Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient letermovir (Prevymis) was listed for the first time on 15 February 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

At its session on 2 August 2018, the G-BA decided on the benefit assessment of letermovir in the therapeutic indication "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)" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an

amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 15 December 2023, due to exceeding the € 30 million turnover limit within the period from December 2021 to November 2022.

On 15 November 2023, letermovir received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 12 December 2023, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient letermovir with the new therapeutic indication "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-]".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 March 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, the G-BA decided on the question on whether an additional benefit of letermovir compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG[1] according to the General Methods was not used in the benefit assessment of letermovir – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

2.1.1 Approved therapeutic indication of Letermovir (Prevymis) in accordance with the product information

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 06.06.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for letermovir:

Ganciclovir or valganciclovir

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the

Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to letermovir, the active ingredients ganciclovir (in patients with drug-induced immunosuppression (e.g. after organ transplant or chemotherapy for cancer)), valaciclovir (after organ transplant), valganciclovir (in CMV-negative patients who have received an organ transplant from a CMV-positive donor) and human cytomegalovirus immunoglobulin (in patients undergoing immunosuppressive therapy) are approved for the prophylaxis of cytomegalovirus disease.

on 2. In the present therapeutic indication, no non-medicinal measures are considered.

on 3. A resolution on the benefit assessment of new medicinal products according to Section 35a SGB V for the active ingredient letermovir in the indication "prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)" of 6 June 2024 is available.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

As part of the evidence search, the S2k guideline of the Society of Virology (GfV) and the German Association for the Control of Viral Diseases (DVV) on "viral infections in organ and allogeneic stem cell transplant recipients: diagnostics, prevention and therapy" and two systematic reviews were identified.

When determining the appropriate comparator therapy, it is assumed that the present therapeutic indication aims at prophylactic therapy and not pre-emptive therapy.

According to the guidelines, it is recommended that prophylaxis for six months or, if necessary, a pre-emptive strategy (with close monitoring) be carried out after kidney transplantation in high-risk constellations, i.e. in CMV-seronegative recipients and CMV-seropositive donors. The approved active ingredients ganciclovir and valganciclovir are recommended as priority medicinal therapy options for prophylaxis. Both active ingredients are considered equally appropriate.

According to the guideline, the additionally approved active ingredient valaciclovir is inferior to the use of ganciclovir and valganciclovir in terms of long-term renal function. CMV-specific immunoglobulins are approved for the prophylaxis of CMV infection in asymptomatic patients, but are not further recommended in the guidelines. Valaciclovir and CMV-specific immunoglobulins are therefore not designated as appropriate comparator therapy.

In the overall assessment of the available evidence, prophylaxis with ganciclovir or valganciclovir is determined as appropriate comparator therapy for adult, CMV-seronegative recipients [R-] who have received a kidney transplant from CMV-seropositive donors [D+] and for whom prophylaxis of cytomegalovirus (CMV) reactivation is indicated.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of letermovir is assessed as follows:

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits evaluations of the MK-8228-002 study. This is a randomised and double-blind study to investigate the efficacy and safety of letermovir in comparison with valganciclovir, which was conducted as a multicentre study at 94 study sites in 16 countries.

In this study, adult CMV-negative kidney transplant recipients from CMV-positive donors were randomised 1:1 to receive letermovir (N = 301) or valganciclovir (N = 300). 15 of the study participants received a dose of the study medication, but were not included in the evaluation of the efficacy endpoints because CMV viraemia was already detected at the start of study in a check-up, the result of which was available only after randomisation. The FAS (full analysis set) population thus consists of 586 (letermovir: N = 289; valganciclovir: N = 297) patients. Results in the side effects category are based on the all-participants-as-treated population (letermovir: N = 292; valganciclovir: N = 297).

According to the marketing authorisation, treatment began between the day of transplantation and up to 28 days after transplantation and continued until 28 weeks after

transplantation. In the intervention arm, acyclovir (400 mg orally twice daily) was also administered for the prophylaxis of herpes simplex virus (HSV) and varicella zoster virus (VZV) infections. Although no standard prophylaxis for HSV and VZV is recommended in the S2k guideline[2], this procedure is considered a possible approach based on the opinions from the written and oral statements.

The endpoints for mortality, morbidity and health-related quality of life were collected up to week 52 (end of observation) after transplantation, the adverse events up to week 30 (period of treatment with the study medication plus two weeks). For the assessment of additional benefit, the evaluations up to week 52, if available, are generally used, as these cover the longest observation periods.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, no statistically significant difference between the study arms were detected at the time of evaluation at week 52.

Morbidity

Graft loss

For the endpoint of overall mortality, no statistically significant difference between the study arms were detected at the time of evaluation at week 52.

The composite endpoint "dysfunction/ rejection of the transplant", which was also evaluated by the pharmaceutical company, is not used for assessment of the additional benefit. Graft loss is also a component here. Those other components that are based solely on a change in the glomerular filtration rate are not considered to be directly patient-relevant. The effects collected with the component "acute kidney transplant rejection" (side effects of the therapy of acute rejection and graft loss) are mapped by further endpoints.

