25 February 2016
EMA/CHMP/175628/2016

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Cymevene i.v. and associated names

INN of the active substance: ganciclovir

Procedure no: EMEA/H/A-30/1406

Note

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

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 15 September 2014 the European Commission on behalf of all marketing authorisation holders presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Cymevene i.v. and associated names for which the MAH is F. Hoffman – La Roche Ltd (see Annex I of CHMP opinion).

The CHMP appointed Rugile Pilviniene (Lithuania) as rapporteur and Alar Irs (Estonia) as co-rapporteur.

Cymevene i.v. was first approved in United Kingdom on 15 June 1988, which marks its International Birth Date (IBD). National approval was obtained in most of the European countries. Cymevene is approved in all EU Member States except Latvia, Malta and Slovenia.

2. Scientific discussion during the referral procedure

2.1. Introduction

Cymevene i.v. contains ganciclovir, a synthetic analogue of 2'-deoxyguanosine which inhibits replication of herpes viruses. Sensitive human viruses include human cytomegalovirus (HCMV), herpes-simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and hepatitis B virus.

An oral formulation of ganciclovir (capsules 250 mg) was developed and first granted approval in United Kingdom on 16 December 1994. The oral formulation of Cymevene was withdrawn for non-safety reasons in 2006 and has been replaced by Valcyte (valganciclovir) formulations (powder for oral solution and film-coated tablets).

From this point onwards in this report if Cymevene is referred to, it refers only to the parenteral pharmaceutical forms. Cymevene is administered parenterally by intravenous infusion over 1 hour. The medicinal product is available in 10ml vials containing 500mg ganciclovir as powder for concentrate for solution for infusion.

Different summaries of product characteristics (SmPCs) are approved nationally across EU Member States. The main divergences are found in section 4.1 (Therapeutic indications) and consequently also in section 4.2 (Posology and method of administration). Further divergences exist in section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use) and section 4.6 (Fertility, pregnancy and lactation).

Due to the divergent national decisions taken by Member States concerning the authorisation of Cymevene i.v. and associated names, the European Commission notified the EMA of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised product information for the above-mentioned products and thus to harmonise them across the EU. In the following parts of this report the sections with the main changes in the product information are presented.

2.2. Clinical aspects

Summary of product characteristics (SmPC)

Section 4.1 – Therapeutic Indications

These medicinal products have been authorised for treatment and prevention of cytomegalovirus (CMV) disease. Both indications are discussed below.

Indication for treatment of CMV disease

Cymevene is currently indicated for the treatment of life- or sight-threatening CMV infections in immunocompromised individuals in the majority of E.U. Member States. The terminology used in the individual current SmPCs differs.

In Belgium, Bulgaria, Croatia, Estonia, France, Germany, Greece, Ireland, Lithuania, Luxembourg, the Netherlands, Romania, Slovakia, and the United Kingdom, Cymevene is indicated for the treatment of life- or sight-threatening CMV infections in immunocompromised individuals. In most SmPCs, the term "immunocompromised individuals" is defined. Although the precise definitions differ slightly across Member States, the SmPCs generally state that immunocompromised individuals include patients with acquired immunodeficiency syndrome (AIDS) and iatrogenic immunosuppression following organ or bone marrow transplantation or chemotherapy for neoplasia.

In Denmark, Iceland, and Sweden, treatment or prevention are not specified but treatment is implied as the SmPCs specify retinitis caused by CMV in patients with AIDS.

Similarly, the current Norwegian SmPC specifies visual or life-threatening infections in patients with immunodeficiency.

The current Czech, Finnish, Hungarian, Polish, Italian, Portuguese, and Spanish SmPCs include both the prevention and treatment of life- or sight-threatening CMV disease in immunocompromised individuals. Many SmPCs currently specify treatment of CMV infections in oncology patients receiving immunosuppressive therapy. Other SmPCs address treatment of this patient group by use of the general term "immunocompromised individuals" without further qualification.

There is some inconsistency in local SmPCs and literature regarding the use of terms "CMV infection" and "CMV disease". For the sake of consistency, the term "CMV disease" is used, as CMV infection is defined as CMV antigenaemia without clinical signs of disease, whereas CMV disease is CMV antigenaemia with signs or symptoms of disease.

The age groups are not specified in current approved local SmPCs within section 4.1. However, most current local SmPCs include a statement in section 4.2 under the special patient populations heading.

The MAH provided data to support this indication in adults. The studies have been conducted by MAH in the treatment of CMV disease in patients with AIDS. Ten clinical studies were conducted during the period from 1986 till 1996, and some later. The majority of these studies were open-label controlled studies. In most of the studies efficacy of ganciclovir 2.5 mg/kg, 5 mg/kg, (induction treatment) 6 mg/kg i.v. b.i.d. doses used for 2 weeks followed by 5 mg/kg or 6 mg/kg maintenance doses were evaluated for treatment of CMV retinitis in AIDS patients. Results of these studies demonstrated beneficial effect on progression of disease and relapse of CMV infections.

In the following table 1 the summary of Company-Sponsored Studies in Patients with AIDS is given.

