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 (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: CMV reactivation/ disease, prophylaxis after stem cell 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. Annex XII is amended as follows:

1. The information on letermovir in the version of the resolution of 2 August 2018 (BAnz AT 28.02.2018 B3) is repealed.
2. Annex XII shall be amended in alphabetical order to include the active ingredient letermovir as follows:

Letermovir

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

Therapeutic indication (according to the marketing authorisation of 08 January 2018):

Prevymis is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). 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 therapeutic indication according to marketing authorisation.

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

Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant, for the prophylaxis of CMV disease

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of letermovir compared to a monitoring wait-and-see approach:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant, for the prophylaxis of CMV disease

1 Data from the dossier assessment of the IQWiG (A23-139) and from the addendum (A24-48), 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	↑	Advantage for severe CMV reactivation/ disease and clinically significant CMV infection.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences overall for the benefit assessment. In detail, disadvantage in nervous system disorders and advantage in renal and urinary disorders.
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: randomised controlled trial, double-blind, direct comparison of letermovir vs placebo, treatment until week 14 after stem cell transplantation, observation until week 48 after stem cell transplantation.

Mortality

Endpoint	Letermovir		Placebo		Letermovir vs placebo
	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	HR[b] or RR [95% CI]; p value
Overall survival (up to week 24)	325	n.r. 40 (12.3)	170	n.r. 32 (18.8)	HR: 0.62 [0.39; 0.98]; 0.042 RR: 0.65 [0.43; 1.001]; 0.052
Overall survival (up to week 48)[c]	325	n.r. 76 (23.4)	170	n.r. 46 (27.1)	HR: 0.79 [0.55; 1.14]; 0.214 RR: 0.86 [0.63; 1.19]; 0.422

Morbidity

Endpoint	Letermovir		Placebo		Letermovir vs placebo
	N[d]	Patients with event n (%)	N[d]	Patients with event n (%)	RR [95% CI]; p value[e]
Morbidity					
Clinically significant CMV infection (composite endpoint of "occurrence of CMV end organ damage" and "initiation of pre-emptive therapy")					
– week 24	325	57 (17.5)	170	71 (41.8)	0.42 [0.31; 0.56]; < 0.001
– occurrence of CMV end organ damage[f]					
– week 24	325	5 (1.5)	170	3 (1.8)	0.87 [0.21; 3.60]; 0.879
– week 48	325	8 (2.5)	170	6 (3.5)	0.70 [0.25; 1.98]; 0.571[g]
– initiation of pre-emptive therapy					
– week 24	325	52 (16.0)	170	68 (40.0)	0.40 [0.29; 0.55]; < 0.001
Severe CMV reactivation/ CMV disease[h] (week 48)	325	10 (3.1)	170	15 (8.8)	0.35 [0.16; 0.77]; 0.009
Total hospitalisation (Week 48)	325	181 (55.7)	170	103 (60.6)	0.92 [0.79; 1.07]; 0.325[g]
Acute GvHD[i] (Week 48)	325	85 (26.2)	170	48 (28.2)	0.93 [0.69; 1.25]; 0.638[g]

Endpoint;	Letermovir			Placebo			Letermovir vs placebo
	N[j]	Values at the start of study MV (SD)	Change at week 48 MV[k] (SE)	N[j]	Values at the start of study MV (SD)	Change at week 48 MV[k] (SE)	MD [95% CI] p value[k]
EQ-5D VAS[l]	243	62.9 (20.5)	14.0 (1.6)	135	62.3 (19.5)	10.7 (2.1)	3.27 [-0.91; 7.46]; 0.125

