9 January 2018
EMA/785410/2017
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Prevymis (letermovir)
Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk
EU/3/11/849 (EMA/OD/090/10)
Sponsor: Merck Sharp & Dohme Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Product and administrative information

Product	
Active substance	(S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid
International Non-Proprietary Name	Letermovir
Orphan indication	Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk
Pharmaceutical form	Film-coated tablets Concentrate for solution for infusion
Route of administration	Oral use Intravenous use
Pharmaco-therapeutic group (ATC Code)	Antivirals for Systemic Use, ATC code: J05AX18
Sponsor's details:	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	AiCuris GmbH & Co. KG
COMP opinion date	12 January 2011
EC decision date	15 April 2011
EC registration number	EU/3/11/849
Post-designation procedural history	
Transfer of sponsorship	Transfer from AiCuris GmbH & Co. KG to Merck Sharp & Dohme Limited – EC decision of 15 March 2013
Marketing authorisation	
Rapporteur / co-Rapporteur	F.Josephson / S. B. Sarac
Applicant	Merck Sharp & Dohme Limited
Application submission date	31 March 2017
Procedure start date	20 April 2017
Procedure number	EMA/H/C/H0004536
Invented name	Prevymis
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). Further information on Prevymis can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	9 November 2017
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	A. Magrelli/ F. Naumann-Winter
Sponsor's report submission date	3 April and 10 August 2017

COMP discussion and adoption of list of questions	5-7 September 2017
Sponsor's response to list of questions	19 October 2017
Oral explanation	30 October 2017
COMP opinion date	17 November 2017

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

- the population of patients eligible for prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk (hereinafter referred to as "the condition") was estimated to be approximately 3.1 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life threatening due to complications such as pneumonitis, hepatitis, inflammation of the gastrointestinal tract and reduced graft survival in transplanted patients;
- although satisfactory methods of prevention of the condition have been authorised in the European Union, sufficient justification has been provided that (S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid may be of significant benefit to the population at risk of developing the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the new mechanism of action which may confer improved efficacy in resistant CMV strains. This is in line with the preclinical studies and preliminary clinical data presented.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that Cytomegalovirus disease in patients with impaired mediated immunity deemed at risk is a distinct medical entity which was the indication that they obtained in their orphan designation in 2010. For this application the COMP agreed to expand this orphan condition to just cytomegalovirus disease.

Human CMV or human herpesvirus 5 is a ubiquitous double-stranded DNA virus belonging to the Betaherpesvirinae. There is a large heterogeneity of CMV strains. The seroprevalence of CMV in the general population ranges from 30%-97% and increases with age. CMV can be transmitted through saliva, urine, sexual contact, placental transfer, breastfeeding, blood transfusion, solid-organ transplantation, or hematopoietic stem cell transplantation. After primary infection, the virus establishes a lifelong latency within the host. Periodical reactivation with production and shedding of lytic virus occurs in both immunocompetent and immunocompromised individuals. In an

immunocompetent host, primary CMV infection often is asymptomatic, although it can manifest as a mononucleosis-like syndrome. In contrast, in immunocompromised hosts, primary CMV infection, reactivation of latent infection, or reinfection with a different strain usually causes CMV disease (Am J Kidney Dis. 2011;58(1):118-126).

The diagnosis of CMV disease is made based on the presence of "typical" clinical signs and symptoms combined with the detection of CMV in blood and/or the involved organs as shown in Table 2 below, taken from *Clin Infect Dis.2002;34(8):1094-1097.*

The term disease is generally used in the context of patients who have developed a cytomegalovirus infection within the context of the latent virus becoming active due to the immune system becoming compromised under one of 4 underlying conditions namely; i) HIV infection, ii) haematopoietic stem cell transplantation, iii)solid organ transplantation and iv) primary immune deficiency disease. The term infection is not used as this would also encompass latent infection in both healthy and immunocompromised patients as noted above. The two tables below highlight the differences between infection and disease.