Table 1. Summary of Company-Sponsored Studies in Patients with AIDS

Author, Year	Pt Population/ Indication (age range)	Strategy	N	Study Design	Follow-up Period	Efficacy Results	Conclusion
Syntex ICM 1257 Induction, 1986	Life- or sight-threatening CMV Eligibility for efficacy evaluation: minimum 10 d induction treatment and positive CMV culture at baseline (4 mo-77 y)	5 mg/kg IV GCV b.i.d. for 1hr for 10-21 d, 14 d recommended	314	Open-label controlled	N/A	Viral response with reduction of CMV in 111/121 (92%) GCV-treated patients. Progression of CMV in 28/167 (87%) control patients, compared to 34/39 (17%) GCV-treated patients	IV GCV effectively reduces CMV progression in patients with life- and sight-threatening CMV infections
Syntex ICM 1257 Maintenance, 1986	Life- or sight-threatening CMV For efficacy: received minimum 10 d induction and positive CMV culture at baseline (2-63 y)	5 or 6 mg/kg IV GCV od 3 or 5 times weekly	127	Open-label controlled Long term maintenance	N/A	Control of CMV infection in 81% CMV retinitis, 86% CMV colitis and 100% CMV pneumonia patients. Time to relapse of retinitis was longer in high dose group (128 d) vs. no maintenance (41 d; p=0.0001) or low dose (51 d; p=0.0032). Time to relapse of CMV viruria was delayed from mean 30 d in no maintenance to 59 d in high dose; p=0.0214. GCV treated patients with retinitis or GI tract infections survived a mean of 185 d after CMV diagnosis, vs. 78 d for no treatment controls (p=0.0074)	IV GCV maintenance treatment at 25-35 mg/kg/week is efficacious in preventing or delaying clinical and viral relapse of CMV infections
Syntex AV/006-Europe, 1986	Chorioretinitis due to CMV infections in AIDS patients (28-50 y)	2.5 mg/kg IV b.i.d. or 5 mg/kg IV b.i.d. for 1hr over 14 d	9	Randomized multiple-dose	6 weeks	Improvement in 3/5 patients treated with GCV, 4/4 patients treated with 5 mg/kg b.i.d., no change in retinitis in 2/5 patients treated with 2.5 mg/kg.	Progression of CMV retinitis was halted in all 9 patients.
Syntex, Study ICM 1734, 1989	CMV retinitis in AIDS patients (24-51 y)	GCV 5 mg/kg IV b.i.d. for 2 weeks induction, then 6 mg/kg/d (30 mg/kg/wk) maintenance and 5 mg/kg/d (35 mg/kg/wk) induction for breakthrough CMV retinitis	157	Open-label compassionate care study	18 months	By fundus photographs, CMV retinitis progressed in 72% (75/104) of patients in oral group and 76% (28/37) in the IV group. Mean time to progression was 51 d with oral GCV and 62 d with IV GCV (p=0.15). By funduscopy, CMV retinitis progression in 59% (65/110) of oral patients and 43% (19/44) of IV patients. Mean time to progression was 86 d with oral GCV and 109 d with IV patients GCV(p=0.02)	Subgroup of patients with CMV retinitis at higher risk for development of retinal detachments. Suggests greater immune compromise in patients who failed to respond to GCV.
Syntex GANS1697, Spector et al. 1993	CMV retinitis in AIDS patients (21-50 y)	Immediate treatment with 5 mg/kg IV b.i.d. for 2 weeks induction, then 5 mg/kg/d for 14 weeks or deferred treatment with GCV if progression of CMV retinitis	18 (13 final) 24 (22 final)	Prospective randomized multicenter controlled	20 weeks	76.9% (10/13) of patients in immediate treatment group had progression of retinitis Median time to progression 49.5 d 90.9% (20/22) of patients in deferred treatment group had progression of retinitis Median time to progression 13.5 d	Induction followed by maintenance GCV (called immediate treatment in this study) delays the progression and incidence of CMV retinitis