Health-related quality of life

Endpoint;	Letermovir			Placebo			Letermovir vs placebo
	N[j]	Values at the start of study MV (SD)	Change at week 48 MV[k] (SE)	N[a]	Values at the start of study MV (SD)	Change at week 48 MV[k] (SE)	MD [95% CI] p value[k]
FACT-BMT[m]							
Total score	258	99.0 (20.3)	8.6 (1.6)	138	99.2 (18.3)	5.5 (2.2)	3.11 [-1.63; 7.84]; 0.198
Physical well-being	258	17.6 (6.4)	4.4 (0.5)	138	17.9 (6.4)	3.6 (0.6)	0.86 [-0.32; 2.05]
Social/ family well-being	258	23.1 (3.9)	-1.5 (0.4)	138	23.0 (4.5)	-1.6 (0.5)	0.09 [-1.01; 1.18]
Emotional well-being	258	18.9 (3.8)	0.3 (0.3)	138	18.6 (3.9)	0.1 (0.4)	0.22 [-0.71; 1.15]
Functional well-being	258	14.4 (5.8)	2.8 (0.5)	138	14.6 (5.3)	2.1 (0.6)	0.64 [-0.74; 2.03]
Stem cell transplantation -specific subscale	258	25.1 (6.1)	2.6 (0.5)	138	25.1 (5.7)	1.3 (0.7)	1.28 [-0.18; 2.74]

Side effects

Endpoint	Letermovir		Placebo		Letermovir vs placebo
	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p value[n]
Side effects[o] (until week 16)					
AEs (presented additionally)	373	0.4 [0.4; 0.6] 357 (95.7)	192	0.6 [0.4; 0.7] 185 (96.4)	–
SAEs	373	15.3 [15.1; 15.6] 145 (38.9)	192	n.r. [11.1; n.c.] 72 (37.5)	0.90 [0.67; 1.19]; 0.450
Discontinuation due to AEs	373	n.r. 47 (12.6)	192	n.r. 21 (10.9)	1.06 [0.63; 1.78]; 0.818
Specific adverse events (until week 16)					

Endpoint	Letermovir		Placebo		Letermovir vs placebo
	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	N[a]	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p value[n]
Nervous system disorders (SOC, SAEs)	373	n.r. 12 (3.2)	192	n.r. 0 (0)	n.c.; 0.020
Renal and urinary disorders (SOC, SAEs)	373	n.r. 10 (2.7)	192	n.r. 11 (5.7)	0.39 [0.16; 0.92]; 0.032

a. Mortality, side effects: All-participants-as-treated population, defined as all randomised patients who received at least 1 dose of the study medication. Morbidity: EQ-5D-VAS and health-related quality of life:
b. Cox proportional hazards model, stratified by CMV risk group (high vs low), p value from Wald test
c. For 10 patients in the intervention arm and 4 patients in the comparator arm, no information is available on survival status after study discontinuation.
d. Full analysis set population, defined as all randomised patients who received at least 1 dose of the study medication and in whom no CMV viraemia was detected by the central laboratory at the start of treatment.
e. Cochran-Mantel-Haenszel method, stratified by CMV risk group (high vs low), p value from Wald test
f. The following events have occurred: gastrointestinal disorders (n = 11), pneumonia (n = 1) and retinitis (n = 2).
k. IQWiG calculation of RR, 95% CI (asymptotic) and p value (unconditional exact test, CSZ method)
h. Operationalised as re-admission to hospital due to CMV reactivation or CMV disease
i. Defined as acute GvHD with severity ≥ 2
j. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
k. cLDA model adjusted for CMV risk group (high vs low), taking into account the survey time points
l. Higher (increasing) values mean better symptomatology; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
m. Higher (increasing) values mean better health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range: Total score 0 to 148 points; physical well-being, social/ family well-being and functional well-being 0 to 28 points each; emotional well-being 0 to 24 points; stem cell transplant-specific subscale 0 to 40 points).
n. Cox proportional hazards model without stratification, p value from Wald test
o. Without taking into account the events of CMV infection, CMV viraemia, GvHD and bacterial and/or fungal infections

Abbreviations used:
cLDA: constrained Longitudinal Data Analysis; CMV: cytomegalovirus; FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant; GvHD: Graft-versus-Host Disease; HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; MD: mean difference; MV: mean value; N: number of patients evaluated; n.c.: not calculable; n.r. = not reached; RR: relative risk; SD: standard deviation; SE: standard error; 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

Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant, for the prophylaxis of CMV disease

Approx. 1,400 – 1,800 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 an allogeneic haematopoietic stem cell transplantation.

4. Treatment costs

Annual treatment costs:

Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant, for the prophylaxis of CMV disease

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Letermovir	€ 26,245.69 - € 38,178.08
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable"

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

Costs for additionally required SHI services:

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:

Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant, 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