Severe CMV disease and total hospitalisation

The endpoint of severe CMV disease is defined as new hospitalisation due to CMV disease after initial discharge from hospital (rehospitalisation). A reduction in hospital stays is fundamentally patient-relevant. At the time of evaluation at week 52, there was no statistically significant difference between the treatment arms.

There was also no statistically significant difference in the total hospitalisation rate at the same evaluation time.

CMV end organ damage

The endpoint of CMV end organ damage was operationalised as a clinical symptom in at least one organ system in addition to CMV detection. The events "gastrointestinal disorders" and

2 Society for Virology (GfV), 2019: Viral infections in organ and allogeneic stem cell transplant recipients: diagnostics, prevention and therapy; S2k guideline,

"pneumonia" occurred, which were associated with symptoms and therefore directly patient-relevant. There was no statistically significant difference between the treatment arms.

New onset diabetes mellitus after transplant (NODAT)

For the NODAT endpoint, defined as the first occurrence of (manifest) diabetes mellitus after kidney transplantation according to the criteria of the WHO and the American Diabetes Association, there was no statistically significant difference between the treatment groups. There was an effect modification by age, which showed an advantage of letermovir compared to valganciclovir for patients ≥ 65 years of age. However, this effect modification is not taken into account for the assessment of the entire target population, in particular due to the small sample size (no cases with letermovir; 4 cases with valganciclovir).

Health status (EQ-5D-VAS)

The patients' health status, which was mapped using the visual analogue scale of the EQ-5D (EuroQoL 5 Dimensions)-3L questionnaire, is patient-relevant. The evaluation of subjects with an improvement of at least 15% (15 points within a scale range of 100 points) showed no statistically significant difference between the treatment groups.

Quality of life

SF-36v2

Health-related quality of life was surveyed using the generic SF-36v2 instrument. Patients with an improvement of 9.4 points (physical component summary score) or 9.6 points (mental component summary score) were categorised as responders. This corresponds to an improvement of 15% of the respective scale range and is taken into account in the assessment of the additional benefit. In addition, the results for the subscales physical functioning, physical role functioning, physical pain, perception of general health status, vitality, social functioning, emotional role functioning and psychological well-being were evaluated. There was no statistically significant difference between the treatment arms in any of the summary scores.

Side effects

For the assessment of adverse events, the data at week 30 after transplantation, i.e. with a follow-up of 2 weeks after the end of therapy, were used.

In this evaluation, events that could be attributed to CMV infection were not excluded, as they only account for a negligible percentage of all events that occurred.

The percentage of patients with severe adverse events was comparable between the treatment arms. There was a statistically significant difference in favour of letermovir for the endpoint of therapy discontinuation due to adverse events. For the events that led to therapy discontinuation, there is insufficient information on the severity category to allow categorisation as serious or severe. The endpoint of therapy discontinuation due to adverse events is therefore assigned to the endpoint category of non-serious/ non-severe side effects.

For this endpoint, there is an effect modification based on the sex characteristic. The statistically significant advantage in the endpoint of therapy discontinuation due to adverse events was only observed in the male sex.

A detailed analysis of specific adverse events shows a statistically significant disadvantage of letermovir in the endpoint "General disorders and administration site conditions".

Overall assessment

In the endpoint categories of mortality, morbidity and health-related quality of life, there were neither advantages nor disadvantages of letermovir. In the endpoint category of side effects, an advantage of letermovir over valganciclovir was only seen in the endpoint of therapy discontinuation due to adverse events.

For this endpoint, however, there was an effect modification for the sex characteristic. The advantage was only evident in the sub-population of men, but not in the sub-population of women. Due to the low return rates in both treatment arms, there was also a high degree of uncertainty in the assessment of the endpoints of health status (EQ-5D-VAS) and health-related quality of life (SF-36v2).

In the overall assessment, the benefit observed exclusively in the endpoint of therapy discontinuation due to adverse events is considered insufficient to derive an additional benefit.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient letermovir. Letermovir (Prevymis) was approved as an orphan drug; the EUR 30 million turnover limit was exceeded.

The therapeutic indication assessed here is as follows: Prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R−].

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

The G-BA determined ganciclovir or valganciclovir as the appropriate comparator therapy.

The pharmaceutical company presents evaluations of RCT MK-8228-002, in which letermovir was compared with valganciclovir.

In the endpoint category of mortality, there was no statistically significant difference between the study arms. In the endpoint category of morbidity, the results for the endpoints of graft loss, severe CMV disease, total hospitalisation, CMV end organ damage, new onset diabetes mellitus after transplant (NODAT) and health status were evaluated. There were no advantages or disadvantages of letermovir for any of the endpoints.

In terms of health-related quality of life (surveyed using the SF36v2 questionnaire), there were also no advantages or disadvantages of letermovir.