Syntex Study AVI034; The Oral Ganciclovir European and Australian Cooperative Study Group 1995,	CMV retinitis in adult AIDS patients	Induction of 5 mg/kg IV b.i.d. for 2-3 weeks, then either 500 mg oral 6 times daily or 5 mg/kg IV od over 1hr	159	Randomized multicenter open-label	20 weeks	By fundus photographs, CMV retinitis progressed in 72% of patients in oral group and 76% in the IV group. Mean time to progression was 51 d with oral GCV and 62 d with IV GCV (p=0.15). By funduscopy, CMV retinitis progression in 59% of oral patients and 43% of IV patients. Mean time to progression was 86 and 109 d respectively (p=0.02).	Oral GCV offers a safe and effective alternative to IV GCV in the maintenance therapy of CMV retinitis.
Syntex, GAN1774, 1994	CMV retinitis in AIDS patients (22-56 y)	Maintenance therapy with Oral GCV 500 mg six times daily or 1000 mg three times daily IV GCV 5 mg/kg a d for 20 weeks	237	Randomized open-label parallel	20 weeks	Based on the time to treatment failure, all three treatment regimens were equivalent. Based on the ophthalmologic assessment, the mean/median times to progression in the IV-, oral 500 mg six times daily- and oral 1000 mg three times daily treatment groups were 100/106 d, 75/76 d and 76/62 d, respectively (log-rank p-values were 0.014 and 0.051). Based on the masked assessment of the fundus photographs, the mean/median d to progression in the IV-, oral 500 mg six times daily- and oral 1000 mg three times daily treatment groups were 66/54 d, 53/32 d and 54/53 d respectively (log-rank p-values were 0.153 and 0.065).	Maintenance therapy with 3000 mg oral GCV is equivalent to IV GCV.
Drew et al. 1995 (ICM 1653)	AIDS and newly diagnosed, stable CMV patients ≥13 years old	Induction of 5 mg/kg b.i.d. for 14 d, then 5 mg/kg od for 7d. Maintenance of 5 mg/kg IV od or 3 g oral od	161	Random-ized open-label	20 weeks	117 pts evaluated for efficacy. Fundus photography: mean time to progression of retinitis 62 d (IV GCV), 57 d (oral GCV; p=0.63). Funduscopy: mean time to progression 96 d (IV GCV), 68 d (oral GCV; p=0.03). Survival, changes in visual acuity, incidence of viral shedding, incidence of adverse GI events, sepsis similar for both groups	Oral GCV is a safe and effective alternative to IV GCV for maintenance therapy for CMV retinitis.
Roche, MV15139 (GANS2226), 1996	Adult AIDS patients with CMV retinitis	IV GCV 5 mg/kg/d or oral GCV 3 g, 4.5 g or 6 g in 3 divided doses for 26 weeks	281	Random-ized open-label parallel	26 weeks	Mean time to progression of CMV retinitis in patients with CMV retinitis for >100 d: IV GCV: 71 d Oral GCV 3 g: 43 d (p=0.025) Oral GCV 4.5 g: 72 d (p=0.028 compared to 3 g group) No significant difference between groups in time to progression in pts diagnosed with retinitis for <100 d. For pts with bilateral retinitis at baseline or active border lesions, mean time to progression was significantly longer in pts receiving IV or high dose oral GCV than in those receiving 3 g GCV daily.	Patients with longstanding retinitis, bilateral retinitis or active border lesions may derive greater benefit from higher doses of oral GCV or IV GCV.
Roche, GAN041, 1996	Adult AIDS patients with stable CMV retinitis	Maintenance therapy with oral GCV 3 g daily or oral GCV 6 g daily for 30 weeks	270	Random-ized multi-center double-blind	30 weeks	Progression of CMV retinitis in 68% (90/132) in 3 g group and 63% (86/137) in 6 g group. Mean/median times to progression based on retinal photographs in 3 g group were 74/43 d compared to 79/56 d for the 6 g group. When time to progression assessed according to a history of previous treatment for CMV retinitis the difference between groups was larger.	The 6 g dose of GCV was not superior to the 3 g dose but may offer increased benefit to those with retinitis of longer duration
Roche, MV15094 (GAN042), 2001	Adult AIDS patients with CMV retintits previously treated in GAN041	Maintenance therapy with oral GCV 6 g daily for 6 months with reinduction in case of progression	117	Open-label follow-up study	6 months	26% (31/117) patients required reinduction. Mean time from start of maintenance to first reinduction 139 d (SEM, 6.8 d, range 1-186).	Long-term maintenance treatment with 6 g GCV daily was generally well tolerated.
Roche WV15376, 2004. Martin et al. 2002	Adult AIDS patients with newly diagnosed CMV retinitis	Induction therapy oral VGCV 900 mg b.i.d. or IV GCV5 mg/kg b.i.d. for 3 weeks followed by oral VGCV 900 mg od or IV GCV5 mg/kg od for 1 week. Maintenance therapy (all pts) oral VGCV 900 mg od with reinduction permitted in case of progression	160	Randomized controlled multicenter phase II/III clinical study	Median 376 d (oral VGCV) 419 d (IV GCV)	Progression of CMV retinitis in first 4 weeks: 9.9% (7/71) oral VGCV vs. 10% (7/70) IV GCV Satisfactory response to induction: 71.9% (46/64) oral VGCV vs. 77% (47/61) IV GCV Median time to progression of retinitis: 160 d oral VGCV vs. 125 d IV GCV	Oral VGCV appears as effective as IV VGCV for induction treatment, convenient and effective for long-term management of CMV retinitis in AIDS patients.

Table 2. Non-Company Sponsored Studies: Treatment of CMV Disease in Patients with AIDS

Author, Year	Study Objectives	Study Design	Diagnosis	No. of subjects (M/F)	Treatment (GAN)	Control	Efficacy Results	Conclusions
Martin et al. 2007	Comparison of incidence of resistance to anti-CMV therapy in the pre-HAART and HAART eras	Prospective observational	CMV retinitis and AIDS (adults)	257 (69.3%/ 30.7%)	Not available	Either GCV oral, VGCV, or GCV intraocular implant	2 year incidence of GCV resistance was 28% for those enrolled before 1996 and 8.8% for those enrolled after 1996	Antiviral therapy has contributed to a decrease in GCV resistance
Jabs et al. 2010	To evaluate the effect of drug-resistant CMV on survival among pts with CMV retinitis	Prospective	AIDS and newly diagnosed CMV retinitis	266 (69.2%/ 30.8%)	Details not available. Pts were treated with either GCV or foscarnet	None	Median survival was 12.6 months; Resistant CMV was associated with increased mortality (HR [95% CI] 1.65 [1.05, 2.56], p=0.032); Time since AIDS diagnosis was associated with mortality, (HR 1.10 per year since AIDS diagnosis, p=0.001)	Among pts with CMV retinitis, the occurrence of resistant CMV is associated with an increased risk for mortality in addition to the previously noted increased risk of poor visual outcomes

The efficacy of ganciclovir in treating CMV retinitis in patients with AIDS has been established in studies including over 2500 patients (both i.v. and oral therapies). The studies demonstrate the efficacy of i.v. ganciclovir in the treatment, maintenance, and prevention of CMV disease but long-term i.v. therapy is less convenient for patients than oral therapy and is associated with higher costs. The use of oral ganciclovir was investigated where it was shown that oral ganciclovir is an efficacious treatment option for maintenance therapy of CMV retinitis (table 1) and that compared with placebo, prophylactic oral ganciclovir reduces the risk of CMV disease in patients with advanced AIDS. However, oral ganciclovir is not in use any longer.

One randomised open-label parallel clinical study (multicentre Study MV17973 (VICTOR)) assessed the effectiveness of valganciclovir compared with i.v. ganciclovir for the treatment of CMV disease in solid organ transplant (SOT) patients. 326 patients were enrolled in the study. Patients received oral valganciclovir 900 mg twice daily for 21 days, or i.v. ganciclovir 5 mg/kg twice daily for 21 days. Thereafter, maintenance (secondary prophylaxis) treatment with oral valganciclovir was given to all patients in both arms up to Day 49 at a dose of 900 mg once daily. The proportion of patients with virological and clinical recurrence of CMV disease was similar between the two treatment groups, while the time to first CMV disease recurrence was shorter among patients in the valganciclovir group (104 vs. 143 days; p = not significant).

