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
Maribavir (cytomegalovirus infection (refractory to therapies))

of 1 June 2023

At its session on 1 June 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 Maribavir as follows:

Maribavir

Resolution of: 1 June 2023
Entry into force on: 1 June 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 November 2022):

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT).

Therapeutic indication of the resolution (resolution of 1 June 2023):

See therapeutic indication according to marketing authorisation.

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

Maribavir is approved as a medicinal product for the treatment of rare diseases under 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 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).

<u>Adults who have undergone haematopoietic stem cell transplantation or solid organ transplantation with cytomegalovirus infection and/or disease refractory to one or more prior therapies (including ganciclovir, valganciclovir, cidofovir or foscarnet)</u>

Extent of the additional benefit and significance of the evidence of maribavir:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults who have undergone haematopoietic stem cell transplantation or solid organ transplantation with cytomegalovirus infection and/or disease refractory to one or more prior therapies (including ganciclovir, valganciclovir, cidofovir or foscarnet)

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	↑	Advantages in the endpoint of infection control
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↑	Advantages in the endpoint "AE which led to the discontinuation of the study medication"
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		

SHP620-303 study:

Label-enabling, multicentre, unblinded, randomised-controlled phase III study with 352 patients with refractory CMV infection after SOT or HSCT; maribavir vs investigator-assigned anti-CMV treatment (IAT) with ganciclovir, valganciclovir, foscarnet, cidofovir

Mortality

Endpoint	Maribavir		Anti-CMV therapy		Intervention vs control
	N[a]	Median survival duration in days [95% CI] *Patients with event n (%)*	N[a]	Median survival duration in days [95% CI] *Patients with event n (%)*	Hazard ratio[b] [95% CI] p value[c]
Overall mortality (data cut-off of 14.11.2020)					
	235	182.0 [177.0; n.c.] *27 (11.5)*	117	n.r. [186.0; n.c.] *13 (11.1)*	1.14 [0.55; 2.36] 0.65

[1] Data from the dossier assessment of the G-BA (published on 1 Mars 2023), and from the drafted amendment (published on 1 June 2023), unless otherwise indicated.

Morbidity

Endpoint	Maribavir		Anti-CMV therapy		Intervention vs control
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Relative risk [95% CI] p value[d, e]
Infection control					
Responder infection control (week 8)[f, g]	235	131 (55.7)	117	28 (23.9)	2.37 [1.69; 3.34] < 0.001
Responder maintenance of infection control (week 20)[e, h]	235	44 (18.7)	117	11 (9.4)	2.10 [1.14; 3.89] 0.012
Symptom control[i] *(presented additionally)*					
Responder symptom control (week 8)[e]	235	224 (95.3)	117	109 (93.2)	1.03 [0.97; 1.09] 0.36
Responder maintenance of symptom control (week 20)[e]	235	211 (89.8)	117	96 (82.1)	1.1 [1; 1.21] 0.036
Graft endpoints[j]					
Graft loss	235	1 (0.4)	117	0 (0)	-
Solid organ transplantation (SOT)					
- Acute rejection[k]	142	9 (6.3)	69	7 (10.1)	-
- Chronic rejection[k]	142	0 (0)	69	0 (0)	-
Haematopoietic stem cell transplantation (HSCT)					
- Graft-versus-host disease (GVHD)[k]	93	25 (26.9)	48	18 (37.5)	-

Health-related quality of life

Endpoint	
SF-36	No data could be considered.