Table 1. Definitions of CMV Infection

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Type of Infection	Definition
CMV infection	Isolation of CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen
Viremia	Isolation of CMV using conventional tube cell cultures or shell vial assays
Antigenemia	Detection of CMV pp65 in peripheral-blood leukocytes
DNAemia	Detection of CMV DNA in plasma, whole blood, isolated peripheral-blood leukocytes, or buffy-coat specimens
Primary CMV infection	1. Detection of CMV infection in a seronegative patient 2. Appearance of de novo specific antibodies in a seronegative patient (provided that passive transfer of antibodies through immunoglobulin or blood products is excluded)
Recurrent CMV infection	New detection of CMV infection in a patient with previously documented infection and in whom no virus has been detected for an interval of at least 4 weeks during active surveillance

Abbreviations: CMV, cytomegalovirus; pp65, phosphoprotein 65.
Based on definitions provided in Ljungman et al.[12]

Table 2. Definitions of CMV Disease

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Type of Disease	Definition
CMV syndrome	Fever (temperature >38°C) for at least 2 d within a 4-d period + neutropenia and/or thrombocytopenia + detection of CMV infection in blood
CMV pneumonia	Signs and/or symptoms of pulmonary disease + detection of CMV infection in BAL fluid or a lung biopsy specimen
CMV GI disease	Symptoms from the upper or lower GI tract + macroscopic mucosal lesions on endoscopy + detection of CMV infection in GI tract biopsy specimen
CMV hepatitis	Increased bilirubin and/or liver enzyme levels + absence of another documented cause of hepatitis + detection of CMV infection in a liver biopsy specimen
CMV encephalitis	Central nervous system symptoms + detection of CMV infection in CSF or a brain biopsy specimen
CMV retinitis	Symptoms of retinitis + typical retinal lesions on dilated eye ophthalmoscopy
CMV nephritis	Signs and/or symptoms of kidney dysfunction + detection of CMV infection + identification of conventional histologic features of CMV infection in a kidney biopsy specimen
CMV cystitis	Signs and/or symptoms of cystitis + detection of CMV infection + identification of conventional histologic features of CMV infection in a bladder biopsy specimen
CMV myocarditis	Signs and/or symptoms of myocarditis + detection of CMV infection + identification of conventional histologic features of CMV infection in a heart biopsy specimen
CMV pancreatitis	Signs and/or symptoms of pancreatitis + detection of CMV infection + identification of conventional histologic features of CMV infection in a pancreatic biopsy specimen

Abbreviations: BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CSF, cerebrospinal fluid; GI, gastrointestinal.
Based on definitions provided in Ljungman et al.[12]

Cytomegalovirus disease is an acute condition in immunocompromised patients and is different from cytomegalovirus infection which can occur in normal individuals because it does not manifest in the same manner nor present with the same morbidity and mortality.

The approved 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). Consideration should be given to official guidance on the appropriate use of antiviral agents.*" falls within the scope of the designated orphan indication "prevention of cytomegalovirus disease".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat, prevent or diagnose the condition has been justified. Please refer to the EPAR for PREVYMIS.

Chronically debilitating and/or life-threatening nature

CMV is a problematic infection in many transplant patients. It can be acquired by seronegative patients from seropositive organ donors or via reactivation of latent infections in seropositive transplant recipients upon immunosuppression. CMV-related disease manifests differently depending on which organ is transplanted. CMV is known to damage various organs, including the lung, liver, gastrointestinal tract, bone marrow, and retina. It has been noted that CMV disease is associated with substantial increases in the risk of graft rejection and mortality (Hakimi Z et al, Transplant Infection Disease July 2017).

In bone marrow recipients, CMV disease occurs often as an interstitial pneumonia with high mortality.

CMV remains a leading cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients. CMV can cause tissue-invasive disease including pneumonia, hepatitis, colitis, retinitis, and encephalitis. Mortality in HSCT recipients with CMV disease can be as high as 60%. CMV infection is associated with increased risk of secondary bacterial and fungal infections, increased risk of graft-versus host disease, and high rates of non-relapse mortality following HSCT (Camargo J et al, Hematol Oncol Stem Cell Ther (2017)).

An association of CMV infection with increased HIV disease progression and death in HIV-infected individuals has been reported (Jennifer A Slyker J Virus Erad. 2016 Oct; 2(4): 208–214.).

Around 12% of solid tumour transplant patients develop CMV disease and associated complications of graft rejection and damage to other organs (HAKIMI et al, 2017)

In liver recipients, hepatitis can be problematic and may be difficult to discern from organ rejection.

Number of people affected or at risk

To date no notable registries in Europe specifically record cases of CMV disease within the context of patients with an immune compromised system as those found in the four patients populations describe in the condition section namely: i) solid organ transplant recipient, ii) hematopoietic stem cell transplantation recipients, iii) HIV patients and iv) primary immunodeficiency disease. However, there is a European Society for Immunodeficiencies which has a dedicated registry with focus on primary immunodeficiencies.

