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 (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

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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. 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. Prevymis for the prophylaxis of CMV reactivation/ disease after stem cell transplantation 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.

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. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO on 12 December 2023.

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), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of letermovir compared with the appropriate comparator therapy could be determined on the basis of 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of letermovir.

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:

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 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 06.06.2024):

see the approved therapeutic indication

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for letermovir:

Monitoring wait-and-see approach

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. The resolution on the benefit assessment of new medicinal products in accordance with Section 35a SGB V for the active ingredient letermovir of 2 August 2018 is available.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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.

The guidelines generally do not recommend prophylaxis after allo-HSCT, but only for high-risk patients (among others, active CMV infection before allo-HSCT, E+ or S+ patients after in vivo T-cell depletion). If prophylactic therapy is nevertheless indicated in this treatment setting, prophylactic administration of ganciclovir or valganciclovir can be possible, although this is burdened by the high risk of therapy-induced neutropenia, which represents a considerable problem, especially shortly after transplantation in the haematological reconstitution phase.

To minimise the CMV risk, the clinical scientific-medical societies recommend adequate donor selection with regard to CMV serostatus, prophylactic administration of the assessed letermovir in CMV-seropositive patients and prospective monitoring by means of CMV-PCR at least once a week. Pre-emptive administration of CMV-effective antivirals such as (val) ganciclovir or foscarnet should only take place in the case of clinically relevant viraemia.

In the overall assessment of the available evidence, "monitoring wait-and-see approach", i.e. not performing medicinal prophylaxis while continuing to observe the patient, is therefore defined as appropriate comparator therapy for adult, CMV-seropositive recipients after allogeneic haematopoietic stem cell transplantation for whom prophylaxis of cytomegalovirus (CMV) reactivation and disease is indicated. However, it is assumed that pre-emptive therapy will be initiated upon occurrence of a CMV infection.

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:

Hint for a non-quantifiable additional benefit.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits evaluations of the MK-8228-001 study. This is a randomised and double-blind study to investigate the efficacy and safety of letermovir in comparison with placebo, which was conducted as a multicentre study at 67 study sites in 20 countries.

In this study, adult CMV-positive recipients of an allogeneic stem cell transplant were randomised 2:1 to receive letermovir (N = 373) or placebo (N = 192) (all participants as treated, APaT population). 70 of the study participants received a dose of the study medication, but could not be 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 495 (letermovir: N = 325; placebo: N = 170) patients.

According to the marketing authorisation, treatment began between the day of transplantation and up to 28 days after transplantation and continued until the 100th day (14 weeks) after transplantation. The CMV-DNA concentration was regularly analysed in all study participants up to week 48 and pre-emptive therapy was initiated, if necessary. The appropriate comparator therapy "monitoring wait-and-see approach" is therefore considered to have been implemented.

According to the marketing authorisation, an extension of prophylaxis with letermovir beyond 100 days may be beneficial for some patients who are at high risk of late CMV reactivation. However, this possibility of extension did not exist in the MK-8228-001 study.

The endpoints of mortality, morbidity and health-related quality of life were collected at weeks 14, 24 and 48 respectively, and the adverse events at week 16. For the assessment of additional benefit, the evaluations up to week 48, if available, are generally used, as these cover the longest observation periods.

In addition, the pharmaceutical company presented evaluations of the retrospective observational study CELESTIAL. These data are not taken into account in the assessment of

additional benefit, as it was not possible to exclude relevant confounding variables due to the study design.

Extent and probability of the additional benefit

Mortality

At the time of evaluation at 48 weeks after stem cell transplantation, there was no statistically significant difference between the study arms. Information on survival status was missing for a total of 14 study participants, but this is of no consequence for the benefit assessment due to the small percentage that is also comparable in both study arms.

The first 6 months after transplantation are particularly important with regard to possible CMV reactivation and the any complications of an infection. Although there is a statistically significant difference in favour of letermovir for this period in the time-to-event analysis (effect estimate using hazard ratio) after 24 weeks, this advantage is not confirmed over the entire observation period of 48 weeks.

Morbidity

Clinically significant CMV infection, CMV organ disease and initiation of pre-emptive therapy

The occurrence of CMV organ disease is directly patient-relevant. With regard to the observed events, no statistically significant difference was detected between the treatment arms at any of the evaluation time points. Due to the high percentage of missing values compared to the actually observed events (> 30% in both treatment arms), the substitution strategy (non-completer = failure) implemented by the pharmaceutical company cannot be taken into account for the assessment of the additional benefit.