Side effects

Endpoint (during the treatment period)	**Maribavir**			**Anti-CMV therapy**			Intervention vs control
	N	Patients with event n (%)	Median[m] [95% CI] days	N	Patients with event n (%)	Median[m] [95% CI] days	Hazard ratio[n] [95% CI] p value[o]
Adverse events (AEs) (presented additionally)	234	228 (97.4)	4 [1; 10]	116	106 (91.4)	5 [1.5; 16]	-
Severe AEs	234	75 (32.1)	n.r. [43; n.r.]	116	44 (37.9)	n.r. [15; n.r.]	0.6 [0.4; 0.9] 0.014
Serious AEs (SAEs)	234	90 (38.5)	n.r. [29; n.r.]	116	43 (37.1)	63.0 [19; n.r.]	0.8 [0.5; 1.1] 0.19
AE which led to the discontinuation of the study medication[p]	234	31 (13.2)	n.r.	116	37 (31.9)	n.r. [19; n.r.]	0.3 [0.2; 0.5] < 0.001
SAE in ≥ 5% of subjects in at least one study arm MedDRA system organ class							
Infections and infestations	234	53 (22.6)	n.r. [66; n.r.]	116	17 (14.7)	n.r.	1.1 [0.6; 1.9] 0.8
Gastrointestinal disorders	234	13 (5.6)	n.r.	116	6 (5.2)	n.r.	0.8 [0.3; 2.1] 0.63
General disorders and administration site conditions	234	12 (5.1)	n.r.	116	3 (2.6)	n.r.	1.3 [0.4; 4.6] 0.69
Blood and lymphatic system disorders	234	9 (3.8)	n.r.	116	7 (6.0)	n.r.	0.5 [0.2; 1.2] 0.12
Renal and urinary disorders	234	9 (3.8)	n.r.	116	6 (5.2)	n.r.	0.6 [0.2; 1.8] 0.39
Severe AEs in ≥ 5% of subjects in at least one study arm MedDRA system organ class							
Blood and lymphatic system disorders	234	17 (7.3)	n.r.	116	21 (18.1)	n.r.	0.3 [0.2; 0.6] < 0.001
Gastrointestinal disorders	234	12 (5.1)	n.r.	116	3 (2.6)	n.r.	1.6 [0.4; 5.5] 0.49
Infections and infestations	234	30 (12.8)	n.r.	116	11 (9.5)	n.r.	1.0

							[0.5; 2.0] 0.96
Respiratory, thoracic and mediastinal disorders	234	12 (5.1)	n.r.	116	2 (1.7)	n.r.	2.6 [0.6; 11.5] 0.21
Adverse events with incidence ≥ 10% according to MedDRA system organ class							
Blood and lymphatic system disorders	234	66 (28.2)	n.r. [42; n.r.]	116	42 (36.2)	n.r. [16; n.r.]	0.6 [0.4; 0.9] 0.006
Gastrointestinal disorders	234	118 (50.4)	56 [11; n.r.]	116	57 (49.1)	52 [8; n.r.]	0.9 [0.6; 1.2] 0.39
General disorders and administration site conditions	234	81 (34.6)	n.r. [30; n.r.]	116	43 (37.1)	63 [14; n.r.]	0.7 [0.5; 1.0] 0.073
Immune system disorders	234	30 (12.8)	71 [71; 71]	116	9 (7.8)	n.r.	1.3 [0.6; 2.7] 0.54
Infections and infestations	234	135 (57.7)	50 [19; n.r.]	116	48 (41.4)	55 [17; n.r.]	1.1 [0.8; 1.5] 0.73
Injury, poisoning and procedural complications	234	24 (10.3)	n.r.	116	5 (4.3)	n.r.	1.7 [0.6; 4.5] 0.28
Investigations	234	80 (34.2)	n.r. [31; n.r.]	116	26 (22.4)	n.r. [48; n.r.]	1.2 [0.8; 1.9] 0.33
Metabolism and nutrition disorders	234	67 (28.6)	n.r. [43; n.r.]	116	31 (26.7)	n.r. [18; n.r.]	0.8 [0.5; 1.3] 0.42
Diseases of the musculoskeletal and connective tissue disorders	234	48 (20.5)	n.r.	116	24 (20.7)	n.r. [49; n.r.]	0.7 [0.5; 1.2] 0.23
Nervous system disorders	234	133 (56.8)	23 [2; n.r.]	116	31 (26.7)	n.r. [35; n.r.]	2.5 [1.7; 3.7] < 0.001
Psychiatric disorders	234	27 (11.5)	n.r.	116	13 (11.2)	n.r.	0.8 [0.4; 1.5] 0.49
Renal and urinary disorders	234	40 (17.1)	n.r.	116	31 (26.7)	n.r. [35; n.r.]	0.5 [0.3; 0.8] 0.002
Respiratory, thoracic and mediastinal disorders	234	55 (23.5)	n.r. [62; n.r.]	116	22 (19.0)	n.r.	1.0 [0.6; 1.6] 0.93