A risk calculation of CMV disease for each of the four targeted patient populations has been provided by the applicant and is summarised in the table below.

Table 3.

	Calculations in 2010		**Updated calculations in 2017**	
Patients	N	Prevalence per 10,000	N	Prevalence per 10,000
SOT Recipients	26,671	0.5	31,165	0.6
HBPCT* Recipients	23,333	0.6	36, 469	0.7
allogeneic HSCT recipients	-		15,765	0.3
autologous HSCT recipients	-		20,704	0.4
HIV Patients (with CD4 <= 50 cells/mL)	-	1.5	96,000	1.9
CCL (Oncology patients receiving alemtuzumab	-	0.5	-	-
Primary immunodeficiency diseases (PIDD)	-	-	30,952	0.6
Total	-	**3.1**	***194,586***	***3.8***

* HBPCT, human blood precursor cell transplant, which is the term used previously for HSCTs in the report in 2010.

This calculation indicates that reporting has increased since 2010 in HIV patients, SOT patients and HSCT patients. These assumptions are based on recent publications and reports from European databases. It is acknowledged that the incidences submitted by the sponsor offer a more current calculation of the situation in Europe because there has been an increase in the number of CMV disease cases reported since 2010.

The assumptions for acquired immune deficiency patients focus primarily on oncology patients who have received alemtuzumab. In view that alemtuzumab for the treatment of patients with CLL had been withdrawn from the EU market in 2012, the number of patients in this group is highly uncertain.

Primary immunodeficiency diseases (PIDD) are indicated as one of the causes of CMV disease in several publications and has been highlighted in the condition section. The incidence of these conditions in 2004 was reported to be 1 in 10,000 (Lim M et al, Journal of Molecular Diagnostics, Vol. 6, No. 2, May 2004). According to this publication the reporting rates increased. The sponsor showed that primary immunodeficiency diseases comprised of more than 200 rare, inherited chronic diseases that result in defects in the immune system. As stated by the sponsor, the European Society for Immunodeficiencies (ESID) registry reported 19,355 cases in 2014. The prevalence ranges across Europe varied from 0.023 in 100,000 in Croatia to 6.2 in 100,000 in France. The sponsor has proposed to use the higher prevalence of 0.6 in 10,000 for the overall European prevalence. This has been added to the prevalences of the other three conditions linked to CMV disease.

Based on these assumptions the sponsor concluded on a prevalence of 3.8 in 10,000. The COMP accepted this calculation as the final prevalence.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently there are two products authorised for the prevention of cytomegalovirus disease in Europe. These are ganciclovir and valganciclovir. There are no specific European Guidelines for the treatment of CMV disease however different reviews and guidance documents address treatment of the patients receiving HSCT, solid organ transplant and with HIV infection. The use of either of these products is highlighted in the prevention of the CMV disease and highlighted in the Summary of Product Characteristics of each product. In the case of valganciclovir section 4.1 limits the use to "*the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18years) who have received a solid organ transplant from a CMV-donor*". In the case of ganciclovir the Summary of Product Characteristics states in section 4.1: "*prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy)".* Valganciclovir is available as a 450mg tablet which is taken bid. Ganciclovir is only available as an IV formulation.

Current reviews and guidelines support the recommendation of the use of either of these antiviral agents within the context of the management of the risk of CMV disease. (Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation; Contemporary management of cytomegalovirus infection in transplant recipients: guidelines from an IHMF workshop, 2007(external link); 2008 prevention of opportunistic infections in HIV-infected adolescents and adults guidelines: recommendations of GESIDA/National AIDS Plan AIDS Study Group

(GESIDA) and National AIDS Plan; Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with haematological malignancies and after SCT).

Significant benefit

The sponsor proposed that letermovir offers an alternative to ganciclovir, valganciclovir and foscarnet in the prophylaxis of CMV disease. The sponsor notes that valganciclovir and foscarnet are not authorised for the prophylaxis of CMV disease in HSCT. In its assessment of the current SmPC the COMP has confirmed the use of valganciclovir in the prevention of CMV disease in solid organ transplantation (Section 4.2 11 March 2015).

No question on significant benefit was raised by the sponsor during the protocol assistance (October 2013).

The sponsor claims a significant benefit based on a clinically relevant advantage due to a better safety profile compared to ganciclovir and a major contribution to patient care based on the oral formulation compared to the IV formulation of ganciclovir, in the prevention of CMV disease in patients receiving HSCT. As oral valganciclovir is not authorised in this particular target population it is not considered for the assessment of significant benefit.