There are no MAH-sponsored studies of CMV treatment in stem cell transplant recipients. Various clinical treatment guidelines advise on appropriate treatment and prevention of CMV disease in stem cell transplant recipients. One non-systematic review of CMV disease diagnosis, prevention, and treatment in hematopoietic stem cell transplant (HSCT) recipients was conducted. In allogenic HSCT recipients, the review concluded that CMV disease should be treated with antiviral agents such as ganciclovir or foscarnet with 2-3 weeks of induction therapy followed by 3-4 weeks of maintenance therapy.

There are no MAH-sponsored studies of CMV treatment in oncology patients. Guidelines recommend using ganciclovir for CMV prophylaxis in allogenic stem cell transplant recipients and in patients receiving alemtuzumab therapy. Recommendations from the European Conference on Infections in

Leukaemia say that patients receiving alemtuzumab should receive antiviral therapy with ganciclovir, valganciclovir, or foscarnet. Patients with end-organ disease should receive antiviral therapy.

The treatment of CMV disease in stem cell transplant (SCT) and solid organ transplant (SOT) recipient is recommended by all guidelines, the data supporting the proposed indication are obtained from published literature.

Indication for the prevention of CMV disease

Cymevene is currently specifically indicated for the prevention of CMV disease in transplant recipients in the majority of E.U. Member States. Transplant recipients are described as organ or bone marrow recipients in some Member States.

In Finland, Italy, Portugal, Poland, the Czech Republic, and Spain, Cymevene is indicated for the prevention of CMV disease in immunocompromised individuals, which encompasses patients with AIDS, transplant recipients, and oncology patients with iatrogenic immunosuppression.

The MAH provided data of several clinical studies to support this indication.

Early clinical studies showed the benefit of Cymevene for primary CMV prophylaxis in patients with AIDS. However, since highly active antiretroviral therapy (HAART) was established, prevention of CMV infection is achieved by using anti-retroviral medicines and routine use of ganciclovir for prevention of CMV disease is not recommended. (HAART) has reduced the risk of CMV disease in patients with AIDS. Before the introduction of HAART, approximately 30% of patients with AIDS experienced CMV retinitis, making CMV prophylaxis necessary. When early manifestations of CMV disease have been identified, therapy for CMV disease should be initiated.

In patients with AIDS routine prevention of CMV disease with ganciclovir is no longer recommended because the highly active antiretroviral therapy (HAART) has reduced the risk of CMV disease in patients with AIDS. Before the introduction of HAART, approximately 30% of patients with AIDS experienced CMV retinitis, making CMV prophylaxis necessary. CMV prophylaxis in patients with HIV or AIDS is best achieved by using HAART to maintain CD4 count >100 cells/mm3 and monitoring patients to identify early manifestations of CMV disease.

Later studies have been conducted with solid organs transplantation (SOT) recipients (tables 3 and 4) and stem cell transplantation (SCT) recipients (tables 5 and 6).

A Syntex –sponsored multicenter, double-blind, randomized, placebo-controlled Study ICM 1496, was conducted to evaluate the efficacy and safety of i.v. ganciclovir for the prevention of CMV disease in adolescent and adult heart transplant recipients. Ganciclovir effectively reduced incidence of CMV, CMV and transplant recipients.

A MAH-sponsored, multicentre, double-blind, randomized, placebo-controlled, parallel-group, Phase III Study MV15093 (GAN040) was conducted to evaluate the efficacy and safety of oral ganciclovir for the prevention of CMV disease in liver transplant recipients. Oral ganciclovir effectively reduced incidence of CMV disease in R+, R- and D+/R- liver transplant recipients.

MAH-sponsored, single centre, retrospective study was conducted to evaluate the efficacy of i.v. ganciclovir for the prophylaxis of CMV disease in adult heart transplant recipients. It was concluded that longer CMV prophylaxis with ganciclovir reduces the risk of CMV disease.

A Syntex –sponsored randomized, controlled Study ICM 1570, (table x, above) was conducted to evaluate the efficacy and safety of i.v. ganciclovir for the prevention of CMV interstitial pneumonia in

adolescent and adult bone marrow recipients. Ganciclovir effectively reduced the development interstitial pneumonia in recipients with asymptomatic infection.

A Syntex –sponsored randomized, double blind controlled Study ICM 1689, was conducted to evaluate the efficacy of i.v. ganciclovir for early treatment of CMV infection in asymptomatic allogenic bone marrow recipients with positive CMV cultures. Early treatment with ganciclovir in CMV positive patients reduces the incidence of CMV disease and improves survival.

Several non –MAH sponsored supportive studies were also presented to support the indication.

There have been no MAH-sponsored studies conducted solely in oncology patients other than those in patients undergoing stem cell transplants.

Table 3. Summary of MAH-Sponsored/Supported Studies of CMV Disease Prevention in SOT (solid organ transplant) Recipients

