Letermovir (CMV prophylaxis after stem cell transplantation, < 18 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Letermovir, Cytomegalovirus Infections, Child, Child – Preschool, Adolescent, Benefit Assessment

Medical and scientific advice

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the patient organization 'Förderkreis für krebskranke Kinder und Jugendliche Bonn e. V.' for participating in the written exchange and for their suppport. The respondent and the 'Förderkreis für krebskranke Kinder und Jugendliche Bonn e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CMV	cytomegalovirus
DNA	deoxyribonucleic acid
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug letermovir. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 15 May 2025.

Research question

The aim of this report is to assess the added benefit of letermovir compared with watchful waiting as the appropriate comparator therapy (ACT) used for prophylaxis of cytomegalovirus (CMV) reactivation and disease in paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of letermovir

Therapeutic indication	**ACT**[a]
Prophylaxis of CMV reactivation and disease in paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee	

The company named watchful waiting as the ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company, the review of the completeness of the study pool did not identify any randomized controlled trials (RCTs) on the direct comparison of letermovir versus the ACT in the given therapeutic indication.

Due to the lack of studies of direct comparison, the company conducted an information retrieval for non-randomized controlled trials with the intervention and identified the single-arm study MK-8228-030. Furthermore, the company conducted an exploratory information retrieval for clinical studies for the ACT, but was unable to identify any suitable studies. For

the assessment of the added benefit, the company sought to transfer study results from adult patients in the therapeutic indication to the paediatric population relevant for this benefit assessment. To this end, the company drew on the single-arm study MK-8228-030 in paediatric patients and the RCT MK-8228-001 in adults, which it had already presented in the procedure for the benefit assessment of letermovir in adults in the therapeutic indication.

The data presented by the company were unsuitable for drawing any conclusions on the added benefit of letermovir in comparison with the ACT for the population of the present research question. The evidence presented by the company is described below, and the reasons for its unsuitability for the benefit assessment are provided.

Data presented by the company

Study MK-8228-030 in paediatric patients

Study MK-8228-030 is a completed single-arm study investigating treatment with letermovir in patients < 18 years. The study enrolled paediatric recipients of an allogeneic haematopoietic stem cell transplant. The stem cell transplant must have taken place no more than 28 days before inclusion in the study. Participation in the study required a negative test for CMV deoxyribonucleic acid (DNA) from a plasma or whole blood sample taken within 5 days prior to inclusion in the study.

Depending on their age, patients were allocated to 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) or age group 3 (< 2-year-olds; N = 8). The study medication could be administered either orally (film-coated tablets or granules) or as an intravenous infusion. Treatment with letermovir was started within 28 days after a stem cell transplant and continued until 100 days (14 weeks) after the stem cell transplant.

The primary outcome of MK-8228-030 was the pharmacokinetics of letermovir. Secondary outcomes were clinically significant CMV infections and outcomes in the side effects category.

Approach and reasoning of the company on the transferability of the study results

The company drew on the results of the single-arm study MK-8228-030 on paediatric patients described above, and additionally transferred the results from the adult age group from RCT MK-8228-001 to the paediatric population. The RCT MK-8228-001 was the subject of the dossier assessment as part of the procedure for the benefit assessment of letermovir in adults in this therapeutic indication. The company justified the transfer with what it considered to be comparability of the mode of action, the disease profile and the results with regard to all-cause mortality, clinically significant CMV infections and side effects between adult and paediatric patients. The company considered the characteristics of the studies and study populations to be comparable.

Assessment of the data presented by the company

The study MK-8228-030 used by the company for the paediatric population of the present research question is a single-arm study that does not allow a comparison versus the ACT. Thus, this study is not suitable for assessing the added benefit of letermovir in comparison with watchful waiting as the ACT in the therapeutic indication in question.

Due to the lack of studies of direct comparison in paediatric patients, the company's approach of transferring study results from adult patients to the population of the present research question is understandable. However, the company did not provide any studies or other information on the basis of which it assessed the course of the disease under the ACT (watchful waiting) for the population of the research question. For the ACT, the company conducted only an exploratory information retrieval on clinical studies in the population of the research question at hand. However, the company did not present a systematic information retrieval that would be suitable for identifying all potentially relevant studies on the ACT. The company did not conduct any information retrieval for the adult population.

