Gemeinsamer Bundesausschuss

Justification

to 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 reactivation/ disease, prophylaxis after stem cell transplant, < 18 years, ≥ 5 kg)

of 6 November 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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 decide 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 (letermovir) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indications, the sales volume of letermovir with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore be provided for letermovir in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 25 April 2025, 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 14 May 2025, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company have submitted a dossier in due time 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 cytomegalovirus (CMV) reactivation and disease in paediatric patients weighing at least 5 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)"

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 August 2025 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 as well as the addendum to the benefit assessment prepared by IQWiG, 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 have 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 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:

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 and paediatric patients weighing at least 5 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

Therapeutic indication of the resolution (resolution of 6 November 2025):

PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in paediatric patients weighing at least 5 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant aged 0 to < 18 years weighing at least 5 kg for whom prophylaxis of cytomegalovirus (CMV) reactivation and disease is indicated

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)), valganciclovir (in CMV-negative adults and children who have received an organ transplant from a CMV-positive donor) and human cytomegalovirus immunoglobulin (in patients undergoing immunosuppressive therapy, in particular transplant recipients) are approved for the prophylaxis of cytomegalovirus disease in children and adolescents. Valaciclovir is approved for adolescents who have received an organ transplant. In addition, the active ingredient foscarnet is approved for the treatment of cytomegalovirus infection in children and adolescents in the therapeutic indication, but not for prophylaxis.

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

On 3. There are no resolutions on the prophylaxis of CMV disease/ reactivation in children and adolescents who have received an allogeneic haematopoietic stem cell transplant. 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" was identified.

It is assumed that the present therapeutic indication aims at preventive therapy and not pre-emptive therapy.

The guideline recommends prophylaxis with letermovir until day 100 for CMV-positive recipients of allogeneic haematopoietic stem cell transplant in adulthood and until day 200 for high-risk patients in adulthood who have received allogeneic haematopoietic stem cell transplant. In exceptional cases (e.g. pre-existing resistance to letermovir or as part of secondary prophylaxis), a prophylactic strategy with ganciclovir or valganciclovir can be carried out. However, it must be taken into account that preventive therapy with ganciclovir or valganciclovir may be associated with a high risk

of therapy-induced neutropenia, which poses a major problem, especially shortly after transplantation in the haematological reconstitution phase.

The recommendations in the guideline relate to adults and children. However, differentiated recommendations for the prophylaxis of cytomegalovirus (CMV) reactivation and disease in children and adolescents are not made.

In the overall assessment of the available evidence, "monitoring wait-and-see approach", i.e. not performing medicinal prophylaxis while continuing to observe the children and adolescents, is therefore defined as the appropriate comparator therapy for CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant aged 0 to < 18 years weighing at least 5 kg and for whom prophylaxis of cytomegalovirus (CMV) reactivation and disease is indicated.

It is assumed that pre-emptive therapy will be initiated upon occurrence of CMV reactivation and disease.

Placebo can also be used in the comparator arm for the purpose of blinding in order to implement the appropriate comparator therapy "monitoring wait-and-see approach".

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:

<u>CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant aged 0 to < 18 years weighing at least 5 kg for whom prophylaxis of cytomegalovirus (CMV) reactivation and disease is indicated</u>

- Hint for a non-quantifiable additional benefit.

Justification:

The pharmaceutical company submitted the results of the MK-8228-030 study (P030). This is an open-label, single-arm phase 2b study for the assessment of pharmacokinetics, efficacy, safety and tolerability of letermovir in the prophylaxis of cytomegalovirus infection in children and adolescents aged 0 to <18 years who are at risk of developing clinically significant cytomegalovirus infection following an allogeneic haematopoietic stem cell transplant. Depending on their age, patients were enrolled in one of the following groups: age group 1 (12 to < 18-year-olds; N = 28), age group 2 (2 to < 12-year-olds; N = 29) and age group 3 (< 2-year-olds; N = 8). Of the 65 patients enrolled, 63 received at least a dose of the study medication. On day 1 (at the first administration of the study medication), 7 (11%) of the treated patients had detectable CMV viraemia. In addition, 7 (11%) seronegative recipients of a stem cell transplant are included in the analysis population.

