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
Selinexor (multiple myeloma (at least 1 prior therapy, combination with bortezomib and dexamethasone))

of 16 March 2023

At its session on 16 March 2023, 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 (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 Selinexor in accordance with the resolution of 16 March 2023 for the therapeutic indication "in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies":

Selinexor

Resolution of: 16 March 2023
Entry into force on: 16 March 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 18 July 2022):

Nexpovio is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Therapeutic indication of the resolution (resolution of 16 March 2023):

See therapeutic indication according to marketing authorisation.

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

<u>Adults with multiple myeloma who have received at least one prior therapy</u>

Appropriate comparator therapy:

- Bortezomib in combination with pegylated liposomal doxorubicin

  or
- Bortezomib in combination with dexamethasone

  or
- Lenalidomide in combination with dexamethasone

  or
- Elotuzumab in combination with lenalidomide and dexamethasone

  or
- Carfilzomib in combination with lenalidomide and dexamethasone

  or
- Carfilzomib in combination with dexamethasone

  or
- Daratumumab in combination with lenalidomide and dexamethasone

  or
- Daratumumab in combination with bortezomib and dexamethasone

Extent and probability of the additional benefit of selinexor in combination with bortezomib and dexamethasone compared with bortezomib in combination with dexamethasone:

An additional benefit is not proven.

Study results according to endpoints:[1]

<u>Adults with multiple myeloma who have received at least one prior therapy</u>

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	↓	Disadvantages in the endpoints of severe AEs and SAEs. In detail, disadvantages in specific AEs.
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		

<u>*BOSTON study*</u>

Study design: open-label, randomised, controlled, phase 3

Comparison: Selinexor in combination with bortezomib and dexamethasone **vs** Bortezomib in combination with dexamethasone

Data cut-off: Data cut-off of 15 February 2021, data cut-off of 22 March 2022 and data cut-off of 5 June 2022

[1] Data from the dossier assessment of the IQWiG (A22-100) and from the addendum (A23-09), unless otherwise indicated.

Mortality

Endpoint	**Selinexor + bortezomib + dexamethasone**		**Bortezomib + dexamethasone**		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
Overall survival (data cut-off of 22 March 2022)					
	195	36.7 [31.7; n.c.] 74 (38.0)	207	n.r. [26.9; n.c.] 83 (40.1)	0.93 [0.67; 1.27] 0.633

Morbidity

Endpoint	**Selinexor + bortezomib + dexamethasone**		**Bortezomib + dexamethasone**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS) (data cut-off of 15 February 2021)[b]					
	195	13.24 [11.73; 23.43] 92 (47.2)	207	9.46 [8.11; 10.78] 137 (66.2)	0.71 [0.54; 0.93] 0.0124 AD: + 3.78 months
Symptomatology					
EORTC QLQ-C30 (symptom scales)	No suitable data				
EORTC QLQ-CIPN20	No suitable data				
Health status					
EQ-5D VAS	No suitable data				

Health-related quality of life

EORTC QLQ-C30 (functional scales)	No suitable data

Side effects

(Data cut-off of 5 June 2022)

Endpoint	Selinexor + bortezomib + dexamethasone		Bortezomib + dexamethasone		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Relative risk [95% CI] p value[c] Absolute difference (AD)[a]
Adverse events (AEs) in total					
	195	– 194 (99.5)	204	– 198 (97.1)	
Serious adverse events (SAEs)					
	195	– 109 (55.9)	204	– 79 (38.7)	1.44 [1.17; 1.79] < 0.001
Severe adverse events (CTCAE grade ≥ 3)					
	195	– 169 (86.7)	204	– 128 (62.7)	1.38 [1.23; 1.56] < 0.001
Therapy discontinuation due to adverse events					
	195	– 42 (21.5)	204	– 35 (17.2)	1.26 [0.84; 1.88] 0.275
Specific adverse events					
Gastrointestinal disorders (SOC, severe AEs (CTCAE grade ≥ 3))	195	– 35 (17.9)	204	– 7 (3.4)	5.23 [2.38; 11.50] < 0.001
Peripheral neuropathy (PTs, severe AEs (CTCAE grade ≥ 3))	No suitable data				
Cataract (PTs, severe AEs (CTCAE grade ≥ 3))	195	– 22 (11.3)	204	– 4 (2.0)	5.75 [2.02; 16.40] < 0.001
Cardiac disorders (SOC, AEs)	195	– 35 (17.9)	204	– 16 (7.8)	2.29 [1.31; 4.00] 0.003
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	195	– 14 (7.2)	204	– 5 (2.5)	2.93 [1.08; 7.98] 0.027

