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)
Midostaurin (reassessment of an orphan drug after exceeding the 30 million euro limit: acute myeloid leukaemia (AML), FLT3 mutation)

of 2 May 2024

At its session on 2 May 2024, 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 is amended as follows:

1. The information on Midostaurin in the version of the resolution of 5 April 2018 (BAnz AT 24.04.2018 B3) is repealed.

2. In Annex XII, the following information is added after No. 4 to the information on the benefit assessment of Midostaurin in the version of the resolution of 5 April 2018 for the therapeutic indication "Treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL)":

Midostaurin

Resolution of: 2 May 2024
Entry into force on: 2 May 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 September 2017):

Rydapt is indicated in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive.

Therapeutic indication of the resolution (resolution of 2 May 2024):

See therapeutic indication according to marketing authorisation.

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

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

Appropriate comparator therapy:

- Induction chemotherapy:
  - cytarabine in combination with daunorubicin *or* idarubicin *or* mitoxantrone

  or

  - daunorubicin/ cytarabine (liposomal formulation) [only for subjects with therapy-related AML (t-AML) or AML with myelodysplastic changes (AML-MRC)]

- Followed by consolidation therapy:

  A patient-individual therapy under selection of chemotherapy (cytarabine or daunorubicin/ cytarabine (liposomal formulation)) and allogeneic stem cell transplantation, depending in particular on the subtype of AML, the patient's general condition and comorbidity.

- Followed by maintenance therapy:

  A patient-individual therapy under selection of:

  - azacitidine (only for subjects who are unsuitable for allogeneic stem cell transplantation)
  - sorafenib (only for subjects who are FLT3-ITD mutation-positive after allogeneic stem cell transplantation)
  - monitoring wait-and-see approach (only for subjects without FLT3-ITD mutation after allogeneic stem cell transplantation)

taking into account the induction and consolidation therapy as well as the FLT3 mutational status.

Extent and probability of the additional benefit of midostaurin in combination with daunorubicin and cytarabine, followed by midostaurin in combination with cytarabine, followed by midostaurin monotherapy versus the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

There are no assessable data.

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 ∅: No data available. n.a.: not assessable		

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

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

Approx. 380 to 1040 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

[1] Data from the dossier assessment of the IQWiG (A23-110) and from the addendum (A24.34), unless otherwise indicated.

product characteristics, SmPC) for Rydapt (active ingredient: midostaurin) at the following publicly accessible link (last access: 25 March 2024):

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

Treatment with midostaurin should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with acute myeloid leukaemia.

FLT3 detection

Before taking midostaurin, a FLT3 mutation (as internal tandem duplication [ITD] or in the tyrosine kinase domain [TKD]) must be confirmed with a validated test.

4. Treatment costs

Annual treatment costs[2]:

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Induction therapy (midostaurin + cytarabine + daunorubicin)	
Midostaurin	€ 7,539.88 - € 15,079.76
Cytarabine	€ 135.27 - € 270.54
Daunorubicin	€ 638.10 - € 1,276.20
Total	€ 8,313.25 - € 16,626.50
Consolidation therapy (midostaurin + cytarabine)	
Midostaurin	€ 30,159.52
Cytarabine	€ 5,278.08
Total	€ 35,437.60
Maintenance therapy	
Midostaurin	€ 104,481.19 - € 117,406.70
Total costs[3]	€ 154,848.27 - € 161,008.29
Appropriate comparator therapy:	
Induction therapy	

[2] Only the costs for the first year of treatment are presented
[3] In patients undergoing haematopoietic stem cell transplantation, midostaurin should be discontinued 48 hours prior to conditioning therapy for SCT. The total costs are therefore different for these patients.