Author, Year	Pt Population (Indication)	Strategy	N	Study Design	Follow-up Period	Efficacy Results	Conclusion
Syntex ICM 1496, Merigan et al. 1992	CMV prophylaxis in heart tx recipients ≥ 13 years of age (youngest patient in GCV group was 16)	IV GCV 5 mg/kg b.i.d. post-op days 1-14 then 6 mg/kg od for 5 days/week to week 28 or placebo	56 (CMV positive) 37 (CMV negative)	Randomized double-blind placebo-controlled multicenter	120 days	CMV disease up to 120 days post transplant in CMV positive patients: GCV 9%(5/56) Placebo 46% (26/56) p<0.001 CMV disease up to 120 days post transplant in CMV negative patients: GCV 35% (7/20) Placebo 29% (5/17) p = not significant	Prophylactic GCV after heart tx reduces incidence of CMV disease in CMV positive pts
Roche, MV15093 (GAN040), 1996	Prevention of CMV disease in adult liver tx recipients	Oral GCV 1 g three times daily started by Day 10 post-tx and continued until week 14 or placebo	304	Randomized multicenter double-blind placebo-controlled parallel-group phase III	6 months	CMV disease at 6 months: GCV 4.8% Placebo 19.5% p<0.001 CMV disease at 6 months in R+ pts: GCV 3.2% Placebo 14.9% p=0.001 CMV disease at 6 months in R– pts: GCV 14.1% Placebo 42.3% p=0.019 CMV disease at 6 months in D+/R– GCV 14.8% Placebo 44% p=0.019 Tissue invasive CMV disease at 6 mo: GCV 0.7% Placebo 9.8% p<0.001	Oral GCV effectively reduced the incidence of CMV disease in R+, R–, and D+/R– liver tx recipients
Roche, PV16000, 2003	CMV disease prophylaxis in D+/R– heart, liver, kidney, and kidney-pancreas tx recipients ≥ 13 years of age (study included <10 pts aged 13-18 y)	Oral VGCV (900 mg od) vs. oral GCV (1 g three times daily) for 100 days	239 VGCV 125 GCV	Randomized double-blind double-dummy active-comparator controlled multicenter phase III	6 months	CMV disease at 6 months post-tx: VGCV 12.1% (n=239) GCV 15.2% (n=125) CMV disease at 12 months post-tx: VGCV 18.4% (n=239) GCV 17.2% (n=125)	Efficacy of oral GCV (1 g three times daily) is comparable to that of VGCV (900 mg od) given up to 100 days post-tx for CMV disease prevention in D+/R– pts.
Roche-supported, Li et al. 2007	CMV prophylaxis in adult heart tx recipients	Before Dec 1986: IV GCV 5 mg/kg b.i.d. (postop days 1-14), 6 mg/kg/day (postop days 15-28), oral aciclovir 800 mg 4 times daily for 3 months After Dec 1986: IV GCV 5 mg/kg until oral meds tolerated then oral GCV 1 g three times daily for 3 months	274	Retrospective single-center (to assess incidence and clinical features of GCV-resistant CMV disease)	12 months	CMV disease incidence at 12 months in D+/R– group 53.8% in short-term prophylaxis group vs. 25.8% in long-term prophylaxis group	Longer CMV prophylaxis with GCV reduces the risk of CMV disease in heart tx recipients

Roche supported, Chmiel et al. 2008	CMV prophylaxis in lung tx recipients ≥16 years of age	IV GCV 5 mg/kg b.i.d. (postop Day 7-21), then oral GCV 1 g three times daily until prednisone dose tapered to <0.1 mg/kg/d. Pts treated from April 2003 received VGCV 900 mg daily instead of GCV. Pts compared to 8 historical controls	96	Prospective	5 years	CMV disease: 11% GCV/VGCV 75% historic control (p<0.001) Active CMV infection at 5 years: 31% GCV/VGCV 75% historic control (p<0.01) CMV disease at 5 years: 16% GCV/VGCV 75% historic control (p<0.01) 5-year survival: 73% GCV/VGCV 47% historic control (p=0.036)	GCV/VGCV prophylaxis significantly decreased incidence of CMV-related events compared to historic controls
Roche-supported., Shiley et al. 2009	CMV prophylaxis in high-risk adult liver tx recipients	Oral VGCV 900 mg daily or oral GCV 1 g three times daily or IV GCV 6 mg/kg/day for 100 days post-tx	66	Retrospective cohort study	12 months	Overall 12.1% (8/66) patients developed CMV disease: VGCV groups 22.2% (6/27) Oral GCV 5.9% (1/17) IV GCV 4.5% (1/22) All patients with CMV disease responded to IV GCV.	Risk of late-onset CMV disease higher with VGCV than GCV in high-risk liver tx recipients.

Table 4. Summary of Non-MAH Sponsored Studies of CMV Disease Prevention in SOT Recipients

Author, Year	Pt Population (Indication)	Strategy	N	Study Design	Follow-up Period	Efficacy Results	Conclusion
Winston et al. 2012	D+/R− adult liver transplant recipients	Oral maribavir 100 mg b.i.d. or oral GCV 1 g three times daily for up to 14 weeks	147 156	Randomized, double-blind, multicenter study	6 months	Recruitment stopped due to lack of efficacy in separate study. Primary endpoint was confirmed CMV disease within 6 months. Non-inferiority of maribavir compared to GCV was not established, significantly fewer GCV patients had confirmed CMV disease or CMV infection at 100 days (20% vs. 60%, p < 0.0001) and at 6 months (53% vs. 72%, p = 0.0053) post-transplant.	Maribavir was not adequate for prevention of CMV disease in liver transplant recipients at high risk of CMV disease
Fayek et al. 2010	Adult liver transplant recipients	Oral VGCV 900 mg/day or oral GCV 1 g three times daily for 90 days (D+/R− patients received induction with IV GCV for the first 14 days of prophylaxis)	86 65	Single-center, retrospective analysis	1 year	Similar incidence of CMV disease (VGCV 7%, GCV 4.6%, p = 0.4). Incidence of CMV disease in high-risk patients similar (VGCV 8.0%, GCV 11.7%) 1-year patient survival: VGCV 84.2%, GCV 84.6% (p = 0.8). 1 year graft survival: VGCV 84.2%, GCV 84.6% (p = 0.9).	VGCV non-inferior to GCV
Antolin et al. 2011	Liver transplant recipients	Universal prophylaxis with oral aciclovir or GCV (n = 38) or VGCV (n = 149)	187	Retrospective chart review	≥6 months	5.26% of aciclovir or GCV patients were CMV seronegative compared to 5.37% of VGCV patients (p>0.05). CMV infection rate was 2.6% in patients with aciclovir or GCV while no CMV disease was detected in VGCV patients	Universal prophylaxis is beneficial in preventing CMV infection. VGCV was most effective
Abou-Ayache R., 2011	D+/R− adult kidney transplant recipients	Follow-up of patients who received 90-days of oral GCV in the ECTAZ study	109	Multicenter observational follow-up study	3 years	45.0% (49/109) patients developed CMV infections, syndrome or disease. Patient survival was similar in patients irrespective of CMV status. There was a tendency for increased numbers of cancer events and infections in patients with CMV infection.	CMV prophylaxis might reduce the incidence of long-term complications in renal transplant recipients.
McGee et al. 2012	Adult renal transplant recipients	D+/R− patients Oral VGCV or IV GCV 3-month prophylaxis Other serostatus No prophylaxis	448	Retrospective analysis	3 years	Incidence of CMV disease: Overall 7% D+/R− 16.9% D+/R+ 6.3% D−/R+ 4.9% D−/R− 2.4% Death-censored graft survival: D+/R− 75% D+/R+ 92% D−/R+ 94% D−/R− 96% (log rank p=0.01)	3-month prophylaxis delayed onset of CMV disease in D+/R− but did not prevent it. Prolonged prophylaxis might be required to improve graft survival in high risk renal tx recipients