In order to assess whether a transfer of the study results from adult to paediatric patients is possible, a complete comparison of all data relevant for the transfer for the different age groups would be required. However, for adult patients in the present therapeutic indication, the company did not present any processed data for the transfer from the MK-8228-001 study it drew upon. In its reasoning, the company only cited results for the adult age group in the running text. Subgroup analyses for the characteristic age, especially in the directly adjacent age group, were completely missing in the company's dossier. The company also did not provide a comparison of the data in the dossier for the assessment of the comparability of the studies and study populations. The insufficiently processed data presented by the company were therefore not suitable for transferring the results from adult to paediatric patients.

Regardless of this, the outcome of severe CMV reactivation/CMV disease was not recorded in MK-8228-030 on paediatric patients, although the added benefit of letermovir for the adult population is largely based on this outcome. It was therefore not possible to transfer the added benefits observed in adult patients to the paediatric population, irrespective of the deficiencies in the company's information retrieval process and the insufficient processing of the data.

Results on added benefit

Since no suitable data were available for the benefit assessment, there is no hint of an added benefit of letermovir in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of letermovir.

Table 3: Letermovir – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Prophylaxis of CMV reactivation and disease in paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of letermovir compared with watchful waiting as the ACT used for prophylaxis of CMV reactivation and disease in paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of letermovir

Therapeutic indication	**ACT**[a]
Prophylaxis of CMV reactivation and disease in paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee	

The company named watchful waiting as the ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on letermovir (status: 20 February 2025)
- Bibliographical literature search on letermovir (last search on 17 February 2025)
- Search of trial registries/trial results databases for studies on letermovir (last search on 17 February 2025)
- Search on the G-BA website for letermovir (last search on 18 February 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on letermovir (last search on 26 May 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the review of the completeness of the study pool did not identify any RCTs on the direct comparison of letermovir versus the ACT in the given therapeutic indication.

Due to the lack of studies of direct comparison, the company conducted an information retrieval for non-randomized controlled trials with the intervention and identified the single-arm study MK-8228-030 [3]. Furthermore, the company conducted an exploratory information retrieval for clinical studies for the ACT, but was unable to identify any suitable studies. For the assessment of the added benefit, the company sought to transfer study results from adult patients in the therapeutic indication to the paediatric population relevant for this benefit assessment. To this end, the company drew on the single-arm study MK-8228-030 in paediatric patients and the RCT MK-8228-001 in adults, which it had already presented in the procedure for the benefit assessment of letermovir in adults in the therapeutic indication [4].

The data presented by the company were unsuitable for drawing any conclusions on the added benefit of letermovir in comparison with the ACT for the population of the present research question. The evidence presented by the company is described below, and the reasons for its unsuitability for the benefit assessment are provided.

I 3.1 Data presented by the company

Study MK-8228-030 in paediatric patients

Study MK-8228-030 is a completed single-arm study investigating treatment with letermovir in patients < 18 years. The study enrolled paediatric recipients of an allogeneic haematopoietic stem cell transplant. The stem cell transplant must have taken place no more

than 28 days before inclusion in the study. Participation in the study required a negative test for CMV DNA from a plasma or whole blood sample taken within 5 days prior to inclusion in the study.

Depending on their age, patients were allocated to 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) or age group 3 (< 2-year-olds; N = 8). According to inclusion criteria, a positive CMV serostatus had to be documented for the recipient of the stem cell transplant [R+] for age group 1. For age groups 2 and 3, a positive CMV serostatus had to be documented for the recipient [R+] and/or for the donor [D+]. The company's analysis population (N = 63) included a total of 7 (11%) seronegative recipients who were not part of the therapeutic indication to be assessed (see Table 4).

The study medication could be administered either orally (film-coated tablets or granules) or as an intravenous infusion. Treatment with letermovir was started within 28 days after a stem cell transplant and continued until 100 days (14 weeks) after the stem cell transplant. According to the summary of product characteristics (SmPC), prolonged letermovir prophylaxis beyond 100 days after a stem cell transplant may be of benefit in some patients at high risk for late CMV reactivation [5-7]. However, prolonged prophylaxis was not possible in MK-8228-030. In the event of CMV end-organ disease or initiation of pre-emptive therapy due to documented CMV viraemia and the clinical condition of the patient, treatment with the study medication was discontinued and treatment according to local practice could be initiated.