Endpoint	**Selinexor + bortezomib + dexamethasone**		**Bortezomib + dexamethasone**		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Relative risk [95% CI] p value[c] Absolute difference (AD)[a]
Blood and lymphatic system disorders (SOC, severe AEs (CTCAE grade ≥ 3))	195	– 96 (49.2)	204	– 48 (23.5)	2.09 [1.57; 2.78] < 0.001
Infections and infestations (SOC, severe AEs (CTCAE grade ≥ 3))	195	– 65 (33.3)	204	– 36 (17.6)	1.89 [1.32; 2.70] < 0.001
General disorders and administration site conditions (SOC, severe AEs (CTCAE grade ≥ 3))	195	– 50 (25.6)	204	– 16 (7.8)	3.27 [1.93; 5.54] < 0.001
Metabolism and nutrition disorders (SOC, severe AEs (CTCAE grade ≥ 3))	195	– 43 (22.1)	204	– 17 (8.3)	2.65 [1.56; 4.48] < 0.001

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Data from Module 4 of the dossier
[c] IQWiG calculation (effect estimate, 95% CI and p value)

Abbreviations used:
AD = Absolute Difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-CIPN20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-induced Peripheral Neuropathy; 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.r. = not reached; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

Adults with multiple myeloma who have received at least one prior therapy

approx. 4,700 – 7,000 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 Nexpovio (active ingredient: selinexor) at the following publicly accessible link (last access: 6 February 2023):

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

Treatment with selinexor should only be initiated and monitored by specialists in internal medicine, haematology and, oncology experienced in the treatment of patients with multiple myeloma.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of treatment.

Adults with multiple myeloma who have received at least one prior therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Selinexor in combination with bortezomib and dexamethasone	
Selinexor	€ 128,508.77
Dexamethasone	€ 243.05
Bortezomib	€ 7,282.91
Total	€ 136,034.73
Appropriate comparator therapy	
Bortezomib in combination with pegylated liposomal doxorubicin	
Bortezomib	€ 5,602.24
Doxorubicin (pegylated, lysosomal)	€ 17,454.00
Total	€ 23,056.24
Bortezomib in combination with dexamethasone	
Bortezomib	€ 2,801.12 - € 5,602.24
Dexamethasone	€ 104.10 - € 168.90
Total	€ 2,905.22 - € 5,771.14
Carfilzomib in combination with lenalidomide and dexamethasone	
Carfilzomib	€ 76,695.24
Lenalidomide	€ 774.93
Dexamethasone	€ 193.44
Total	€ 77,663.61
Additionally required SHI services	€ 106.40

Designation of the therapy	Annual treatment costs/ patient
Carfilzomib in combination with dexamethasone	
Carfilzomib	€ 144,716.22
Dexamethasone	€ 243.05
Total	€ 144,959.27
Additionally required SHI services	€ 106.40
Daratumumab in combination with lenalidomide and dexamethasone	
Daratumumab	€ 128,183.14
Lenalidomide	€ 774.93
Dexamethasone	€ 107.88
Total	€ 129,065.95
Additionally required SHI services	€ 341.49 - € 344.80
Daratumumab in combination with bortezomib and dexamethasone	
Daratumumab	€ 117,036.78
Bortezomib	€ 5,602.24
Dexamethasone	€ 147.23
Total	€ 122,786.25
Additionally required SHI services	€ 292.01 - € 295.02
Elotuzumab in combination with lenalidomide and dexamethasone	
Elotuzumab	€ 84,540.00
Lenalidomide	€ 774.93
Dexamethasone	€ 185.70
Total	€ 85,500.63
Additionally required SHI services	€ 359.57 - € 363.88
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 774.93
Dexamethasone	€ 312.48
Total	€ 1,087.41
Additionally required SHI services	€ 106.40

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2023)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Selinexor in combination with bortezomib and dexamethasone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	41.6	€ 4,160
Appropriate comparator therapy					
Bortezomib in combination with pegylated liposomal doxorubicin					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	32	€ 3,200
Doxorubicin (pegylated, liposomal)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	Day 4 21-day cycle	8	€ 800
Bortezomib in combination with dexamethasone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	16 - 32	€ 1,600 - € 3,200
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1st - 12th cycle: 6 From 13th cycle: 4	76	€ 7,600
Carfilzomib in combination with dexamethasone					
Carfilzomib	Surcharge for production of a	€ 100	6	78	€ 7,800

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	parenteral preparation containing cytostatic agents				
Daratumumab in combination with bortezomib and dexamethasone					
Bortezomib	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	32	€ 3,200
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1st - 2nd cycle: 4 From 3rd cycle: 2	30	€ 3,000

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Selinexor

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with selinexor for the treatment of adult patients with multiple myeloma who have received at least one prior therapy:

Adults with multiple myeloma who have received at least one prior therapy

– No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 March 2023.

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

Berlin, 16 March 2023

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

Prof. Hecken