In the endpoint category of side effects, an advantage of letermovir over valganciclovir was only seen in the endpoint of therapy discontinuation due to adverse events.

For this endpoint, however, there was an effect modification for the sex characteristic (the advantage was only observed in the sub-population for men). In the overall assessment, the

benefit observed exclusively in the endpoint of therapy discontinuation due to AEs is considered insufficient to derive an additional benefit. An additional benefit is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on patient number (approx. 320 patients) is based on the descriptions provided by the pharmaceutical company and the IQWiG assessment. On the one hand, there were uncertainties due to the restriction of hospital cases to specific diagnosis-related groups (DRGs) when determining those patients who received a kidney transplant in 2022. On the other, uncertainties also exist in the calculation of the percentage of CMV-seronegative patients, for which different figures can be derived from different sources. Overall, the patient numbers are considered plausible, although uncertainties must be assumed.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2024).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were calculated on the basis of the costs per pack after deduction of the statutory rebates.

The recommended dose of letermovir is 480 mg daily according to the product information. The dose should be reduced to 240 mg daily if letermovir is used in combination with ciclosporin. Treatment can be started on the day of the stem cell transplantation and can be continued no later than 7 days after the transplantation and for a period of 200 days after the transplantation.

The recommended dose of valganciclovir is 900 mg once daily according to the product information. Treatment should be started within 10 days of transplantation. The use of valganciclovir should be continued until 100 days after transplantation. Prophylaxis can be carried out up to 200 days after transplantation.

For treatment with ganciclovir, either maintenance treatment with 5 mg/kg once a day for 7 days a week or 6 mg/kg once a day for 5 days a week is recommended according to the product information. The duration of maintenance treatment depends on the risk of CMV disease according to the product information and it should be referred to local treatment guidelines. According to the S2k guideline "viral infections in organ and allogeneic stem cell transplant recipients: diagnosis, prevention and therapy", treatment with ganciclovir or valganciclovir is recommended as prophylaxis. It is also possible to switch between the two active ingredients at any time. Since the duration of use of ganciclovir can be different from patient to patient, the duration of valganciclovir use is shown analogously for the cost representation.

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Letermovir	Continuously, 1 x daily	194 – 201	1	194 – 201
Appropriate comparator therapy				
Ganciclovir	Continuously, 1 x daily	137 – 201	1	137 - 201
Valganciclovir	Continuously, 1 x daily	191 – 201	1	191 – 201

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[3] were used as a basis (average body weight 77.7 kg).

[3] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Letermovir oral	480 mg	480 mg	1 x 480 mg	194 – 201	191 x 480 mg – 201 x 480 mg
Letermovir IV	480 mg	480 mg	1 x 480 mg	194 – 201	194 x 480 mg – 201 x 480 mg
Appropriate comparator therapy					
Ganciclovir	5 mg/kg BW = 388.5 mg	5 mg/kg BW = 388.5 mg	1 x 500 mg	191 – 201	191 x 500 mg (= 191 x 10 ml) - 201 x 500 mg (= 201 x 10 ml)
	6 mg/kg BW = 466.2 mg	6 mg/kg BW = 466.2 mg	1 x 500 mg	137 – 144	137 x 500 mg (= 137 x 10 ml) - 144 x 500 mg (= 144 x 10 ml)
Valganciclovir	900 mg	900 mg	2 x 450 mg	191 – 201	382 x 450 mg – 402 x 450 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Letermovir 240 mg	28 FCT	€ 5,089.45	€ 2.00	€ 287.37	€ 4,800.08
Letermovir 240 mg	1 CIS	€ 196.70	€ 2.00	€ 10.26	€ 184.44
Letermovir 480 mg	28 FCT	€ 10,121.26	€ 2.00	€ 574.74	€ 9,544.52
Letermovir 480 mg	1 CIS	€ 382.06	€ 2.00	€ 20.53	€ 359.53
Appropriate comparator therapy					
Ganciclovir 500 mg	5 PCI	€ 305.27	€ 2.00	€ 13.95	€ 289.32
Valganciclovir 450 mg	60 FCT	€ 549.26	€ 2.00	€ 25.53	€ 521.73
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PCI = powder for concentrate for solution for infusion;					

LAUER-TAXE® last revised: 1 May 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

References:
Product information for letermovir (Prevymis); Prevymis 240 mg - 480 mg film-coated tablets/ concentrate for solution for infusion; last revised: November 2023

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 11 July 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 December 2023 the pharmaceutical company submitted a dossier for the benefit assessment of letermovir to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 14 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient letermovir.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2024. The deadline for submitting statements was 5 April 2024.

The oral hearing was held on 22 April 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 May 2024, and the proposed resolution was approved.

At its session on 6 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 July 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	16 April 2024	Information on written statements received, preparation of the oral hearing

Subcommittee Medicinal products	22 April 2024	Conduct of the oral hearing,
Working group Section 35a	29 April 2024 14 May 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 May 2024	Concluding discussion of the draft resolution
Plenum	6 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 June 2024

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

Prof. Hecken