09 November 2022
EMADOC-1700519818-911372
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Livtencity (maribavir)
Sponsor: Takeda Pharmaceuticals International AG Ireland Branch

Note

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

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1. Introductory commnet

The approved therapeutic indication:

"Livtencity is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)" falls within the scope of the two designated orphan conditions "prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk" and "treatment of cytomegalovirus disease in patients with impaired cell mediated immunity".

The maintenance of the two respective orphan designations is covered in this one document.

2. Livtencity (maribavir) - EU/3/07/519 - EMA/OD/0000091090

2.1. Product and administrative information

Product	
Designated active substance	Maribavir
Other name(s)	--
International Non-Proprietary Name	Maribavir
Tradename	Livtencity
Orphan condition	Prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk
Sponsor's details:	Takeda Pharmaceuticals International AG Ireland Branch 50-58 Baggot Street Lower Block 3 Miesian Plaza Dublin 2 D02 Y754 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	ViroPharma Limited
COMP opinion	8 November 2007
EC decision	18 December 2007
EC registration number	EU/3/07/519
Post-designation procedural history	
Sponsor's name change	Name change from ViroPharma SPRL to Shire Services BVBA – EC letter of 19 February 2016
Transfers of sponsorship	Transfer from ViroPharma Limited to ViroPharma SPRL – EC decision of 20 February 2009 Transfer from Shire Services BVBA to Shire Pharmaceuticals Ireland Limited – EC decision of 15 March 2016 Transfer from Shire Pharmaceuticals Ireland Limited, Ireland to Takeda Pharmaceuticals International AG Ireland Branch – EC decision of 16 September 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Janet Koenig/Filip Josephson
Applicant	Takeda Pharmaceuticals International AG Ireland Branch
Application submission	31 May 2021
Procedure start	17 June 2021
Procedure number	EMA/H/C/005857/0000
Invented name	Livtencity

Proposed therapeutic indication	Treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)
CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Olimpia Neagu
EMA scientific officer	Kristina Larsson
Expert	NA
Sponsor's report submission	16 February 2022
COMP discussion	6-8 September 2022
COMP opinion (adoption via written procedure)	16 September 2022

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2007 designation was based on the following grounds:

- the population of patients eligible for prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk (hereinafter referred to as "the condition") was estimated to be less than 4 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to the development of serious complications and the overall increased of mortality;
- although satisfactory methods of prevention of the condition have been authorised in the Community, justifications have been provided that maribavir may be of significant benefit to the population at risk of developing the condition.

2.3. 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

Human cytomegalovirus (HCMV) infection is common, with serologic evidence of prior infection in 40% to 100% of various adult populations. CMV disease though is a rather rare and serious condition mainly affecting individuals with a compromised immune system. In these patients, uncontrolled replication of CMV can result after a primary infection, reactivation of latent virus, reinfection, and superinfection. This can lead to extensive organ disease in a variety of organs (eye, gastrointestinal track, liver, lung)

with potentially significant morbidity and mortality. The factors which lead to CMV disease are poorly understood but vary according to the degree of immunodeficiency. Populations at greatest risk of CMV disease include hematopoietic stem cell (HSC) and solid organ transplant (SOT) recipients, AIDS patients with deficiencies in cell mediated immunity and oncology patients. If left untreated, CMV disease, especially if this involves the lung and the central nervous system, can rapidly evolve and progress to death in immunocompromised transplant recipients.

The approved therapeutic indication "*LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).*

Consideration should be given to official guidance on the appropriate use of antiviral agents." falls within the scope of the designated orphan conditions "Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk" (EU/3/07/519) and "Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity" (EU/3/13/1133).

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor state that there have been no major changes in the chronically debilitating or life-threatening nature of the orphan condition. New therapies introduced since the designation and improvement in general care might have impacted on morbidity and mortality.

Letermovir (Prevymis) has been approved in 2018 for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). There is evidence that letermovir use will reduce the incidence of clinically significant CMV infection and mortality in HSCT patients (Camargo et al. 2018, Koch et al. 2021, Smith et al. 2021), however, no new agents have been approved for the treatment of CMV infection and/or disease.

The options for successful treatment of resistant or refractory CMV viremia or disease are still limited. El Chaer reported that only 10% of HSCT recipients with drug-resistant CMV infection responded to alternative therapy (El Chaer et al. 2016). This is aligned with the generally dismal responses Avery notes in her review of 7 other historical studies published after the year 2000 in this unmet need population. Mortality rates for those that require treatment for resistant or refractory CMV infection range from 31-50% within 1 year of transplantation (Avery et al. 2016; Mehta et al. 2020).

