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 Glasdegib (Acute Myeloid Leukaemia (AML), Combination with Cytarabine (LDAC))

of 18 February 2021

At its session on 18 February 2021 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 amended on DD 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 glasdegib as follows:

Glasdegib

Resolution of: 18 February 2021
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 June 2020):

Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.

Therapeutic indication of the resolution (resolution of 18 February 2021):

See therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

Glasdegib is approved as a medicinal product for the treatment of a rare disease in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are not candidates for standard induction chemotherapy

Extent of the additional benefit and significance of the evidence for glasdegib in combination with low-dose cytarabine (LDAC):

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Pivotal Study B1371003:

Study design: open-label Ib/II study, glasdegib + LDAC vs LDAC (2:1)

Relevant sub-population: "unfit" patients with AML in the randomised-controlled Phase II part of the study

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	n.a.	No patient-relevant data
Health-related quality of life	∅	There are no data on quality of life
Side effects	↑	Advantage in therapy discontinuation because of 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

Mortality

Endpoint	Glasdegib + LDAC		LDAC		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 Absolute difference (AD)[a]
Overall survival					
	78	8.3 [4.7; 12.2] 59 (75.6)	38	4.3 [1.9; 5.7] 35 (92.1)	0.46 [0.3; 0.72] 0.0004 AD: 4.0 months

(Continuation)

[1] Data from the dossier assessment of the G-BA (published on 1 December 2020) unless indicated otherwise.

Morbidity

Endpoint	Glasdegib + LDAC		LDAC		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Transfusion independence (over 24 weeks) – presented additionally					
	29	14 (48.3)	2	0 (0)	
Complete response (CR) – presented additionally					
	78	14 (17.9)	38	1 (2.6)	7.10 [0.89; 56.83]

Health-related quality of life

Endpoint	Glasdegib + LDAC		LDAC		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value
not surveyed					

Side effects

Endpoint	Glasdegib + LDAC		LDAC		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]
Total adverse events [b]					
	75	- 75 (100)	36	- 36 (100)	-

(Continuation)

Endpoint	Glasdegib + LDAC		LDAC		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]
Serious adverse events (SAE) [b]					
	75	1.1 [0.8; 1.8] 59 (78.7)	36	1.3 [0.8; 1.9] 28 (77.8)	0.95 [0.60; 1.51] 0.8374
Severe adverse events (CTCAE grade ≥ 3) [b]					
	75	0.4 [0.3; 0.5] 69 (92.0)	36	0.3 [0.1; 0.5] 35 (97.2)	0.87 [0.57; 1.33] 0.5113
Therapy discontinuations because of adverse events [b]					
Discontinuation of at least one active ingredient component [c]	75	25.9 [8.2; 32.0] 27 (36.0)	36	3.9 [1.7; 5.8] 17 (47.2)	0.48 [0.25; 0.92] 0.025 AD: 22.0 months
Severe AEs (CTCAE grade ≥ 3) with incidence ≥ 5% in one of the two treatment groups System Organ Class (SOC) Preferred Terms (PT)					
General disorders and administration site conditions	75	17.1 [8.2; n.a.] 24 (32.0)	36	8.7 [3.0; 8.7] 10 (27.8)	0.75 [0.35; 1.64] 0.4718
Fatigue	75	n.a. [n.a.; n.a.] 9 (12.0)	36	n.a. [n.a.; n.a.] 2 (5.6)	1.60 [0.33; 7.72] 0.5579
Disease progression	75	n.a. [n.a.; n.a.] 7 (9.3)	36	8.7 [n.a.; n.a.] 4 (11.1)	0.51 [0.14; 1.82] 0.2910
Pyrexia	75	n.a. [21.3; n.a.] 2 (2.7)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.20 [0.02; 2.21] 0.1452
Respiratory, thoracic and mediastinal disorders	75	n.a. [n.a.; n.a.] 11 (14.7)	36	n.a. [n.a.; n.a.] 7 (19.4)	0.65 [0.25; 1.70] 0.3771

