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
Melphalan Flufenamide (multiple myeloma (after at least 3 prior therapies, combination with 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. Annex XII shall be amended in alphabetical order to include the active ingredient Melphalan Flufenamide as follows:**

**Melphalan flufenamide**

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

**Therapeutic indication (according to the marketing authorisation of 17 August 2022):**

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.

**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

Adults with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy; the time to progression at least three years for subjects with prior autologous stem cell transplantation

**Appropriate comparator therapy:**

A patient-individual therapy under selection of:

- Bortezomib monotherapy
- Bortezomib + pegylated liposomal doxorubicin
- Bortezomib + dexamethasone
- Carfilzomib + lenalidomide and dexamethasone
- Carfilzomib + dexamethasone
- Daratumumab + lenalidomide + dexamethasone
- Daratumumab + bortezomib + dexamethasone
- Daratumumab monotherapy (only for subjects with disease progression on last therapy)
- Daratumumab + pomalidomide + dexamethasone
- Elotuzumab + lenalidomide + dexamethasone
- Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)

- Isatuximab + pomalidomide + dexamethasone (only for subjects with disease progression on the last therapy)
- Ixazomib + lenalidomide + dexamethasone
- Lenalidomide + dexamethasone
- Panobinostat + bortezomib and dexamethasone
- Pomalidomide + bortezomib and dexamethasone
- Pomalidomide + dexamethasone (only for subjects with disease progression on the last therapy)
- Cyclophosphamide (in combination with other antineoplastic medicinal products)
- Melphalan
- Doxorubicin
- Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)
- Vincristine
- Dexamethasone
- Prednisolone
- Prednisone
- Best supportive care

taking into account prior therapies as well as the severity and duration of the response.

**Extent and probability of the additional benefit of melphalan flufenamide in combination with dexamethasone compared to the appropriate comparator therapy:**

An additional benefit is not proven.

**Study results according to endpoints:**

Adults with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy; the time to progression at least three years for subjects with prior autologous stem cell transplantation

No adequate data are available to allow an assessment of the additional benefit.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | n.a. | There are no assessable data. |
| Morbidity | n.a. | There are no assessable data. |
| Health-related quality of life | n.a. | There are no assessable data. |
| Side effects | n.a. | There are no assessable data. |

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

Adults with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy; the time to progression at least three years for subjects with prior autologous stem cell transplantation

approx. 1,200 – 1,300 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 Pepaxti (active ingredient: melphalan flufenamide) at the following publicly accessible link (last access: 12 December 2022):

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

Treatment with melphalan flufenamide 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 three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy; the time to progression at least three years for subjects with prior autologous stem cell transplantation

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| *Melphalan flufenamide in combination with dexamethasone* | |
| Melphalan flufenamide | € 158,123.68 |
| Dexamethasone | € 193.44 |
| Total | € 158,317.12 |
| Best supportive care | Different from patient to patient |
| Appropriate comparator therapy | |
| *Bortezomib monotherapy* | |
| *Bortezomib* | € 5,602.24 |
| *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 |
| *Carfilzomib in combination with dexamethasone* | |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| 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 |
| *Daratumumab monotherapy (only for subjects with disease progression on last therapy)* | |
| Daratumumab | € 128,183.14 |
| Additionally required SHI services | € 399.30 - € 649.54 |
| *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 |
| *Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)* | |
| Elotuzumab | € 84,540.00 |
| Pomalidomide | € 106,253.29 |
| Dexamethasone | € 188.54 |
| Total | € 190,981.83 |
| Additionally required SHI services | € 266.74 - € 269.47 |
| *Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with disease progression on last therapy)* | |
| Isatuximab | € 73,272.92 |
| Pomalidomide | € 106,253.29 |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Dexamethasone | € 89.28 |
| Total | € 179,615.49 |
| Additionally required SHI services | € 106.40 |
| *Ixazomib in combination with lenalidomide and dexamethasone* | |
| Ixazomib | € 75,468.38 |
| Lenalidomide | € 774.93 |
| Dexamethasone | € 193.44 |
| Total | € 76,436.75 |
| Additionally required SHI services | € 106.40 |
| *Lenalidomide in combination with dexamethasone* | |
| Lenalidomide | € 774.93 |
| Dexamethasone | € 312.48 |
| Total | € 1,087.41 |
| Additionally required SHI services | € 106.40 |
| *Panobinostat in combination with bortezomib and dexamethasone* | |
| Panobinostat | € 33,633.12 - € 67,266.24 |
| Bortezomib | € 5,602.24 - € 8,403.36 |
| Dexamethasone | € 168.90 - € 233.70 |
| Total | € 39,404.26 - € 75,903.30 |
| *Pomalidomide in combination with bortezomib and dexamethasone* | |
| Pomalidomide | € 94,810.63 |
| Bortezomib | € 8,893.56 |
| Dexamethasone | € 237.44 |
| Total | € 103,941.62 |
| Additionally required SHI services | € 106.40 |
| *Pomalidomide in combination with dexamethasone (only for subjects with disease progression on last therapy)* | |
| Pomalidomide | € 106,253.29 |
| Dexamethasone | € 193.44 |
| Total | € 106,446.73 |
| Additionally required SHI services | € 106.40 |
| *Cyclophosphamide (in combination with other antineoplastic medicinal products)* | |
| Cyclophosphamide | € 198.28 |
| Melphalan | € 332.40 |
| Carmustine | € 38,015.12 |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Vincristine | € 357.55 |
| Prednisone | € 132.64 |
| Total | € 39,035.99 |
| *Melphalan* | |
| Melphalan | € 603.20 |
| *Doxorubicin* | |
| Doxorubicin | € 2,497.92 - € 3,746.88 |
| *Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)* | |
| Carmustine | € 38,015.12 |
| Cyclophosphamide | € 198.28 |
| Melphalan | € 332.40 |
| Vincristine | € 357.55 |
| Prednisone | € 132.64 |
| Total | € 39,035.99 |
| *Vincristine* | |
| Vincristine | € 1,791.20 |
| *Dexamethasone* | |
| Dexamethasone | € 877.50 |
| *Daratumumab in combination with pomalidomide and dexamethasone* | |
| Daratumumab | € 128,183.14 |
| Pomalidomide | € 106,253.29 |
| Dexamethasone | € 107.88 |
| Total | € 234,544.31 |
| Additionally required SHI services | € 341.49 - € 344.80 |
| *Prednisolone* | |
| Prednisolone | Incalculable |
| *Prednisone* | |
| Prednisone | Incalculable |
| *Best supportive care* | |
| Best supportive care | Different from patient to patient |