The initiation of pre-emptive therapy is triggered by CMV viraemia both in clinical practice and in the study, whereby the patient-individual assessment of the clinical symptomatology by the treating subject is also taken into account in the decision. In this therapeutic indication, this viraemia is always associated with the risk of a clinically relevant CMV infection. Due to this potentially life-threatening situation for patients, the endpoint is used for the benefit assessment in addition to the collection of the specific organ diseases. Data on this are available for week 24, which show a statistically significant difference in favour of letermovir. No data are available for the entire duration of the study up to week 48.

The endpoint "clinically significant CMV infection" is the primary endpoint of the study. It is made up of the endpoints "CMV organ disease" and "initiation of pre-emptive therapy". There was a statistically significant difference in favour of letermovir at week 24 due to the advantage in the component "initiation of pre-emptive therapy". No data are available for the composite endpoint at week 48.

Severe CMV reactivation/ CMV disease and total hospitalisation

The endpoint of severe CMV reactivation/ CMV disease is defined as re-hospitalisation due to CMV reactivation/ disease after initial discharge from hospital. A reduction in hospital stays is fundamentally patient-relevant. However, there is a risk of bias in the endpoints due to country and health-system-specific factors in a multicentre study design. At week 48, there

was a statistically significant difference in favour of letermovir. A high percentage of missing values also results in a risk of bias for this endpoint, particularly in view of the low number of events overall.

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

Acute graft-versus-host disease

Only acute graft-versus-host disease (GvHD) was categorised according to severity grade in the study. For the evaluation, the analyses of acute GvHD with severity grade ≥ 2, which requires the administration of systemic corticosteroids, are considered patient-relevant, as GvHD with severity grade 1 is potentially only based on changes in laboratory parameters. There were no statistically significant differences in the endpoint of acute graft-versus-host disease between the treatment groups.

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. In the evaluation of the continuous data, no statistically significant difference was detected between the treatment groups.

Quality of life

FACT-BMT

The FACT-BMT instrument for surveying quality of life consists of the generic questionnaire "Functional Assessment of Cancer Therapy – General" (FACT-G) and the 12-item scale "Bone Marrow Transplantation Subscale" (BMTS). The total score is sufficiently validated and the operationalisation is comprehensible. In the evaluation of the continuous data, which was carried out on the basis of 10 items of the BTMS subscale, there were no statistically significant differences between the treatment groups, neither for the total score nor for the subscales (physical well-being, social/ family well-being, emotional well-being, functional well-being and the stem cell transplant-specific subscale).

Side effects

In the MK-8228-001 study, adverse events were collected up to week 16 after transplantation, i.e. with a follow-up of 2 weeks after the end of therapy. The adverse events were therefore collected over a shorter period of time.

In this therapeutic indication, pre-emptive therapy, which is an essential component of the treatment strategy in the event of failure of prophylaxis with letermovir and in the case of monitoring wait-and-see approach, is initiated when CMV reactivation occurs.

Irrespective of a final assessment of the relevance of adverse events for the benefit assessment that occur under any subsequent pre-emptive therapy, the present assessment is based on the results on adverse events up to week 16 after transplantation.

There were no statistically significant differences between the treatment arms at week 16 for the endpoints of severe adverse events and therapy discontinuation due to AEs. The percentage of subjects with severe adverse events and a therapy discontinuation due to adverse events (excluding the events of CMV infection, CMV viraemia, GvHD and bacterial/ fungal infections as events marking the failure of prophylaxis) was comparable between the treatment arms. The presentation of the endpoints of CMV viraemia/ infection and GvHD in the endpoint category of morbidity already ensures collection of the differences between the groups, thereby eliminating the need for an additional evaluation in the endpoint category of side effects.

A detailed analysis of specific adverse events at week 16 shows a statistically significant disadvantage of letermovir in the endpoint "nervous system disorders" and a statistically significant advantage of letermovir in the endpoint "renal and urinary disorders".

Overall assessment

There is an advantage in overall mortality after a duration of observation of 24 weeks, but this is not confirmed after 48 weeks. In addition, advantages of letermovir over placebo were observed in the endpoint category of morbidity (in the endpoints of clinically significant CMV infection and severe CMV reactivation/ CMV disease). In other morbidity endpoints, health-related quality of life and side effects, there were neither clear advantages nor disadvantages of letermovir.