The condition can still be considered bot chronically debilitating and life-threatening.

The COMP has previously considered the condition to be chronically debilitating and life-threatening in particular due to manifestations such as pneumonia, gastrointestinal infections, central nervous system infection, retinitis, and in transplant recipients graft failure, rejection, and graft-versus-host disease.

Number of people affected or at risk

In the initial application the prevalence was considered to be 3.77 in 10,000 cases. For this orphan maintenance report, the sponsor has reconsidered the population at risk of CMV infection and disease in alignment with published orphan designations for CMV Disease and considered the following populations:

- Individuals with human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)
- Solid organ transplant [SOT] recipients
- Hematopoietic stem cell transplant [HSCT] recipients
- Patients with primary immunodeficiency diseases (PIDD)

Prevalence estimates of patients at-risk of CMV infection were derived using the total number of patients in each subpopulation of interest (i.e., SOT, HSCT, HIV/AIDS with <50 CD4+ cells/mm3 and PIDD), as reported in authoritative sources or estimated through pragmatic searches, and the size of the EU population on 1st January 2020 as denominator.

Oncology patients were not included as MabCambath (INN: alemtuzumab) indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) was withdrawn in 2012.

For SOT and HSCT populations, prevalence estimates for the primary analysis were derived considering the number of transplants performed in the year 2019 because transplant activity was impacted by the COVID-19 pandemic. For consistency between numerator and denominator, for these analyses the size of the EU population on 1st January 2020 was used as denominator.

To estimate the prevalence of the potential advanced AIDS population at risk, the conservative estimate of 20% **HIV/AIDS** patients, based on CD4 count <200 cells/mm^3 was applied to the size of the population living with HIV/AIDS (Supervie et al. 2014). Based on this calculation, the estimated number of patients considered at-risk of CMV infection in the EU-27 would be 110,274, corresponding to a prevalence estimate of 2.463 per 10,000.

According to the Global Observatory on Donation and Transplantation (GODT) database, in 2019, there were 29,107 transplants performed in the EU-27 (excluding the UK). Considering Eurostat reported that the population size of the EU-27 was 447,706,209 on 1st January 2020, corresponding prevalence of **SOT** patients at-risk of CMV infection was estimated at 0.650 per 10,000.

According to the European Society for Blood and Marrow Transplantation (EBMT) Annual Report and British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) Registry Annual Activity, in 2019, there were 16,053 allogeneic HSCT performed in the EU excluding the UK. For autologous transplants, a total of 20,416 procedures were reported in the EU excluding the UK. Considering Eurostat reported that the population size of the EU-27 (excluding the UK) was 447,706,209 on 1st January 2020, prevalence of allogeneic and autologous HSCT recipients at-risk of CMV infection was estimated at 0.359 and 0.456 per 10,000, respectively. Hence, the prevalence of all **HSCT** recipients at-risk of CMV infection was 0.815 per 10,000.

To be conservative, a prevalence of **PIDD** in Europe of 0.62 per 10,000 was used (as reported Prevymis orphan maintenance assessment report) and as there is no studies evaluating the CMV infection and/or CMV disease in patients with PIDD, it was assumed that all PIDD patients would develop CMV infection.

Table 1 from the sponsor's application summarises the outcome of the analysis and sensitivity analysis and also compared the numbers with those from the orphan designation in 2007.

Table 1. Estimates of Prevalence and Total Number of Patients At-risk of CMV Infection and Disease among Individuals with Impaired Cell-mediated Immunity in the EU-27 in 2020

Sub-population of interest	Prevalence and Number of Patients Reported in the Initial Application	Updated Prevalence and Number of Patients			
		Primary Analysis		Sensitivity Analysis	
		Prevalence per 10,000	Number of Patients	Prevalence per 10,000	Number of Patients
SOT	0.54 (27,000)	0.650	29,107	0.655	29,257
HSCT	0.50 (25,000)	0.815	36,469	0.985	40,008
HIV/AIDS* (Patients with <200 CD4+ cells/mm^3)	2.65 (131,300)	2.463	110,274	2.463	110,274
Oncology patients receiving alemtuzumab	0.08 (3,800)	n/a	n/a	n/a	n/a
PIDD	n/a	0.620	27,758	0.620	27,758
TOTAL	**3.77 (187,100)**	**4.548**	**203,608**	**4.633**	**207,297**

*Conservative estimate in the absence of recent estimates of the proportion of patients with a CD4+ cell count <50/mm^3

The prevalence of patients at risk of CMV disease in EU is estimated to be 4.548 in 10 000. The prevalence estimate presented is considered conservative by the sponsor, as due to lack of specific data, the prevalence of AIDS and PIDD patients at risk of CMV disease has likely been overestimated.