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: | | | | | |
| *Melphalan flufenamide in combination with dexamethasone* | | | | | |
| Melphalan flufenamide | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 13.0 | € 1,300 |
| Appropriate comparator therapy | | | | | |
| *Bortezomib monotherapy* | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 | 32.0 | € 3,200 |
| *Bortezomib in combination with pegylated liposomal doxorubicin* | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 | 32.0 | € 3,200 |
| Doxorubicin (pegylated, liposomal) | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | Day 4 21-day cycle | 8.0 | € 800 |
| *Bortezomib in combination with dexamethasone* | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 | 16.0 - 32.0 | € 1,600 - € 3,200 |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| *Carfilzomib in combination with lenalidomide and dexamethasone* | | | | | |
| Carfilzomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1st - 12th cycle: 6<br>From 13th cycle: 4 | 76.0 | € 7,600 |
| *Carfilzomib in combination with dexamethasone* | | | | | |
| Carfilzomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 6 | 78.0 | € 7,800 |
| *Daratumumab in combination with bortezomib and dexamethasone* | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 4 | 32.0 | € 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<br><br>From 3rd cycle: 2 | 30.0 | € 3,000 |
| *Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)* | | | | | |
| Elotuzumab | Surcharge for the preparation of a parenteral solution containing monoclonal antibodies | € 100 | 1st - 2nd cycle<br>4<br><br>From 3rd cycle<br>1 | 19.0 | € 1,900 |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| *Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with disease progression on last therapy)* | | | | | |
| Isatuximab | Surcharge for the preparation of a parenteral solution containing monoclonal antibodies | € 100 | 1st cycle<br>4<br><br>From 2nd cycle<br>2 | 28.0 | € 2,800 |
| *Panobinostat in combination with bortezomib and dexamethasone* | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1st - 8th cycle:<br>4<br>9th - 16th cycle:<br>2 | 32.0 - 48.0 | € 3,200 - € 4,800 |
| *Pomalidomide in combination with bortezomib and dexamethasone* | | | | | |
| Bortezomib | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1st - 8th cycle<br>4<br><br>From 9th cycle<br>2 | 50.8 | € 5,800 |
| *Cyclophosphamide (in combination with other antineoplastic medicinal products)* | | | | | |
| Cyclophosphamide | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 10.4 | € 1,040 |
| Carmustine | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 10.4 | € 1,040 |
| Vincristine | Surcharge for production of a | € 100 | 1 | 10.4 | € 1,040 |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| | parenteral preparation containing cytostatic agents | | | | |
| *Melphalan monotherapy* | | | | | |
| Melphalan | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 13.0 | € 1,300 |
| *Carmustine* | | | | | |
| Cyclophosphamide | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 10.4 | € 1,040 |
| Carmustine | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 10.4 | € 1,040 |
| Vincristine | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 10.4 | € 1,040 |
| *Doxorubicin monotherapy* | | | | | |
| Doxorubicin | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 6.0 - 9.0 | € 6,000 - € 9,000 |
| *Vincristine monotherapy* | | | | | |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| Vincristine | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 52.1 | € 5,210 |



**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 Melphalan Flufenamide**

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 melphalan flufenamide for the treatment of adult patients with multiple myeloma who have previously received at least three lines of therapy, whose disease is refractory to at least one proteasome inhibitor, an immunomodulatory agent and a CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last line of therapy (for patients with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years):

Adults with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy; the time to progression at least three years for subjects with prior autologous stem cell transplantation

- 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