The primary endpoint was the assessment of pharmacokinetics, secondary endpoints were clinically significant CMV infections in the morbidity category as well as endpoints in the side effects category.

The pharmaceutical company transferred the results for the adult age group from the MK-8228-001 RCT (P001) to the paediatric population due to absence of comparator data for the assessment of the additional benefit compared to the appropriate comparator therapy. By resolution of 6 June 2024, a hint for a non-quantifiable additional benefit of letermovir over the monitoring wait-and-see approach was identified due to the advantages in the morbidity endpoint category in the endpoint "severe CMV reactivation/ CMV diseases" and in the endpoint "clinically significant CMV infection" for the adult population.

Assessment with regard to transfer of additional benefit

The transferability of the results is based on the following aspects.

The appropriate comparator therapy (monitoring wait-and-see approach) determined by the G-BA is identical for all paediatric and adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant with an indication for prophylaxis of cytomegalovirus (CMV) reactivation and disease. As a result, a decisive criterion for transfer of evidence in the context of the early benefit assessment is given.

For the acceptance of evidence based on a low degree of evidence, the specificities and limitations of the conduct of paediatric clinical studies on rare diseases in particular will also be taken into account.

In addition, sufficient similarity in pathogenesis and clinical picture between the patient populations is a decisive criterion for transfer of evidence. The assessment report of the regulatory authority European Medicines Agency (EMA) states that the transfer of the results from older patients to children and adolescents is considered appropriate, as the pathogenesis of CMV infection (viraemia) and disease as well as the mode of action of letermovir are not expected to differ in paediatric patients compared to adults.[1] The statements made by clinical experts at the oral hearing confirm this estimate.

[1] European Medicines Agency. Prevymis; Assessment report [online]. 2025 [accessed: 07.10.2025]. P. 37 URL: https://www.ema.europa.eu/en/documents/variation-report/prevymis-h-c-004536-x-0037-g-epar-assessment-report-variation_en.pdf

Identically operationalised morbidity data for adults, adolescents and children are available for the endpoint "clinically significant CMV infection at week 24" after transplantation. In the P030 study, the percentage of participants with a clinically significant cytomegalovirus infection, defined as the occurrence of cytomegalovirus end organ damage or the initiation of pre-emptive anti-cytomegalovirus therapy due to documented cytomegalovirus viraemia, was 10.7% at week 24 post-transplantation, thus being below the percentage value of the total populations of the P001 study (17.5%). The results were comparable in all three age groups (12 to under 18 years, 2 to under 12 years and under 2 years). No cases of cytomegalovirus end organ damage have been observed.

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.

In view of the fact that a sufficiently comparable treatment setting exists, and taking into account the EMA's findings on the medical rationale for data transfer and the observed unidirectional effects in the morbidity endpoint "clinically significant CMV infection at week 24", transferability of the positive effects of letermovir from the population of adults to the population of children and adolescents (< 18 years) is assumed and a non-quantifiable additional benefit is derived.

Reliability of data (probability of additional benefit)

Taking into account the uncertainties identified in relation to the P001 study and those arising from transferring the additional benefit to a younger patient population, only a hint regarding the reliability of the data can be identified.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient letermovir.

The therapeutic indication assessed here relates to the patient population of children and adolescents aged 0 to < 18 years and is as follows: "for prophylaxis of cytomegalovirus (CMV) reactivation and disease in paediatric patients weighing at least 15 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)".

The "monitoring wait-and-see approach" was determined as the appropriate comparator therapy.

No direct comparator study data are available for the population of children adolescents (< 18 years). Nevertheless, advantages can also be derived for this patient population by transfer of evidence of the results from older patients. Particularly in view of the fact that a sufficiently comparable treatment setting exists, and taking into account the EMA's findings on the medical rationale for data transfer and the observed unidirectional effects in the morbidity endpoint "clinically significant CMV infection at week 24", transferability of the positive effects of letermovir from the population of adults to the population of children and adolescents (< 18 years) is assumed and a non-quantifiable additional benefit is derived.

