB V. The calculation is based on the reimbursement amount plus 19% value-added tax. This differs from the information usually taken into account in LAUER-TAXE®.

Costs of the medicinal product:

Designation of the therapy	Package size	Cost	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs to be borne by the SHI
Medicinal product to be assessed					
Radium-223 dichloride	1 SFI	€ 4,685.00	-	-	€ 5,575.15
Buserelin	2 PS	€ 1,027.81	€ 1.77	€ 56.30	€ 969.74
Goserelin	2 IMP	€ 1,013.23	€ 1.77	€ 55.49	€ 955.97
Leuprorelin	2 IMP	€ 730.45	€ 1.77	€ 86.93	€ 641.75
Triptorelin	1 DSS	€ 944.11	€ 1.77	€ 51.66	€ 890.68
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Patient population a)					
Abiraterone acetate	56 FCT	€ 3,518.41	€ 1.77	€ 0.00	€ 3,516.64
Prednisolone 10 mg[4]	100 TAB	€ 17.48	€ 1.77	€ 0.51	€ 15.20
Prednisone 10 mg[4]	100 TAB	€ 20.90	€ 1.77	€ 0.00	€ 19.13
Buserelin	2 PS	€ 1,027.81	€ 1.77	€ 56.30	€ 969.74
Goserelin	2 IMP	€ 1,013.23	€ 1.77	€ 55.49	€ 955.97
Leuprorelin	2 IMP	€ 730.45	€ 1.77	€ 86.93	€ 641.75

[4] Fixed amount

Triptorelin	1 DSS	€ 944.11	€ 1.77	€ 51.66	€ 890.68
Enzalutamide	112 FCT	€ 3,500.09	€ 1.77	€ 0.00	€ 3,498.32
Cabazitaxel	1 IFK	€ 3,964.24	€ 1.77	€ 223.13	€ 3,739.34
Docetaxel	1 IFK	€ 1,397.30	€ 1.77	€ 175.44	€ 1,220.09
Prednisolone 5 mg[4]	100 TAB	€ 15.10	€ 1.77	€ 0.32	€ 13.01
Prednisone 5 mg[4]	100 TAB	€ 16.41	€ 1.77	€ 0.43	€ 14.21
Patient population b)					
Best supportive care	different for each individual patient				
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; IFC = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder and solvent for solution for injection; IMP = implant; TAB = tablets; DSS = dry substance with solvent					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2019

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown. Additionally required SHI services for the use of the medicinal product to be evaluated in accordance with the technical and instructions for use entail the use of a radionuclide.

A GOP of the EBM is available for radionuclide therapy (GOP 17372). In addition, there is a GOP of the EBM (GOP 40582) for material costs arising from the use of radium-223 dichloride in accordance with the Radiation Protection Ordinance (StrlSchV) and the Medicinal Products Act (AMG). The flat rate 40582 does not include the cost of radium-223 dichloride.

Designation of the therapy	Description of the service	Cost/unit	Number/patient/year	Costs/patient/year
Radium-223 dichloride	Additional flat rate for radionuclide therapy (GOP 17372)	€ 35.39	6	€ 212.34
	Flat rate for radium-223 dichloride (GOP 40582)	€ 65.00	6	€ 390.00

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

Because of new scientific findings, the appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 10 January 2019.

On 1 April 2019, the pharmaceutical company submitted a dossier for the benefit assessment of radium-223 dichloride to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, No. 6 VerfO.

By letter dated 2 April 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient radium-223 dichloride.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 July 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 July 2019. The deadline for submitting written statements was 5 August 2019.

The oral hearing was held on 26 August 2019.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 24 September 2019, and the proposed resolution was approved.

At its session on 17 October 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	8 January 2019	Determination of the appropriate comparator therapy
Working group Section 35a	20 August 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	26 August 2019	Conduct of the oral hearing
Working group Section 35a	4 September 2019 18 September 2019	Consultation on the dossier evaluation of the IQWiG and evaluation of the written statement procedure

Subcommittee Medicinal product	24 September 2019	Concluding discussion of the proposed resolution
Plenum	17 October 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 October 2019

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

Prof Hecken