For the maintenance of Prevymis in 2018, a prevalence of 3.8 was accepted. The difference between that estimate and this one is mainly due to a higher prevalence of HIV/AIDS patients at risk presented for Livtencity (2.5 instead of 1.9). The sponsor's argument that their estimation for the HIV/AIDS population is on the conservative side is accepted. A prevalence of 4.5 was accepted by the COMP.

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

The sponsor discusses the current treatment algorithms and guidelines in patients undergoing SOT or HSCT as that is the target patient population for the therapeutic indication. The following three guidelines are sited:

- Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation (Kotton et al. 2018)
- Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice (Razonable and Humar 2019)
- Guidelines for the management of CMV infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7) (Ljungman et al. 2019).

Table 2. Available Systemic Anti-CMV Agents Approved for Treatment or Prevention of CMV

Drug	Formulation	Indication	Satisfactory method
Cymevene 500 mg (Ganciclovir (cymevene) SmPC 2020)	IV	Cymevene is indicated in adults and adolescents ≥12 years of age for the: **treatment of CMV disease** in immunocompromised patients; prevention of CMV disease using pre-emptive therapy **in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy**). Cymevene is also indicated from birth for the: **prevention of CMV disease** using universal prophylaxis in patients with drug- induced immunosuppression (for example following organ transplantation or cancer chemotherapy).	No, not approved for refractory patients
(Valcyte Prescribing Information 2015) (Valganciclovir (Valcyte) SmPC 2018)	Oral	Valcyte is indicated for the induction and maintenance treatment of CMV retinitis in adult patients with AIDS. Valcyte is indicated for the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.	No, product not approved for refractory patients, nor in HSCT patients

Foscavir 24 mg/mL (Foscavir (Foscarnet) SmPC 2020)	IV	Foscavir is indicated for induction and maintenance therapy of CMV retinitis in patients with AIDS. Foscavir is also indicated for the treatment of mucocutaneous HSV infections, clinically unresponsive to aciclovir in immunocompromised patients. The safety and efficacy of Foscavir for the treatment of other HSV infections (eg, retinitis, encephalitis); congenital or neonatal disease; or HSV in immunocompetent individuals has not been established. The diagnosis of aciclovir unresponsiveness can be made either clinically by treatment with IV aciclovir (5–10 mg/kg t.i.d) for 10 days without response or by in vitro testing. Foscavir is not recommended for treatment of CMV infections other than retinitis or HSV or for use in non-AIDS or non-immunocompromised patients.	No, not approved for SOT or HSCT
Vistide (Cidofovir SmPC 2017)	IV	Cidofovir is indicated for the treatment of CMV retinitis in adults with AIDS and without renal dysfunction. It should be used only when other medicinal products are considered unsuitable.	No, not approved for SOT or HSCT
Cytotect CP Biotest (Human cytomegalovirus immunoglobulin (Cytotect CP Biotest SmPC 2020)	IV	Prophylaxis of clinical manifestations of cytomegalovirus infection in patients subjected to immunosuppressive therapy, particularly in transplant recipients. The concomitant use of adequate virostatic agents should be considered for CMV-prophylaxis **Note: not recommended by treatment guidelines**	No, only approved as prophylaxis.
Valtrex (valaciclovir hydrochloride equivalent to 500 mg valaciclovir, (Valaciclovir (Valtrex) SmPC 2020)		Valtrex is indicated for the prophylaxis of CMV infection and disease following SOT in adults and adolescents	No, not approved for HSCT.
Prevymis (PREVYMIS (letermovir) SmPC 2021)	Oral, IV	PREVYMIS is indicated for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic HSCT.	No, only approved as prophylaxis.

AIDS=acquired immune deficiency syndrome; CMV=cytomegalovirus; CMV Ig=CMV immunoglobulin; HIV=human immunodeficiency virus; IV=intravenous; HSCT=hematopoietic stem cell transplant; SOT=solid organ transplant; TRALI=transplant-related acute lung injury

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

As there are no approved product which cover the full target population of Livtencity there are no satisfactory methods relevant to compare with.