(Continuation)

Endpoint	Glasdegib + LDAC	LDAC	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]
Dyspnoea	75	n.a. [n.a.; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.95 [0.17; 5.19] 0.9524
Skin and subcutaneous tissue disorders	75	n.a. [n.a.; n.a.] 3 (4.0)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.69 [0.12; 4.15] 0.6845
Renal and urinary disorders	75	n.a. [n.a.; n.a.] 7 (9.3)	36	n.a. [n.a.; n.a.] 2 (5.6)	1.54 [0.32; 7.44] 0.5875
Chronic kidney disease	75	n.a. [n.a.; n.a.] 1 (1.3)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.24 [0.02; 2.61] 0.2003
Blood and lymphatic system disorders	75	0.6 [0.4; 1.5] 51 (68.0)	36	0.5 [0.3; 5.3] 23 (63.9)	0.98 [0.60; 1.62] 0.9517
Anaemia	75	32.4 [1.5; 32.4] 32 (42.7)	36	n.a. [0.9; n.a.] 13 (36.1)	1.12 [0.58; 2.14] 0.7398
Febrile neutropoenia	75	n.a. [5.3; n.a.] 26 (34.7)	36	n.a. [3.5; n.a.] 9 (25.0)	1.25 [0.58; 2.69] 0.5682
Leukocytosis	75	n.a. [n.a.; n.a.] 3 (4.0)	36	n.a. [4.5; n.a.] 3 (8.3)	0.26 [0.05; 1.44] 0.0997
Neutropoenia	75	29.8 [n.a.; n.a.] 9 (12.0)	36	n.a. [5.3; n.a.] 5 (13.9)	0.47 [0.14; 1.59] 0.2123
Pancytopenia	75	n.a. [n.a.; n.a.] 1 (1.3)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.20 [0.02; 2.23] 0.1468

(Continuation)

Endpoint	**Glasdegib + LDAC**		**LDAC**		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]
Splenomegaly	75	n.a. [n.a.; n.a.] 0	36	n.a. [n.a.; n.a.] 2 (5.6)	no data available
Thrombocyto-poenia	75	n.a. [7.0; n.a.] 24 (32.0)	36	n.a. [n.a.; n.a.] 8 (22.2)	1.28 [0.57; 2.86] 0.5432
Gastrointestinal disorders	75	n.a. [21.0; n.a.] 12 (16.0)	36	n.a. [n.a.; n.a.] 3 (8.3)	1.49 [0.41; 5.38] 0.5432
Nervous system disorders	75	26.3 [14.3; n.a.] 13 (17.3)	36	n.a. [n.a.; n.a.] 1 (2.8)	3.43 [0.43; 27.33] 0.2160
Syncope	75	n.a. [n.a.; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 0	no data available
Vascular disorders	75	n.a. [n.a.; n.a.] 6 (8.0)	36	n.a. [n.a.; n.a.] 0	no data available
Hypertension	75	n.a. [n.a.; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 0	no data available
Heart diseases	75	n.a. [n.a.; n.a.] 8 (10.7)	36	n.a. [n.a.; n.a.] 3 (8.3)	0.97 [0.25; 3.80] 0.9614
Infections and infestations	75	14.3 [6.2; n.a.] 29 (38.7)	36	3.9 [1.5; n.a.] 15 (41.7)	0.68 [0.35; 1.30] 0.2347
Pneumonia	75	25.9 [14.3; n.a.] 17 (22.7)	36	n.a. [2.3; n.a.] 9 (25.0)	0.55 [0.23; 1.30] 0.1654
Sepsis	75	n.a. [n.a.; n.a.] 5 (6.7)	36	n.a. [5.8; n.a.] 6 (16.7)	0.34 [0.10; 1.13] 0.0661

(Continuation)