For the purpose of establishing significant benefit the sponsor has focused primarily on the Phase III study but it should be noted below that two other studies have been submitted in the report to CHMP which can also be considered for the assessment.

Table 4. Phase 2 and 3 clinical trials conducted by the Sponsor

Trial Type	Merck Trial No. (AiCuris No., as Applicable*)	Trial Short Title / Design	Primary Objective	Number of Subjects who Received Letermovir
Phase 2				
	MK-8228-019 (AIC001-2-001)	Phase 2a, randomized, active controlled, multi-center, open-label dose ranging trial in a majority of kidney and kidney/pancreas transplant recipients (and 1 HSCT recipient) with CMV viremia	To determine the decline in human cytomegalovirus (CMV) DNA load after a 14-day treatment for each letermovir dosing regimen and to compare this to an observational control group	18
	MK-8228-020 (AIC246-01-II-2)	Phase 2b, multi-center, randomized, double-blind, placebo-controlled, dose-ranging trial to investigate safety and efficacy of 3 different oral doses of letermovir in comparison with matching placebo over 12 weeks in CMV-seropositive, allogeneic HSCT recipients	To compare the safety and efficacy of 3 different doses of letermovir with matching placebo as prophylaxis in the prevention of CMV infection	98
Phase 3				
	MK-8228-001	Phase 3 randomized, placebo-controlled trial to evaluate the safety and efficacy of letermovir in adult, CMV-seropositive allogeneic HSCT recipients	To evaluate the efficacy of letermovir as prophylaxis in the prevention of clinically significant CMV infection through Week 24 (~6 months) post-transplant following adminstration of letermovir or placebo.	373

* AiCuris protocol numbers are provided for Phase 2 trials sponsored by AiCuris.
‡ MK-8228-018 Part 2: All 16 subjects received only the IV arginine formulation of letermovir.
ǁ MK-8228-017: Of the 34 subjects exposed to letermovir, 22 subjects received only the IV arginine formulation of letermovir. The remaining 12 subjects received both the oral tablet and IV arginine formulations of letermovir.
QD= once daily; BID=twice daily

The sponsor has not submitted any data associated with the prevention of CMV disease in patients with HIV infection nor in patients who are immunocompromised for any other reason therefore this will not be considered in the assessment.

The primary source of the data used for this assessment comes from the MK-8228-001 a Phase 3 randomized, placebo-controlled trial to evaluate the safety and efficacy of letermovir in adult, CMV-seropositive allogeneic HSCT recipients. This Phase 3 trial was designed to evaluate the safety and efficacy of letermovir at a dose of 480 mg QD, adjusted to 240 mg QD when co-administered with CsA, versus placebo in adult, CMV-seropositive allogeneic HSCT recipients (R+). Treatment was administered through Week 14 (~100 days) post-transplant. Overall, 570 subjects were randomized with 376 in the letermovir group and 194 in the placebo group. The aim of the study was to evaluate the efficacy of letermovir as prophylaxis in the prevention of clinically significant CMV infection through Week 24 (~6 months) post-transplant following administration of letermovir or placebo.

The primary end-point of this study was made up of two end-points namely: *1) onset of CMV end-organ disease and* 2) *initiation of anti-CMV PET based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the subject. Initiation of PET in the trial referred to the practice of initiating therapy with the following anti-CMV agents when active CMV viral replication was documented: GCV, VGCV, foscarnet, and/or cidofovir.*

There are three strategies for the management of CMV: Prophylaxis, pre-emptive therapy and treatment of established CMV disease. The prophylaxis strategy is aimed at preventing all infections. The pre-emptive strategy consists in treating patients with clinical relevant infections (based on documented CMV viremia and the clinical condition of the patient) to prevent disease. Moreover, finally when CMV disease is present, the aim of the treatment is to avoid organ damage and death.

In the case of preemptive therapy for CMV the proof of concept was established by the City of Hope-Stanford-Syntex CMV Study Group in an open, randomized study of 104 allogeneic SCT patients. Asymptomatic patients underwent bronchoalveolar lavage (BAL) on day +35 post-transplant. CMV was evaluated in BAL by classic virologic techniques: shell-vial cell and conventional cell cultures, and cytology. Patients found positive for CMV (40 patients) were randomized to receive (20 patients) or not receive (20 patients) intravenous ganciclovir. At day +120 post-transplant, 75% of patients with positive CMV on BAL not treated developed CMV pneumonitis compared to 25% of those treated with ganciclovir, and 20% in those who were negative for CMV on BAL. This study proved the value of preemptive therapy for the prevention of CMV pneumonitis and started the era of the preemptive therapy for CMV (de la Camera R et al, 2016).