Significant benefit

No applicable

2.4. COMP position adopted on 16 September 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- 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%;
- there is, at present, no satisfactory method for the prevention of the entirety of patients covered by the therapeutic indication of Livtencity.

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 Livtencity, maribavir for prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk (EU/3/07/519) is not removed from the Community Register of Orphan Medicinal Products.

3. Livtencity (maribavir) - EU/3/13/1133 - EMA/OD/0000091101

3.1. Product and administrative information

Product	
Designated active substance(s)	Maribavir
Other name(s)	--
International Non-Proprietary Name	Maribavir
Tradename	Livtencity
Orphan condition	Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity
Sponsor's details:	Takeda Pharmaceuticals International AG Ireland Branch 50-58 Baggot Street Lower Block 3 Miesian Plaza Dublin 2 D02 Y754 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	ViroPharma SPRL
COMP opinion	23 April 2013
EC decision	7 June 2013
EC registration number	EU/3/13/1133
Post-designation procedural history	
Sponsor's name change	Name change from ViroPharma SPRL to Shire Services BVBA – EC letter of 19 February 2016
Transfers of sponsorship	Transfer from Shire Services BVBA to Shire Pharmaceuticals Ireland Limited – EC decision of 15 March 2016 Transfer from Shire Pharmaceuticals Ireland Limited, Ireland to Takeda Pharmaceuticals International AG Ireland Branch – EC decision of 16 September 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Janet Koenig/Filip Josephson
Applicant	Takeda Pharmaceuticals International AG Ireland Branch
Application submission	31 May 2021
Procedure start	17 June 2021
Procedure number	EMA/H/C/005857/0000
Invented name	Livtencity

Proposed therapeutic indication	Treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)
CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Olimpia Neagu
EMA scientific officer	Kristina Larsson
Expert	NA
Sponsor's report submission	16 February 2022
COMP discussion	6-8 September 2022
COMP opinion (adoption via written procedure)	16 September 2022

3.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2013 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing maribavir was considered justified based on preclinical data showing anti-cytomegalovirus in vitro activity, and by early clinical data showing serological and clinical resolution of cytomegalovirus infection in patients not responding to previous antiviral treatment;
- the condition is life-threatening due to complications such as pneumonitis, hepatitis, inflammation of the gastrointestinal tract and acute graft rejection in transplanted patients. It is the leading viral cause of morbidity and mortality in patients with human stem cell or solid organ transplantation, with direct damage resulting from viral invasion of different organs, and indirect effects on the immune system that increase the risk of other infections and promote acute graft rejection. The condition can be chronically debilitating in case of the development of long-term sequelae in the affected organs and in case of reduced graft survival;
- the condition was estimated to be affecting approximately 2 in 10,000 persons per year in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing maribavir may be of significant benefit to those affected by the condition. The sponsor has provided early clinical data in the form of case reports where the product was used in compassionate use in patients not responding to previous antiviral treatment. In this setting maribavir resulted in serological and clinical resolution of cytomegalovirus infection in more than half of the studied patients, indicating the potential to be used in forms of the condition that are resistant to currently authorized antiviral treatments. When confirmed in clinical studies, the Committee considered that this will constitute a clinically relevant advantage for the immunocompromised patients affected by cytomegalovirus disease.

3.3. 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

Human cytomegalovirus (HCMV) infection is common, with serologic evidence of prior infection in 40% to 100% of various adult populations. CMV disease though is a rather rare and serious condition mainly affecting individuals with a compromised immune system. In these patients, uncontrolled replication of CMV can result after a primary infection, reactivation of latent virus, reinfection, and superinfection. This can lead to extensive organ disease in a variety of organs (eye, gastrointestinal track, liver, lung) with potentially significant morbidity and mortality. The factors which lead to CMV disease are poorly understood but vary according to the degree of immunodeficiency. Populations at greatest risk of CMV disease include hematopoietic stem cell (HSC) and solid organ transplant (SOT) recipients, AIDS patients with deficiencies in cell mediated immunity and oncology patients. If left untreated, CMV disease, especially if this involves the lung and the central nervous system, can rapidly evolve and progress to death in immunocompromised transplant recipients.

The approved therapeutic indication "*LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).*

Consideration should be given to official guidance on the appropriate use of antiviral agents." falls within the scope of the designated orphan conditions "Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity" (EU/3/13/1133) and "Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk" (EU/3/07/519).