Skin and subcutaneous tissue disorders	234	47 (20.1)	n.r.	116	8 (6.9)	n.r.	2.2 [1.1; 4.7] 0.032
Vascular disorders	234	28 (12.0)	n.r.	116	14 (12.1)	n.r.	0.7 [0.4; 1.4] 0.35

a. ITT population.
b. Stratified Cox regression model considering the stratification factors "transplantation type" and "baseline CMV DNA concentration".
c. Two-tailed p value using log-rank test and Kaplan-Meier method.
d. Cochran-Mantel-Haenszel method stratified by "transplantation type" and "baseline CMV DNA concentration". Only subjects with information on both stratification factors were included in the analysis.
e. The evaluation was done post hoc.
f. Infection control on week 8: CMV DNA concentration < 137 IU/ml (lower limit of quantification) in blood plasma, in two consecutive samples on weeks 7 and 8.
g. Primary endpoint.
h. Maintenance of infection control: After infection control on week 8, there are no 2 consecutive CMV DNA readings > 137 Iu/ml on weeks 19 and 20.
i. Asymptomatic study participants at baseline were not allowed to develop tissue-invasive CMV disease or CMV syndrome in the course of the study. In symptomatic study participants at baseline, tissue-invasive CMV disease or CMV syndrome should reduce or improve.
j. The results on graft endpoints were presented descriptively in the study report, following the information in the SAP. The graft endpoints were analysed regardless of whether rescue therapy or alternative anti-CMV medication was given.
k. Percentages are based on the number of subjects within that category (HSCT or SOT).
l. The entire evaluation period (excl. maribavir rescue arm) begins with the intake of the study medication and terminates with the end of the study or with the intake of maribavir for subjects in the rescue arm.
m. Median time to first event in days.
n. Post hoc calculation: Hazard ratio based on a Cox regression model, n.d. on stratification.
o. Post hoc calculation of p values based on a log-rank test and Kaplan-Meier method.
p. The study participants received the study medication in the maribavir arm until a CMV infection associated with CNS was present or when one of the non-permitted concomitant medications was administered. In the control arm, the study participants received the study medication until discontinuation of the control medication based on medical assessment or in case of insufficient response and/or intolerance. These possible therapy discontinuation reasons that may occur prior to potential discontinuation due to AEs thus represent a competing event, which is why the reliability and interpretability of the results is limited.
q. Defined as AE of special interest.

Abbreviations used: CMV: Cytomegalovirus; GVHD: Graft-versus-host disease; HR: hazard ratio; HSCT: Haematopoietic stem cell transplantation; ITT: Intention to treat; n.d.: no data available; CI: Confidence interval; MedDRA:: Medical Dictionary for Regulatory Activities; N: Number of patients evaluated; n: Number of patients with (at least one) event; n.c. = not calculable; n.r.: not reached; SOT: Solid organ transplantation; vs: versus

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

Adults who have undergone haematopoietic stem cell transplantation or solid organ transplantation with cytomegalovirus infection and/or disease refractory to one or more prior therapies (including ganciclovir, valganciclovir, cidofovir or foscarnet)

approx. 90 – 130 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 Livtencity (active ingredient: maribavir) at the following publicly accessible link (last access: 15 May 2023):

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

Treatment with maribavir should be initiated and monitored by doctors experienced in the treatment of patients who have undergone solid organ transplantation or haematopoietic stem cell transplantation.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Maribavir	€ 65,738.52

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

Costs for additionally required SHI services: not applicable

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 Maribavir

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 that can be used - on the basis of the marketing authorisation under Medicinal Products Act - in a combination therapy with maribavir for the treatment of cytomegalovirus (CMV) infection and/or disease that is refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet, in adult patients who have undergone haematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT):

- 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 1 June 2023.

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

Berlin, 1 June 2023

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

Prof. Hecken