Due to the uncertainty caused by the transfer of the additional benefit to a younger patient population, a hint for reliability of data can only be identified.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the IQWiG information from the benefit assessment.

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: 14 July 2025):

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 transplant or kidney transplant.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 September 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

The dosage of Letermovir depends on body weight (BW). For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) 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 – body measurements of the population" were used as a basis.

For infants aged 0 years 7.6 kg body weight, for children aged 6 to under 7 years 23.6 kg body weight and for children aged 11 to under 12 years 42.1 kg body weight.[2] For adolescents aged 17 years, an average body weight of 67.2 kg is used as the basis for cost calculation.[3]

In the case of concomitant use of ciclosporin, a dose adjustment is necessary for paediatric patients weighing at least 30 kg who have received a HSCT. The recommended daily dose of 480 mg should be reduced to 240 mg. In the MK-8228-030 study, 66.7% of paediatric patients had ciclosporin administration, so the dose adjustment was taken into account in the cost calculation.

Treatment can be started on the day of the stem cell transplant and no later than 28 days post-transplantation. Prophylaxis with letermovir should be continued for a period of 100 days post-transplantation.

[2] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 0 to 11 years), www.gbe-bund.de

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 17 years), www.gbe-bund.de

CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant aged 0 to < 18 years weighing at least 5 kg for whom prophylaxis of cytomegalovirus (CMV) reactivation and disease is indicated

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 CIS (240 mg)	<u>< 30 kg</u> 40 mg – 120 mg	40 mg – 120 mg	1 x 240 mg	73 - 101	73 x 240 mg – 101 x 240 mg
FCT or CIS	<u>> 30 kg:</u> 240 mg[4] – 480 mg	240 mg – 480 mg	1 x 240 mg – 1 x 480 mg		73 x 240 mg – 101 x 480 mg
Appropriate comparator therapy					
monitoring wait-and-see approach	Not calculable				

[4] In combination with ciclosporin

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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	1 CIS	€ 196.70	€ 1.77	€ 10.26	€ 184.67
Letermovir 480 mg	1 CIS	€ 382.06	€ 1.77	€ 20.53	€ 359.76
Letermovir 240 mg	28 FCT	€ 5,089.45	€ 1.77	€ 287.37	€ 4,800.31
Letermovir 480 mg	28 FCT	€ 10,121.26	€ 1.77	€ 574.74	€ 9,544.75
Appropriate comparator therapy					
monitoring wait-and-see approach	Not calculable				
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 September 2025

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 had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation. According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges of a maximum of € 39 per ready-to-use unit are incurred for the preparation of
infusion solutions containing antibiotics and virustatics. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 designate 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 have 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 have 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 requirements 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 have 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-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant aged 0 to < 18 years weighing at least 5 kg for whom prophylaxis of cytomegalovirus (CMV) reactivation and disease is indicated

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:

Product information for letermovir (Prevymis); PREVYMIS® 240 mg/ 480 mg concentrate for solution for infusion; last revised: April 2025

Product information for letermovir (Prevymis); PREVYMIS® 240 mg/ 480 mg film-coated tablets; last revised: April 2025

Product information for letermovir (Prevymis); PREVYMIS ® granules in sachet. Last revised: April 2025

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 their session on 12 March 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 May 2025, 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 15 May 2025 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 06 August 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 August 2025. The deadline for submitting statements was 5 September 2025.

The oral hearing was held on 22 September 2025.

By letter dated 23 September 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 10 October 2025.

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 October 2025, and the proposed draft resolution was approved.

At their session on 6 November 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 March 2024	Determination of the appropriate comparator therapy
Working group Section 35a	16 September 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 September 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 September 2025 14 October 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 October 2025	Concluding discussion of the draft resolution
Plenum	6 November 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 November 2025

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

Prof. Hecken