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor state that there have been no major changes in the chronically debilitating or life-threatening nature of the orphan condition. New therapies introduced since the designation and improvement in general care might have impacted on morbidity and mortality.

Letermovir (Prevymis) has been approved in 2018 for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). There is evidence that letermovir use will reduce the incidence of clinically significant CMV infection and mortality in HSCT patients (Camargo et al. 2018, Koch et al. 2021, Smith et al. 2021), however, no new agents have been approved for the treatment of CMV infection and/or disease.

The options for successful treatment of resistant or refractory CMV viremia or disease are still limited. El Chaer reported that only 10% of HSCT recipients with drug-resistant CMV infection responded to alternative therapy (El Chaer et al. 2016). This is aligned with the generally dismal responses Avery notes in her review of 7 other historical studies published after the year 2000 in this unmet need population. Mortality rates for those that require treatment for resistant or refractory CMV infection range from 31-50% within 1 year of transplantation (Avery et al. 2016; Mehta et al. 2020).

The condition can still be considered both chronically debilitating and life-threatening.

The COMP has previously considered the condition to be chronically debilitating and life-threatening in particular due to manifestations such as pneumonia, gastrointestinal infections, central nervous system infection, retinitis, and in transplant recipients graft failure, rejection, and graft-versus-host disease.

Number of people affected or at risk

In the initial ODD application, the sponsor proposed a prevalence of 0.7 in 10.000. The COMP however, changed this to 2.1 in 10 000 in line with a previous designation for letermovir (EMA/OD/008/12), which was based on a worst-case scenario (the sponsors suggestion was 1.5).

For the orphan maintenance report, the sponsor reconsidered the population to be treated for CMV disease in alignment with published orphan designations for CMV Disease and considered the following populations:

- Individuals with HIV or AIDS
- SOT recipients
- HSCT recipients
- Patients with primary immunodeficiency disease (PIDD)

Oncology patients were not included as MabCambath (INN: alemtuzumab) indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) was withdrawn in 2012.

To estimate prevalence rates of CMV disease in each at-risk population, a systematic review, including literature and pragmatic searches, was conducted according to methods defined a priori. In order to account for the heterogeneity and uncertainty in prevalence estimates found in different studies, sensitivity analyses were conducted using a conservative approach whereby the highest prevalence estimates of CMV end-organ disease for each subpopulation found was retained.

For SOT and HSCT populations, prevalence estimates for the primary analysis were derived considering the number of transplants performed in the year 2019 because transplant activity was impacted by the COVID-19 pandemic. For consistency between numerator and denominator, for these analyses the size of the EU population on 1st January 2020 was used as denominator.

To be conservative, a prevalence of PIDD in Europe of 0.62 per 10,000 was used (as reported Prevymis orphan maintenance assessment report) and as there is no studies evaluating the CMV infection and/or CMV disease in patients with PIDD, it was assumed that all PIDD patients would develop CMV infection.

Table 20 from the sponsor's application summarises the outcome of the analysis and sensitivity analysis and also compared the numbers with those from the orphan designation in 2013.

Table 3. Estimates of Prevalence and Total Number of Cases of CMV End-organ Disease in Patients with Impaired Cell-mediated Immunity in the EU in 2020

Sub-population	EU-28 (2013)	EU-27 (Excluding UK)			
		Primary Analysis		Sensitivity Analysis	
	Number of Patients	Prevalence per 10,000	Number of Patients	Prevalence per 10,000	Number of Patients
SOT	159	0.003	146	0.026	1,141
HSCT	598	0.014	645	0.016	728
HIV/AIDS	34,340	0.234	10,476	0.310	13,888
Oncology patients receiving alemtuzumab	125	*Indication withdrawn (Aug 2012)*			
PIDD	*n/a*	*No data found*	*No data found*	0.620	27,758
TOTAL	**35,222**	**0.251**	**11,267**	**0.972**	**43,515**

AIDS=acquired immunodeficiency virus; CMV=cytomegalovirus; EU=European Union; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplant; PIDD=primary immunodeficiency disease; SOT=solid organ transplant; UK=United Kingdom

The overall prevalence for CMV end-organ disease in EU is proposed to be 1 in 10,000 derived from the sensitivity analysis.

This is less than the latest designation in 2016 which was 1.6, but the current assessment is much more comprehensive. It seems reasonable, as the sponsor indicated, that the HIV/AIDS and oncology patients are not contributing as much to the total number as they did 10-20 years ago. As already recognised by the COMP in 2012 (in the letermovir designation), with better prophylactic and potent regimens or with pre-emptive treatment strategies the incidence of CMV disease will decrease with time.