Kuo et al. 2010	Adult renal transplant recipients	Impact of CMV serostatus on acute rejection and long-term outcomes of death-censored graft failure and mortality. Impact of antiviral treatment on long-term outcome	25058	Registry analysis of deceased renal transplant recipients	CMV serostatus was not associated with acute rejection. D+/R− status was associated with an increased risk of death-censored graft failure compared to D−/R− (p=0.01). All-cause mortality (p=0.003) and mortality due to viral infection (p=0.04). In D+/R− patients VGCV use was associated with a decreased risk of death-censored graft failure (p=0.007) and mortality due to viral infection (p=0.03) compared to GCV	D+/R− status was not a risk for acute rejection in patients receiving CMV prophylaxis but was still a risk factor for death-censored graft failure, all-cause mortality and mortality due to viral infection

Table 5. Summary of Company-Sponsored Studies of CMV Disease Prevention in Bone Marrow Transplant or Peripheral Blood Stem Cell Transplant Recipients

Author, Year	Pt Population (Indication)	Strategy	N	Study Design	Follow-up Period	Efficacy Results	Conclusion
Syntex ICM 1570, Schmidt et al. 1991	Allogenic bone marrow recipients with asymptomatic pulmonary CMV infection (aged 17 -46 years)	IV GCV 5 mg/kg b.i.d. for 2 weeks then 5 mg/kg 5 times a week until day 120 post transplant or observation	40	Randomized, controlled study	120 days	Incidence of death or CMV pneumonia by day 120: 25% (5/20) GCV 70% (14/20) control group (relative risk 0.36; p = 0.01).	Prophylactic GCV reduces the development of CMV interstitial pneumonia in pts with asymptomatic infection.
Syntex ICM 1689, Goodrich et al. 1991	Allogenic bone marrow recipients with asymptomatic CMV infection (aged 3-56 years)	IV GCV 5 mg/kg b.i.d. for 1 week then 5 mg/kg/daily for 100 days post transplant or placebo	72	Double blind, randomized, controlled study	180 days	Incidence of CMV disease 3% (1/37) GCV 43% (15/35) placebo (p<0.0001) Survival at 100 days 1 death GCV 6 deaths placebo (p = 0.041) Survival at 180 days 4 deaths GCV 11 deaths placebo (p = 0.027)	Early treatment with GCV in CMV positive patients reduces the incidence of CMV disease and improves survival

Table 6. Summary of Non-company Sponsored Studies of CMV Disease Prevention in Bone Marrow Transplant or Peripheral Blood Stem Cell Transplant Recipients

Author, Year	Pt Population (Indication)	Strategy	N	Study Design	Follow-up Period	Efficacy Results	Conclusion
Kim et al. 2010	Allogeneic HSCT patients with CMV infection (aged 16-49)	5 mg/kg IV GCV b.i.d. for 7 days then 5 mg/kg IV GCV od for 6 days/week for up to 6 days after CMV negative or 5 mg/kg IV GCV od 6 days/week for up to 6 days after CMV negative	68	Randomized pre-emptive therapy study	Median 42 months	No recurrence of CMV infection in either group. Overall incidence of CMV disease was similar between the two groups during the follow-up period. No statistically significant difference in the occurrence of early or late CMV disease, in the frequency and severity of GCV-induced neutropenia and mortality rate 180 days after HSCT between treatment groups.	Both doses of GCV were equally effective in the prevention of CMV infection when administered as pre-emptive therapy
Park et al. 2012	Adult allogeneic HSCT patients	Pre-emptive low-dose: 5 mg/kg IV GCV od or standard-dose: 5 mg/kg IV GCV b.i.d. (12 hourly)	97	Prospective interventional	100 days	24% of pts with initial pre-emptive therapy had a second episode of CMV infection, 8/53 (15%, low-dose), 15/44 (34%, standard-dose; p=0.03), time to onset 87 days (both groups). No significant difference between treatment groups in successful viral clearance and CMV disease.	Low-dose GCV is as safe and at least as effective as standard-dose pre-emptive therapy in allogenic HSCT recipients

There are no MAH-sponsored studies of CMV treatment in stem cell transplant recipients but various clinical treatment guidelines advise on appropriate treatment and prevention of CMV disease in these patients. The MAH recommend ganciclovir to be used for iatrogenic immunosuppression associated

with transplantation but do not distinguish between solid organ transplantation and bone marrow transplantation.

There have been no MAH-sponsored studies conducted of CMV prevention in oncology patients but there are 4 non-company sponsored studies shown in table 7. These studies show that ganciclovir should be considered in patients receiving chemotherapy, especially in patients with haematological malignancy. Clinical trials include only patients with haematological malignancies and little is known about CMV prevention in other cancer patients. Other oncology patients receiving chemotherapy do not routinely require CMV prophylaxis but certain high-risk patients, such as Asian patients, particularly those receiving rituximab or hyper-CVAD chemotherapy, may benefit.

