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 Gilteritinib (Relapsed or Refractory Acute Myeloid Leukaemia with an FLT3 Mutation)

of 14 May 2020

At its session on 14 May 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 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 gilteritinib as follows:

Gilteritinib

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 October 2019):

XOSPATA is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation

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

Gilteritinib is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to 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 who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation

Extent of the additional benefit and the significance of the proof for gilteritinib:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

ADMIRAL (2215-CL-0301) study:

Gilteritinib vs salvage chemotherapy

Salvage chemotherapy: low intensity: low-dose cytarabine or azacitidine;
high intensity: MEC or FLAG-IDA

Study design: randomised, open, multi-site phase III study
Parallel group design (2:1) with 2 treatment arms

Mortality

Endpoint	Gilteritinib		Salvage chemotherapy		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					
	247	9.3 [7.7; 10.7] *171 (69.2)*	124	5.6 [4.7; 7.3] *90 (72.6)*	0.64 [0.49; 0.83] 0.0007 AD: + 3.7 months

Morbidity

Endpoint	Gilteritinib		Salvage chemotherapy		Intervention vs control
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
BFI	No usable data				
Leukaemia-specific symptoms	No usable data				
FACIT-Dys-SF	No usable data				
EQ-5D-VAS	No usable data				
Complete remission	No usable data				
Rate of stem cell transplantations[b]	247	- *63 (25.5)*	124	- *19 (15.3)*	1.66[c] [1.05; 2.65] 0.0260

[1] Data from the dossier evaluation by the G-BA (published on 02 March 2020) unless otherwise indicated.

Health-related quality of life

Endpoint	Gilteritinib		Salvage chemotherapy		Intervention vs control
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
FACT-Leu	No usable data				

Side effects

Endpoint	Gilteritinib		Salvage chemotherapy		Intervention vs control
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events in total					
	246	- *246 (100)*	109	- *107 (98.2)*	-
Severe adverse events (CTCAE grade ≥ 3)					
	246	0.3 [0.3; 0.4] *236 (95.9)*	109	0.2 [0.1; 0.2] *94 (86.2)*	0.7 [0.55; 0.90] 0.0044
Serious adverse events (SAE)					
	246	1.6 [1.3; 1.9] *204 (82.0)*	109	2.5 [1.5; n.a.] *33 (30.03)*	1.71 [1.17; 2.50] 0.0057
AE that led to discontinuation of the study medication					
	246	n.a. *58 (23.6)*	109	5.8 [4.9; n.a.] *13 (11.9)*	0.5 [0.25; 0.98] 0.0445
AEs of special interest (any degree of severity)					
Posterior reversible encephalopathy syndrome	246	- 8 (3.3)	109	- 4 (3.7)	0.31 [0.08; 1.27] 0.1029
CTCAE grade ≥ 3		3 (1.2)		2 (1.8)	-

(Continuation)

Endpoint	Gilteritinib		Salvage chemotherapy		Intervention vs control
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Heart failure	246	- 19 (7.7)	109	- 3 (2.8)	1.27 [0.35; 4.57] 0.7140
CTCAE grade ≥ 3		10 (4.1)		1 (0.9)	-
Pericarditis / pericardial effusion	246	- 15 (6.1)	109	- 0	n.c.
CTCAE grade ≥ 3		3 (1.2)		0	-
Arrhythmia due to QT prolongation	246	- 35 (14.2)	109	- 2 (1.8)	3.43 [0.80; 14.74] 0.0978
CTCAE grade ≥ 3		20 (8.1)		2 (1.8)	-
Raised creatine phosphokinase	246	- 64 (26.0)	109	- 5 (4.6)	3.12 [1.23; 7.90] 0.0166
CTCAE grade ≥ 3		19 (7.7)		1 (0.9)	-
Raised liver transaminase	246	- 129 (52.4)	109	- 24 (22.0)	1.61 [1.03; 2.53] 0.0363
CTCAE grade ≥ 3		58 (23.6)		8 (7.3)	-
Gastrointestinal obstruction	246	- 4 (1.6)	109	- 1 (0.9)	0.25 [0.02; 3.55] 0.3035
CTCAE grade ≥ 3		2 (2.8)		0	-
Gastrointestinal perforation	246	- 4 (1.6)	109	- 3 (2.8)	0.27 [0.05; 1.43] 0.1248
CTCAE grade ≥ 3		3 (1.2)		1 (0.9)	-
Gastrointestinal bleeding	246	- 20 (8.1)	109	- 2 (1.8)	1.59 [0.35; 7.19] 0.5475
CTCAE grade ≥ 3		6 (2.4)		2 (1.8)	-

(Continuation)

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] During the study period (gilteritinib) or as follow-up therapy (salvage chemotherapy)
[c] Information from the dossier (module 4)

Abbreviations used:
AD = absolute difference; CTCAE = common terminology criteria for adverse events; HR = hazard ratio; RR: Relative risk; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. n.c: not calculable; n.a.: not achieved; CR = complete remission; CRh = complete remission with partial haematological recovery; BFI = Brief Fatigue Inventory; FACIT-Dys-SF = Functional Assessment of Chronic Illness Therapy – Dyspnea-Short Form; EG-5D-VAS = visual analogue scale of the EuroQol 5-dimensional questionnaire; FACT-Leu = Functional Assessment of Cancer Therapy – Leukaemia;

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 usable data
Health-related quality of life	n.a.	No usable data
Side effects	↔	no relevant difference

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.a.: not assessable

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

approx. 220 to 580 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 XOSPATA (active ingredient: gilteritinib) at the following publicly accessible link (last access: 27 February 2020):

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

Treatment with gilteritinib 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.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on gilteritinib:

- Training material for doctors
- Patient card

FLT3 proof

Before taking gilteritinib, patients with relapsed or refractory AML must be confirmed by means of a validated test as having the FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplications (ITD) or mutations in the tyrosine kinase domain (TKD)).

4. Treatment costs

Annual treatment costs:

Adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with an FLT3 mutation

Designation of the therapy	Annual treatment costs/patient
Gilteritinib	€ 279,434.35–465,723.92

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2020

Costs for additionally required SHI services: not applicable

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 14 May 2020.

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

Berlin, 14 May 2020

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

Prof. Hecken