In the overall assessment, an additional benefit is therefore identified, based on the results for the endpoints of clinically significant CMV infection and severe CMV reactivations/ CMV disease.

There are uncertainties in the results for the endpoints of occurrence of CMV end organ damage, severe CMV reactivation/ disease and acute GvHD due to the high percentage of missing values. In addition, uncertainties result from the shortened duration of observation of the endpoints in the side effects category.

Due to this data basis, the extent of the additional benefit is assessed as non-quantifiable overall.

Reliability of data (probability of additional benefit)

Uncertainties must be taken into account in the available data, as prolonged prophylaxis with letermovir may be considered for some patients with a high risk of late CMV reactivation. However, this was not carried out in the MK-8228-001 study.

Due to the low return rates in both treatment arms, there is a high degree of uncertainty in the assessment of the endpoints of health status (EQ-5D-VAS) and health-related quality of life (FACT-BMT).

In addition, the risk of bias is considered high for severe CMV reactivation/ disease due to the health system-specific factors in hospitalisations. For these reasons, the reliability of data can be categorised as a hint.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient letermovir due to the exceeding of the € 30 million turnover limit.

Letermovir (Prevymis) was approved as an orphan drug. The therapeutic indication assessed here is as follows: Prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

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

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

The pharmaceutical company presents evaluations of the RCT MK-8228-001, in which letermovir was compared with placebo. The retrospective observational study CELESTIAL is not considered, as it was not possible to exclude relevant confounding variables due to the study design.

Although there was a statistically significant difference in favour of letermovir for the endpoint of overall mortality after 24 weeks, this advantage was not confirmed over the entire observation period of 48 weeks. In the endpoint category of morbidity, there is an advantage in the endpoint of severe CMV reactivation/ CMV disease and in the endpoint of clinically significant CMV infection. In other morbidity endpoints (health status, graft-versus-host disease), in health-related quality of life (surveyed using the FACT-BMT questionnaire) and in side effects, there were neither advantages nor disadvantages of letermovir.

However, due to the high percentage of missing values in the results for the endpoints of occurrence of CMV end organ damage, severe CMV reactivation/ disease and acute GvHD, there is a high degree of uncertainty in the assessment of these endpoints. In addition, uncertainties result from the shortened duration of observation for the endpoints in the side effects category.

For patients with a high risk of late CMV reactivation, prolonged prophylaxis with letermovir is an option, but this was not carried out in the study. Due to the low return rates, there is also a high degree of uncertainty in the assessment of the endpoints of health status and health-related quality of life. For severe CMV reactivation/ disease, the risk of bias is considered high due to health system-specific factors in hospitalisations. For these reasons, the reliability of data is classified as a hint.

In the overall assessment, a hint for a non-quantifiable additional benefit of letermovir over monitoring wait-and-see approach is identified.

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

The information on patient number (approx. 1,400 – 1,800 patients) is based on the descriptions provided by the pharmaceutical company and the IQWiG assessment. In the pharmaceutical company's current calculations, there are uncertainties due to the restriction of hospital cases to specific diagnosis-related groups (DRGs) when determining those patients who received an allogeneic haematopoietic stem cell transplantation in 2022. In addition, when calculating the percentage values for CMV-positive patients, the pharmaceutical company implicitly assigns those recipients for whom there is no information on CMV

serostatus to the group of seronegative patients. Overall, this result for patient numbers (1,363 – 1,433 patients) must therefore be assumed to be an underestimate. For this reason, the higher figures from the resolution of 2 August 2018 (1,800 patients) are used for the upper limit. However, these are also subject to uncertainties due to the estimates made on the basis of DRG evaluations, the extrapolation of the figures for 2018 and the estimate of the number of CMV-seropositive patients and may be both underestimated and overestimated.

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 an allogeneic haematopoietic stem cell transplantation.

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.

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.

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 transplant and no later than 28 days after the transplantation. Prophylaxis with letermovir should be continued for a period of 100 days after transplantation.

Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant, 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	73 - 101	1	73 - 101
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

Consumption:

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	73 – 101	73.0 x 480 mg - 101.0 x 480 mg
Letermovir IV	480 mg	480 mg	1 x 480 mg	73 – 101	73.0 x 480 mg - 101.0 x 480 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

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
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

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:

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.

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, no. 6 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.

By letter dated 22 April 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 8 May 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, Commissioning of the IQWiG with the supplementary assessment of documents
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