There is a lack of clinical trials that show CMV prevention efficacy in other oncology patients.

Table 7. Summary of Non-Company Sponsored Studies of CMV Disease Prevention in Oncology Patients

Author, Year	Pt Population (Indication)	Strategy	N	Study Design	Efficacy Results	Conclusion
Laurenti et al. 2004	Adult pre-treated ALL pts receiving alemtuzumab	Alemtuzumab withdrawal and pre-emptive oral GCV treatment initiation (1 g three times daily) if CMV reactivation detected	12	Prospective study	8 pts developed CMV reactivation. GCV therapy was initiated and all pts had negative CMV assays after a median of 14 days with no progression to CMV disease.	Pre-emptive GCV appears effective in pts with CMV reactivation during alemtuzumab therapy.
Visani et al. 2006	Adult pre-treated CLL pts receiving alemtuzumab	GCV prophylaxis during and for 1 month after alemtuzumab discontinuation IV GCV 7.5 mg/kg once weekly for pts enrolled from January 2004, or Oral aciclovir 800 mg twice daily for pts enrolled from February to December 2003 Any pts developing CMV infection were treated with IV GCV 7.5 mg/kg/day for 2 weeks or until negative antigenemia	10 5	Observational study	There were 5 CMV reactivations, 4 in the aciclovir group and 1 in the GCV group. All 5 pts were treated with IV GCV and achieved negative CMV antigenemia after a median of 15 days.	Weekly IV GCV prophylaxis appears effective in preventing CMV reactivation in this high-risk group
O'Brien et al. 2008	Adult pts with CLL, ALL, hairy cell leukaemia and other forms of leukaemia or lymphoma receiving alemtuzumab	Oral VGCV 450 mg twice daily or Oral valaciclovir 500 mg as CMV prophylaxis during and for 2 months after alemtuzumab discontinuation.	20 20	Randomized controlled trial	Study terminated early after enrolling 40 evaluable pts because of superiority of VGCV treatment. 7/20 valaciclovir pts experienced CMV reactivation compared to no VGCV pts (p=0.004).	Oral provides VGCV highly effective CMV prophylaxis in pts receiving alemtuzumab. Study has been criticized for heterogeneity of underlying disease in study population and variability in alemtuzumab regimens employed.
Tay et al. 2014	All pts with lymphoma treated with potentially curative or salvage therapy at Asian cancer center from 2007-2010 were reviewed for occurrence of CMV infection or end-organ disease	Pts with symptomatic CMV infection or end-organ disease treated with GCV or foscarnet	534	Retrospective study	Incidence of CMV infection 9% (48/534) 12/48 pts had end-organ disease, 8 were treated with GCV and 4 with foscarnet. 5 pts died. 36/48 pts had CMV infection that did not progress to end-organ disease. 21 pts were asymptomatic and received no treatment; all pts remained asymptomatic and survived. 15 pts with symptomatic CMV infection were treated with GCV or foscarnet of which 7 died (number of pts receiving each drug not specified). All pts who died had progressive lymphoma. Cause of death was pneumonia (n=9), neutropenic sepsis (n=2) and pulmonary embolism (n=1)	In this high-risk group pre-emptive or prophylactic CMV therapy should be considered, especially in pts receiving hyper-CVAD.

Paediatric Population

The MAH has not conducted formal studies in the paediatric patient population. In clinical practice, ganciclovir is used in children, as in adults, for the treatment of life- or sight-threatening CMV disease in immunocompromised individuals and for the prevention of CMV disease in transplant recipients. Summary of published non-company sponsored clinical studies of ganciclovir in paediatric use are seen in table 8.

Table 8. Summary of published non-company sponsored clinical studies of ganciclovir in paediatric use

Author	Study Objectives	Study Design	Diagnosis	No. of Subjects (age)	Treatment Regimen	Results	Conclusions
HIV/AIDS							
Frenkel et al. 2000	Evaluation of the safety, efficacy and PK of oral GCV (PK results not presented as oral GCV no longer available)	Multi-centre dose escalation trial	HIV with positive CMV culture	36 children (6 months - 16 yrs)	Oral GCV 10-50 mg/kg every 8 hours for 4-116 weeks	Efficacy: CMV detection markedly decreased after 12 weeks Recurrence of CMV infection/new onset CMV disease occurred infrequently (in 7 [19.4%] and 3 [8.3%] respectively). Of the 3 children who developed CMV disease, one developed CMV resistance, one harbored resistant virus at study entry and the third had wild-type CMV. Safety: Toxicity minimal and manageable. Similar toxicity profile to that seen in adults. Neutropenia only severe ADR observed. No patients required treatment cessation, but 4 required G-CSF to maintain absolute neutrophil counts > 400 cells/mm^3.	The authors conclude that oral ganciclovir should prevent CMV disease in severely immunocompromised children with HIV and CMV infection.
SOT recipients							
Megison and Andrews 1991	Evaluation of GCV combined with IgG	Retro-pective review	Liver Tx recipients with symptomatic CMV infection	12 children (1-15 yrs)	IV ganciclovir 5 mg/kg twice daily and IgG 1 g/kg daily for 14 days	Efficacy: 1 death due to refractory CMV pneumonitis requiring mechanical ventilation. 3 patients had recurrent CMV infections (2 symptomatic and responded to 2nd course of GCV and IgG, 1 shed CMV in his urine but was asymptomatic and was not retreated). Safety: 1 patient had myelosuppression, which resolved without a reduction in ganciclovir dose. 7 patients had renal dysfunction possibly due to concomitant administration of nephrotoxic drugs (all received cyclosporine, 3 vancomycin, 2 amphotericin and 1 amikacin).	IV GCV combined with IgG is effective for the treatment of CMV infections in immune-suppressed children following liver transplantation.
Spivey et al. 2007	To assess feasibility, safety, and short-term efficacy of extending IV GCV from six to 12 weeks for CMV prophylaxis	Open label pilot	Lung Tx	9 children (6-18 yrs)	IV GCV started on day of transplantation at a dose of 5 mg/kg/dose every 12 h for 21 days. Then IV GCV dose was decreased to 5 mg/kg/dose every 24 h until end of therapy.	Efficacy: One subject (11%) had a positive viral culture for CMV Safety: No neutropenia, thrombocytopenia or renal toxicity were recorded.	Extending IV GAN to at 12 weeks after paediatric lung Tx appears to be a feasible and safe regimen for the prevention of CMV infection