The primary outcome of MK-8228-030 was the pharmacokinetics of letermovir. Secondary outcomes were clinically significant CMV infections and outcomes in the side effects category.

Approach and reasoning of the company on the transferability of the study results

The company drew on the results of the single-arm study MK-8228-030 on paediatric patients described above, and additionally transferred the results from the adult age group from RCT MK-8228-001 [8,9] to the paediatric population. The RCT MK-8228-001 was the subject of the dossier assessment as part of the procedure for the benefit assessment of letermovir in adults in this therapeutic indication [10,11]. The company justified the transfer with what it considered to be comparability of the mode of action, the disease profile and the results with regard to all-cause mortality, clinically significant CMV infections and side effects between adult and paediatric patients. The company considered the characteristics of the study populations to be comparable, stating that in both studies the majority of patients were male and white. According to the company, the characteristics of MK-8228-030 and MK-8228-001 were also comparable in most respects. In its dossier, the company stated that the primary, secondary and exploratory outcomes were comparable and largely identically

operationalized, the planned observation periods were identical, and both studies were transferable to the German health care context.

I 3.2 Assessment of the data presented by the company

The data presented by the company were unsuitable for the benefit assessment of letermovir in comparison with the ACT. The reasons for this are provided below.

Single-arm study unsuitable for the benefit assessment

The study MK-8228-030 used by the company for the paediatric population of the present research question is a single-arm study that does not allow a comparison versus the ACT. Thus, this study is not suitable for assessing the added benefit of letermovir in comparison with watchful waiting as the ACT in the therapeutic indication in question.

Transfer of results from adult patients to the target population not suitable

The company's approach of transferring study results from adult patients to the population of the present research question would be plausible in view of the lack of studies of direct comparison in paediatric patients. However, the implementation of this by the company was not suitable for the following reasons.

The dossier contained a single-arm study on letermovir for the population of paediatric patients in the therapeutic indication to be assessed. However, the company did not provide any studies or other information on the basis of which it assessed the course of the disease under the ACT (watchful waiting) for the population of the research question. For the ACT, the company conducted only an exploratory information retrieval on clinical studies in the population of the research question at hand. However, the company did not present a systematic information retrieval that would be suitable for identifying all potentially relevant studies on the ACT. The company did not conduct any information retrieval for the adult population.

In order to assess whether a transfer of the study results from adult to paediatric patients is possible, a complete comparison of all data relevant for the transfer for the different age groups would be required. However, for adult patients in the present therapeutic indication, the company did not present any processed data for the transfer from the MK-8228-001 study it drew upon. In its reasoning, the company only cited results for the adult age group in the running text. Subgroup analyses for the characteristic age, especially in the directly adjacent age group, were completely missing in the company's dossier. The company also did not provide a comparison of the data in the dossier for the assessment of the comparability of the studies and study populations. The insufficiently processed data presented by the company were therefore not suitable for transferring the results from adult to paediatric patients.

Regardless of this, the outcome of severe CMV reactivation / CMV disease (operationalized as readmission to hospital due to CMV reactivation or CMV disease) was not recorded in MK-8228-030 on paediatric patients, although the added benefit of letermovir for the adult population is largely based on this outcome (see dossier assessment and addendum to commissions A23-139 and A24-48 [10,11]). It was therefore not possible to transfer the added benefits observed in adult patients to the paediatric population, irrespective of the deficiencies in the company's information retrieval process and the insufficient processing of the data.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of letermovir compared with watchful waiting as the ACT used for prophylaxis of CMV reactivation and disease in paediatric patients who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant. There is no hint of an added benefit of letermovir in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of letermovir in comparison with the ACT.

Table 5: Letermovir – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Prophylaxis of CMV reactivation and disease in paediatric patients with a body weight of at least 5 kg who are CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant	Watchful waiting[b]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. It is assumed that pre-emptive therapy is initiated if a CMV infection occurs. ACT: appropriate comparator therapy; CMV: cytomegalovirus; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit based on the transfer of evidence.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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