Endpoint	Glasdegib + LDAC		LDAC		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]
Musculoskeletal and connective tissue disorders	75	n.a. [16.3; n.a.] 7 (9.3)	36	n.a. [n.a.; n.a.] 1 (2.8)	1.38 [0.15; 12.73] 0.7764
Muscle spasms	75	n.a. [n.a.; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 0	no data available
Metabolism and nutrition disorders	75	n.a. [n.a.; n.a.] 15 (20.0)	36	n.a. [n.a.; n.a.] 4 (11.1)	1.47 [0.48; 4.52] 0.4968
Reduced appetite	75	n.a. [n.a.; n.a.] 2 (2.7)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.18 [0.02; 1.48] 0.0791
Hypokalemia	75	n.a. [n.a.; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 0	no data available
Hyponatremia	75	n.a. [n.a.; n.a.] 5 (6.7)	36	n.a. [n.a.; n.a.] 0	no data available
Investigations	75	n.a. [10.1; n.a.] 23 (30.7)	36	n.a. [2.2; n.a.] 11 (30.6)	0.87 [0.42; 1.80] 0.7049
Elevated C-reactive protein	75	n.a. [n.a.; n.a.] 2 (2.7)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.37 [0.05; 2.69] 0.3087
Decreased levels of neutrophils	75	n.a. [n.a.; n.a.] 8 (10.7)	36	n.a. [n.a.; n.a.] 1 (2.8)	2.48 [0.29; 21.27] 0.3910
Decreased levels of thrombocytes	75	n.a. [n.a.; n.a.] 12 (16.0)	36	n.a. [n.a.; n.a.] 4 (11.1)	1.22 [0.39; 3.80] 0.7313
Low white blood cell count	75	n.a. [17.0; n.a.] 8 (10.7)	36	n.a. [n.a.; n.a.] 1 (2.8)	2.95 [0.36; 24.56] 0.2928

(Continuation)

Endpoint	**Glasdegib + LDAC**		**LDAC**		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]
Injury, poisoning, and procedural complications	75	n.a. [17.5; n.a.] 5 (6.7)	36	n.a. [n.a.; n.a.] 2 (5.6)	0.36 [0.05; 2.70] 0.3067
Serious AE with incidence ≥ 5% in one of the two treatment groups System Organ Class (SOC) Preferred Terms (PT)					
General disorders and administration site conditions	75	n.a. [21.3; n.a.] 14 (18.7)	36	8.7 [3.1; 8.7] 6 (16.7)	0.63 [0.23; 1.72] 0.3602
Disease progression	75	n.a. [n.a.; n.a.] 7 (9.3)	36	n.a. [n.a.; n.a.] 4 (11.1)	0.51 [0.14; 1.82] 0.2910
Respiratory, thoracic and mediastinal disorders	75	n.a. [n.a.; n.a.] 2 (2.7)	36	n.a. [n.a.; n.a.] 3 (8.3)	0.25 [0.04; 1.53] 0.1057
Blood and lymphatic system disorders	75	n.a. [5.3; n.a.] 26 (34.7)	36	n.a. [4.5; n.a.] 9 (25.0)	1.21 [0.56; 2.61] 0.6305
Anaemia	75	n.a. [n.a.; n.a.] 5 (6.7)	36	n.a. [n.a.; n.a.] 0	no data available
Febrile neutropoenia	75	n.a. [n.a.; n.a.] 21 (28.0)	36	n.a. [3.5; n.a.] 6 (16.7)	1.52 [0.61; 3.81] 0.3664
Pancytopenia	75	n.a. [n.a.; n.a.] 0	36	n.a. [n.a.; n.a.] 2 (5.6)	no data available
Gastrointestinal disorders	75	n.a. [21.0; n.a.] 8 (10.7)	36	n.a. [n.a.; n.a.] 3 (8.3)	0.95 [0.24; 3.70] 0.9376

(Continuation)