The sponsor's product was evaluated for the prevention of CMV disease in the prophylaxis setting.

The COMP focused primarily on the data generated regarding the need for preemptive therapy because literature review has demonstrated no meaningful change regarding prophylaxis and the need for preemptive therapy in the last 15-20 years (de la Camera R et al, 2016).

The sponsor presented data on the incidence of pre-emptive therapy for documented CMV viremia through week 24 post-transplant. A certain proportion of these patients received combination therapy with other antivirals such as: ganciclovir, valganciclovir, foscarnet and cidofovir.

Figure 1.

Letermovir is highly efficacious therefore sparing use of PET (ganciclovir)

	Letermovir (N=325) n (%)	Placebo (N=170) n (%)
Proportion of subjects who failed prophylaxis (primary endpoint)	**122 (37.5)**	**103 (60.6)**
Reasons for failure †		
Clinically significant CMV infection by Week 24	57 (17.5)	71 (41.8)
Initiation of PET based on documented viremia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)
Discontinued from study before Week 24	56 (17.2)	27 (15.9)
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (Letermovir-Placebo)		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
p-value	<0.0001	

† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

*Full-Analysis Set ; Non-Completer = Failure Approach

It was noted that among HSCT recipients who are CMV seropositive, ~80% develop CMV reactivation and 20-30% progress to CMV disease without preventative measures. Current practice is to monitor HSCT recipients for CMV reactivation and to use ganciclovir as pre-emptive therapy as it cannot be used prophylactically due to its myelotoxicity. The data submitted by the sponsor indicated that at week 24, 40% of the placebo group needed preemptive therapy using predominantly ganciclovir/valganciclovir compared to only 16% in the letermovir group (results from Study P001). End organ disease occurred only in a low number of patients in both groups.

The cumulative rates of all-cause re-hospitalisation at week 14 and 24 are numerically lower in the letermovir group compared to placebo. Also, the mean number of days in hospital is numerically lower in the letermovir group, while the median is however similar between groups.

This finding is supportive for significant benefit and indicate that letermovir prophylaxis could reduce the overall need of in-patient care compared to a standard-of-care PET approach.

It was noted by the COMP that any significant reduction in the need for preemptive therapy in the management of these patients is considered a clinically relevant advantage. As data presented by the sponsor supported a clinically relevant reduction in the need for preemptive treatment for CMV infection at week 24 the COMP was of the opinion that this could support the basis of significant benefit. This was further supported by data showing the lower rates of re-hospitalisation where for example the re-hospitalisation for CMV in the letermovir group was 3.1% vs 7.6% in the placebo group at week 24. The potential for a major contribution to patient care due to letermovir being an oral formulation was discussed in relation to ganciclovir which is only available as an IV. The sponsor however, did not submit sufficient data to support the major contribution to patient care offered by the oral formulation over the IV formulation. The COMP acknowledged the possible contribution but did not consider this as the principle basis supporting significant benefit at the review for the maintenance.

The COMP conclude that sufficient data was submitted by the sponsor to support a clinically relevant advantage of using letermovir in a prophylactic setting as it has been shown to reduce the need for preemptive therapy compared to the current standard of care. The COMP therefore recommended the granting of the maintenance of the orphan designation.

4. COMP position adopted on 17 November 2017

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the population of patients eligible for prevention of cytomegalovirus disease (hereinafter referred to as “the condition”) was estimated to be approximately 3.8 in 10,000 persons in the European Union, at the time the application was made;
- the condition is life-threatening due to frequent development of acute severe hepatitis, pneumonitis, colitis, haemorrhagic cystitis and encephalitis. Disseminated disease can be rapidly fatal, with mortality rates reported to be as high as 80%;
- although satisfactory methods of prevention of the condition have been authorised in the European Union, the assumption that Prevymis may be of potential significant benefit to the population at risk of developing the condition still holds. The sponsor has provided clinical data which supported a reduction in the number of patients in need of pre-emptive therapy. The COMP considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Prevymis, (S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid, letermovir, EU/3/11/849 for prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk is not removed from the Community Register of Orphan Medicinal Products.