Designation of the therapy	Annual treatment costs/ patient
Cytarabine + daunorubicin	
Cytarabine	€ 90.18 - € 270.54
Daunorubicin	€ 638.10 - € 1,276.20
Total	€ 728.28 - € 1,546.74
Cytarabine + idarubicin	
Cytarabine	€ 90.18 - € 270.54
Idarubicin	€ 2,448.45 - € 4,896.90
Total	€ 2,538.63 - € 5,167.44
Cytarabine + mitoxantrone	
Cytarabine	€ 90.18 - € 135.27
Mitoxantrone	€ 1,033.89 - € 2,067.78
Total	€ 1,124.07 - € 2,203.05
Daunorubicin/ cytarabine (liposomal formulation)	
Daunorubicin/ cytarabine (liposomal formulation)	€ 36,045.06 - € 60,075.10
Consolidation therapy	
High-dose cytarabine	
Cytarabine	€ 5,278.08
Daunorubicin/ cytarabine (liposomal formulation)	
Daunorubicin/ cytarabine (liposomal formulation)	€ 24,030.04 - € 48,060.08
High-dose chemotherapy with allogeneic stem cell transplantation (alloSCT)	
alloSCT	€ 65,407.91 – € 71,031.36
Maintenance therapy	
Oral azacitidine	
Azacitidine	€ 116,300.03 - € 179,196.99
Sorafenib	
Sorafenib	€ 1,459.03 - € 2,741.97
Total costs	
I: Cytarabine + daunorubicin K: High-dose cytarabine E: Oral azacitidine	€ 122,989.58 - € 138,965.77
I: Cytarabine + idarubicin K: High-dose cytarabine E: Oral azacitidine	€ 126,610.28 - € 140,776.12

Designation of the therapy	Annual treatment costs/ patient
I: Cytarabine + mitoxantrone K: High-dose cytarabine E: Oral azacitidine	€ 123,781.160 - € 139,316.47
I: Daunorubicin/ cytarabine (liposomal formulation) K: Daunorubicin/ cytarabine (liposomal formulation) E: Oral azacitidine	€ 224,435.21 - € 239,254.09
I: Cytarabine + daunorubicin K: alloSCT E: Sorafenib	€ 67,997.71 - € 74,967.89
I: Cytarabine + idarubicin K: alloSCT E: Sorafenib	€ 69,808.06 - € 78,588.59
I: Cytarabine + mitoxantrone K: alloSCT E: Sorafenib	€ 68,393.50 - € 75,624.20
I: Daunorubicin/ cytarabine (liposomal formulation) K: alloSCT E: Sorafenib	€ 103,314.49 - € 133,496.25
I: Cytarabine + daunorubicin K: alloSCT E: monitoring wait-and-see approach	€ 66,136.19 - € 72,578.10
I: Cytarabine + idarubicin K: alloSCT E: monitoring wait-and-see approach	€ 67,946.54 - € 76,198.80
I: Cytarabine + mitoxantrone K: alloSCT E: monitoring wait-and-see approach	€ 66,531.98 - € 73,234.41
I: Daunorubicin/ cytarabine (liposomal formulation) K: alloSCT E: monitoring wait-and-see approach	€ 101,452.97 - € 131,106.46
I: Induction therapy K: Consolidation therapy E: Maintenance therapy	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2024)

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					
Induction therapy					
Cytarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	7	7 - 14	€ 700 - € 1,400
Daunorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3 - 6	€ 300 - € 600
Consolidation therapy					
Cytarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	6	24	€ 2,400
Appropriate comparator therapy					
Induction therapy					
Daunorubicin/ cytarabine (liposomal formulation)					
Daunorubicin/ cytarabine (liposomal formulation)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2 - 3	3 - 5	€ 300 - € 500
Cytarabine + daunorubicin/ idarubicin/ mitoxantrone					
Cytarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	7	7 - 14	€ 700 - € 1,400
Daunorubicin/ idarubicin/ Mitoxantrone	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3 - 6	€ 300 - € 600
Consolidation therapy					
Daunorubicin/ cytarabine (liposomal formulation)					
Daunorubicin/ cytarabine (liposomal formulation)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	2 - 4	€ 200 - € 400
High-dose cytarabine					

Cytarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	6	24	€ 2,400

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 May 2024.

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

Berlin, 2 May 2024

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

Prof. Hecken