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)
Letermovir (new therapeutic indication: CMV disease, prophylaxis after kidney transplantation)

of 6 June 2024

At its session on 6 June 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. In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Letermovir in accordance with the resolution of 6 June 2024.

Letermovir

Resolution of: 6 June 2024
Entry into force on: 6 June 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 15 November 2023):

Prevymis is indicated for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-]. Consideration should be given to official guidelines on the appropriate use of antiviral active ingredients.

Therapeutic indication of the resolution (resolution of 6 June 2024):

See new therapeutic indication according to marketing authorisation.

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

CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor, for the prophylaxis of CMV disease

Appropriate comparator therapy:

Ganciclovir or valganciclovir

Extent and probability of the additional benefit of letermovir compared to valganciclovir:

An additional benefit is not proven.

Study results according to endpoints:[1]

CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor, for the prophylaxis of CMV disease

1 Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-137) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↑	Advantage in therapy discontinuation due to adverse events. In detail, disadvantage in general disorders and administration site conditions.
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		

MK-8228-002 study: RCT, comparison of letermovir vs valganciclovir, treatment until week 28 after kidney transplantation, observation until week 52 after kidney transplantation.

Mortality

Endpoint	Letermovir		Valganciclovir		Letermovir vs valganciclovir
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Overall mortality up to week 52	289	4 (1.4)	297	3 (1.0)	1.41 [0.32; 6.33]; 0.651

Morbidity

Endpoint	Letermovir		Valganciclovir		Letermovir vs valganciclovir
	N[a,b]	Patients with event n (%)	N[a,b]	Patients with event n (%)	Effect estimator RR [95% CI] p value[c]
Morbidity until week 52					
Graft loss	289	2 (0.7)	297	6 (2.0)	0.37[d] [0.09; 1.51]; 0.167
Severe CMV disease	289	35 (12.1)	297	34 (11.4)	1.06 [0.68; 1.65]; 0.796
Total hospitalisation	289	127 (43.9)	297	151 (50.8)	0.87 [0.73; 1.03]; 0.098
CMV end organ damage[e]	289	6 (2.1)	297	1 (0.3)	4.42[d] [0.99; 19.61]; 0.051
NODAT[f]	289	18 (6.2)	297	20 (6.7)	0.92 [0.50; 1.69]; 0.782
Health status (EQ-5D VAS) (improvement)[g]	284	100 (35.2)	294	98 (33.3)	1.06 [0.84; 1.32]; 0.639

Health-related quality of life

Endpoint	Letermovir		Valganciclovir		Letermovir vs valganciclovir
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value[c]
SF-36v2 (improvement at week 52)					
Physical Component Summary (PCS) score[h]	284	120 (42.3)	292	101 (34.6)	1.22 [0.99; 1.50]; 0.061
Mental Component Summary (MCS) score[i]	284	33 (11.6)	292	44 (15.1)	0.77 [0.51; 1.18]; 0.227
Physical functioning	284	136 (47.9)	292	141 (48.3)	0.99 [0.84; 1.17]
Physical role functioning	284	125 (44.0)	292	118 (40.4)	1.09 [0.90; 1.32]
Physical pain	284	119 (41.9)	292	106 (36.3)	1.15 [0.94; 1.41]

Endpoint	Letermovir		Valganciclovir		Letermovir vs valganciclovir
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value[c]
Perception of general health status	284	88 (31.0)	292	74 (25.3)	1.22 [0.94; 1.59]
Vitality	284	115 (40.5)	292	99 (33.9)	1.19 [0.96; 1.48]
Social functioning	284	88 (31.0)	292	83 (28.4)	1.09 [0.85; 1.40]
Emotional role functioning	284	64 (22.5)	292	60 (20.5)	1.10 [0.80; 1.50]
Psychological well-being	284	69 (24.3)	292	67 (22.9)	1.06 [0.79; 1.42]

Side effects

Endpoint	Letermovir		Valganciclovir		Letermovir vs valganciclovir
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value[j]
Side effects (until week 30)					
AEs (presented additionally)	292	271 (92.8)	297	276 (92.9)	–
SAEs	292	106 (36.3)	297	113 (38.1)	0.95 [0.77; 1.18]; 0.661
Discontinuation due to AEs	292	12 (4.1)	297	40 (13.5)	0.31 [0.16; 0.57]; < 0.001
Specific adverse events (until week 30)					
General disorders and administration site conditions (SOC, SAEs)	292	13 (4.5)	297	4 (1.4)	3.31 [1.09; 10.02]; 0.025

a. Full analysis set population, defined as all randomised patients who received at least one dose of the study medication, who were assigned to the seronegative recipient category and in whom no CMV deoxyribonucleic acid (DNA) was detectable on day 1 of treatment.
b. Endpoints in the morbidity category (except health status): missing values were replaced using the "observed failure" approach.
c. Cochran-Mantel-Haenszel method, stratified by induction therapy (administration vs non-administration), p value from Wald test.
d. Peto odds ratio (for event proportions of ≤ 1% or ≥ 99% in at least one treatment arm)
e. The following events have occurred: Gastrointestinal disorders and pneumonia, each in conjunction with CMV detection and confirmed by a blinded Clinical Adjudication Committee
f. Defined as the first occurrence of diabetes after kidney transplantation, according to WHO (World Health Organisation) and ADA (American Diabetes Association) guidelines.
g. Percentage of patients with an increase in the score by ≥ 15 points compared to the start of study at week 52 with a scale range of 0 to 100. Higher (increasing) values mean an improvement of health status.
h. Percentage of patients with improvement: Increase in PCS score by ≥ 9.4 points at week 32 compared to the start of study (corresponds to 15% of the scale range; normalised scale with a minimum of approximately 7 and a maximum of approximately 70).
i. Percentage of patients with improvement: Increase in MCS score by ≥ 9.6 points at week 32 compared to the start of study (corresponds to 15% of the scale range; normalised scale with a minimum of approximately 6 and a maximum of approximately 70).
j. Cochran-Mantel-Haenszel method, unstratified, p value from Wald test

Abbreviations used:
CMV: cytomegalovirus; CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of patients evaluated; NODAT: Newly occurred diabetes mellitus after transplantation; PCS: Physical Component Summary; RR: relative risk; SF-36v2: Short Form-36 Health Survey Version 2; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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

CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor, for the prophylaxis of CMV disease

Approx. 320 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 Prevymis (active ingredient: letermovir) at the following publicly accessible link (last access: 15 May 2024):

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

Treatment with letermovir should only be initiated and monitored by doctors experienced in treating patients who have received a kidney transplant.

4. Treatment costs

Annual treatment costs:

CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor, for the prophylaxis of CMV disease

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Letermovir	€ 33,600.56 - € 76,365.16
Appropriate comparator therapy:	
Ganciclovir	€ 8,100.96 - € 11,862.12
Valganciclovir	€ 3,652.11

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2024)

Costs for additionally required SHI services: not applicable

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:

CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor, for the prophylaxis of CMV disease

- 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.

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 6 June 2024.

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

Berlin, 6 June 2024

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

Prof. Hecken