The proposed prevalence of 1 in 10,000 was accepted by the COMP.

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

The sponsor discusses the current treatment algorithms and guidelines in patients undergoing SOT or HSCT as that is the target patient population for the therapeutic indication. The following three guidelines are sited:

- Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation (Kotton et al. 2018)

- Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice (Razonable and Humar 2019)
- Guidelines for the management of CMV infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7) (Ljungman et al. 2019).

Table 4. Available Systemic Anti-CMV Agents Approved for Management of CMV Infection and/or Disease, adapted from sponsor's table 22 including satisfactory methods

Drug	**Formulation**	**Indication**	**Satisfactory method**
Cymevene 500 mg (Ganciclovir (cymevene) SmPC 2020)	IV	Cymevene is indicated in adults and adolescents ≥12 years of age for the: **treatment of CMV disease** in immunocompromised patients; prevention of CMV disease using pre-emptive therapy in patients **with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy**). Cymevene is also indicated from birth for the: **prevention of CMV disease** using universal prophylaxis in patients with drug- induced immunosuppression (for example following organ transplantation or cancer chemotherapy).	No, not approved for refractory patients
(Valcyte Prescribing Information 2015) (Valganciclovir (Valcyte) SmPC 2018)	Oral	Valcyte is indicated for the induction and maintenance treatment of CMV retinitis in adult patients with AIDS. Valcyte is indicated for the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.	No, product not approved for refractory patients, nor in HSCT patients

Foscavir 24 mg/mL (Foscavir (Foscarnet) SmPC 2020)	IV	Foscavir is indicated for induction and maintenance therapy of CMV retinitis in patients with AIDS. Foscavir is also indicated for the treatment of mucocutaneous HSV infections, clinically unresponsive to aciclovir in immunocompromised patients. The safety and efficacy of Foscavir for the treatment of other HSV infections (eg, retinitis, encephalitis); congenital or neonatal disease; or HSV in immunocompetent individuals has not been established. The diagnosis of aciclovir unresponsiveness can be made either clinically by treatment with IV aciclovir (5–10 mg/kg t.i.d) for 10 days without response or by in vitro testing. Foscavir is not recommended for treatment of CMV infections other than retinitis or HSV or for use in non-AIDS or non-immunocompromised patients.	No, not approved for SOT or HSCT
Vistide (Cidofovir SmPC 2017)	IV	Cidofovir is indicated for the treatment of CMV retinitis in adults with AIDS and without renal dysfunction. It should be used only when other medicinal products are considered unsuitable.	No, not approved for SOT or HSCT
Cytotect CP Biotest (Human cytomegalovirus immunoglobulin (Cytotect CP Biotest SmPC 2020)	IV	Prophylaxis of clinical manifestations of cytomegalovirus infection in patients subjected to immunosuppressive therapy, particularly in transplant recipients. The concomitant use of adequate virostatic agents should be considered for CMV-prophylaxis Note: not recommended by treatment guidelines	No, only approved as prophylaxis.
Valtrex (valaciclovir hydrochloride equivalent to 500 mg valaciclovir, (Valaciclovir (Valtrex) SmPC 2020)		Valtrex is indicated for the prophylaxis of CMV infection and disease following SOT in adults and adolescents	No, not approved for HSCT.
Prevymis (PREVYMIS (letermovir) SmPC 2021)	Oral, IV	PREVYMIS is indicated for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic HSCT.	No, only approved as prophylaxis.

AIDS=acquired immune deficiency syndrome; CMV=cytomegalovirus; CMV Ig=CMV immunoglobulin; HIV=human immunodeficiency virus; IV=intravenous; HSCT=hematopoietic stem cell transplant; SOT=solid organ transplant; TRALI=transplant-related acute lung injury

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

As there are no approved product which cover the full target population of Livtencity there are no satisfactory methods relevant to compare with.

Significant benefit

Not applicable

3.4. COMP position adopted on 16 September 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of cytomegalovirus disease in patients with impaired cell mediated immunity (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- 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%;
- there is, at present, no satisfactory method for the treatment of the entirety of patients covered by the therapeutic indication of Livtencity;

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 Livtencity, maribavir, for treatment of cytomegalovirus disease in patients with impaired cell mediated immunity (EU/3/13/1133) is not removed from the Community Register of Orphan Medicinal Products.