Endpoint	**Glasdegib + LDAC**		**LDAC**		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]
Nervous system disorders	75	n.a. [26.3; n.a.] 8 (10.7)	36	n.a. [n.a.; n.a.] 1 (2.8)	2.55 [0.31; 21.31] 0.3699
Heart diseases	75	n.a. [n.a.; n.a.] 6 (8.0)	36	n.a. [n.a.; n.a.] 3 (8.3)	0.66 [0.15; 2.85] 0.5793
Infections and infestations	75	14.3 [8.3; n.a.] 26 (34.7)	36	n.a. [1.5; n.a.] 13 (36.1)	0.69 [0.34; 1.38] 0.2865
Pneumonia	75	25.9 [14.3; n.a.] 16 (21.3)	36	n.a. [n.a.; n.a.] 7 (19.4)	0.71 [0.28; 1.82] 0.4732
Sepsis	75	n.a. [n.a.; n.a.] 3 (4.0)	36	n.a. [5.8; n.a.] 5 (13.9)	0.22 [0.05; 0.92] 0.0237
Metabolism and nutrition disorders	75	n.a. [n.a.; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 0	no data available
Injury, poisoning, and procedural complications	75	n.a. [17.5; n.a.] 4 (5.3)	36	n.a. [n.a.; n.a.] 1 (2.8)	0.60 [0.04; 8.09] 0.6946
AE of special interest [b,d]					
SOC: Infections and infestations (see “Severe AEs (CTCAE grade ≥ 3) with incidence ≥ 5%” and “Serious AE with incidence ≥ 5%”)					
PT: Febrile neuropathies (see “Severe AEs (CTCAE grade ≥ 3) with incidence ≥ 5%” and “Serious AE with incidence ≥ 5%”)					
SMQ QT time prolongation					
CTCAE grade ≥ 3	75	no data available 11 (14.7)	36	no data available 2 (5.6)	1.71 [0.36; 8.13] 0.4943
SAE		7 (9.3)		0 (0)	n.c.

(Continuation)

Endpoint	Glasdegib + LDAC		LDAC		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]
SMQ bleeding					
CTCAE grade ≥ 3	75	no data available 9 (12.0)	36	no data available 4 (11.1)	0.43 [0.11; 1.68] 0.2119
SAE		no data available 8 (10.7)		no data available 3 (8.3)	0.56 [0.13; 2.54] 0.4504

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] AML safety population
[c] Related to the verum arm; in addition to the discontinuation of the entire therapy (both active ingredient components), the discontinuation of glasdegib alone was also evaluated for this purpose (an exclusive discontinuation of LDAC did not occur in the verum arm).
[d] According to the information in Module 4
Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; 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

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

Adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are not candidates for standard induction chemotherapy

approx. 780–840 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 Daurismo (active ingredient: glasdegib) at the following publicly accessible link (last access: 20 November 2020):
https://www.ema.europa.eu/en/documents/product-information/daurismo-epar-product-information_de.pdf

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

Glasdegib can cause embryo-foetal death or severe birth defects when administered to pregnant women. Pregnant women should be informed of the possible risk to the foetus.

Glasdegib should not be used in pregnant women and women of childbearing potential who are not using contraception. Women of childbearing age should be advised to use effective contraception at all times during treatment with glasdegib and for at least 30 days after the last dose.

Glasdegib can pass into the semen. Male patients with female partners should be advised of the possible risk of exposure via semen. At all times during treatment with glasdegib and for at least 30 days after the last dose, such patients should be advised to use effective contraception, including a condom (with spermicide if available), even after a vasectomy, in order to prevent exposure of a pregnant or childbearing partner. Men should seek advice on effective fertility preservation before starting treatment with glasdegib.

In accordance with to the requirements of the EMA regarding additional risk minimisation measures, the pharmaceutical company must ensure that all male patients are provided with a patient card by their prescribing doctors for the reasons mentioned above.

4. Treatment costs

Annual treatment costs:

Adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML) who are not candidates for standard induction chemotherapy

Designation of the therapy	Annual treatment costs/patient
Glasdegib	€ 158,061.55
Cytarabine	€ 418.08
Total:	€ 158,479.63

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2021

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Cytarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	10	130	€ 10,530

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 18 February 2021.**

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

Berlin, 18 February 2021

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

Prof. Hecken