Madan et al. 2009	To assess hybrid prevention using short-course antiviral prophylaxis and pre-emptive CMV PCR monitoring	Retro-spective study	Liver Tx	122 children (16 days -18 yrs)	IV GCV, mean duration 12.9 days	Efficacy: CMV+ by PCR but asymptomatic = 34.4%, High risk = 58.1%, Routine risk = 21.8%, p = 0.0001 CMV disease: High risk = 8, Routine risk = 4, p = 0.03 38.5% of subjects discontinued antivirals after post-operative prophylaxis	Hybrid approach combining short-course antiviral prophylaxis and pre-emptive PCR screening may provide an effective preventative strategy for CMV-related complications
Lapidus-Krol et al. 2010	Assessment of efficacy and safety of VGCV vs. oral GCV in prevention of sympto-matic CMV infection	Retrospective	Renal and liver Tx	92 children (9 months - 17 yrs)	IV GCV (5 mg/kg b.i.d.) for 2 weeks post-Tx, then Oral GCV 30-1000 mg/kg three times daily or IV GCV (5 mg/kg b.i.d.) for 2 weeks post-Tx, then VGCV up to 900 mg od for 3 months in D+/R+ or D–/R+ and for 6 months in D+/R– recipients	Efficacy: Symptomatic CMV infection/ disease: VGCV = 13.7%, GCV = 19.5% Time-to onset of CMV infection was comparable in both groups Rates of acute rejection similar in both groups (3.9% vs. 9.8%). Safety: 3 adverse events: 1 GCV pt. withdrew because of a rash (related to GCV), 1 VGCV pt. had nephrotoxicity and 1 VGCV pt had mild thrombocytopenia	As in adults, VGCV and oral GCV appear to be similarly safe and efficacious
Jongsma et al. 2013	Evaluation of efficacy of prophy-lactic regimens	Retro-spective obser-vational study	SOT recipients	159 children (2-17 yrs)	High-risk pts (D+/R–) VGCV/GCV for 3 months, or aciclovir plus CMV IgG. Intermediate-risk patients (R+) valaciclovir/aciclovir, or aciclovir plus CMV IgG. Low-risk patients (D–/R–) did not receive prophylaxis.	Efficacy: CMV infection in 41% of high-risk, 24% of intermediate-risk, and 13% of low-risk patients, in the latter two groups typically during the first three months. Infection rate highest in the high-risk group after cessation of VGCV/ GCV prophylaxis. VGCV/ GCV provided better protection than aciclovir + CMV IgG. Adding an IL2-receptor blocker to the immunosuppressive regimen did not affect the infection rate. Safety: no safety data available from this study.	Authors concluded VGCV/ GCV prophylaxis effectively prevents CMV infection in high-risk paediatric kidney recipients, but only during prophylaxis. VGCV/ GCV provided better protection than aciclovir plus CMV immunoglobulin.
Renoult et al. 2008	Evaluation of pre-emptive CMV-IG with IV GCV for high risk pts	Retrospective study	Renal Tx	31 children (10-17 yrs)	All high-risk patients received CMV IG prophylaxis with IV GCV 5 mg/kg b.i.d. introduced on CMV detection and continued until two consecutive weeks without CMV detection	Efficacy: CMV infection was seen in 11/31 (35%) patients and 3 of these patients developed CMV. The 11 patients with CMV infection received IV GCV for a mean duration of 27 days. 3 of these patients developed recurrent CMV infections and received further GCV. There were no cases of post-transplant lymphoproliferative disease and no deaths in the study group. Safety: No side effects were reported. There were no bacterial or fungal opportunistic infections.	CMV IgG prophylaxis with pre-emptive ganciclovir was a successful strategy for preventing CMV disease in paediatric kidney transplant recipients.

Saitoh et al. 2011	Evaluation of efficacy of pre-emptive GCV	Obser-vational study	Live-donor liver Tx	113 children (1 month – 21 yrs)	Patients with positive antigenemia received IV GCV 5 mg/kg bd for 14 days then od until antigenemia became negative. From 2009 oral VGCV given for maintenance therapy following induction with IV ganciclovir. 38/44 patients with positive antigenemia received IV GCV as initial therapy (4 received IV foscarnet when GCV resistance was suspected, although no ganciclovir resistant strains were identified). Three patients received oral VGCV after IV GCV induction.	Efficacy: positive CMV antigenemia was documented in 44/113 patients (39%). 38/44 (86%) received IV GCV for a mean duration of 14 days (range 6-24 days). All were successfully treated with GCV with resolution of signs, symptoms and CMV antigenemia. CMV disease was documented in 6/113 (5%) patients and they were successfully treated with GCV without any sequelae. Seven patients were retreated with GCV when CMV-pp65 antigenemia became positive after completion of initial ganciclovir therapy. Safety: Neutropenia was observed in 3 patients (7%) but resolved on therapy discontinuation.	Pre-emptive GCV provides a safe and effective method of targeting drug treatment to those at greatest risk. However, study only included live-donor liver transplant recipients who require less immunosuppression than patients receiving a cadaver liver; results cannot be extrapolated to all paediatric liver transplant recipients.
HSCT recipients							
Schön-berger S., 2010	To assess efficacy of a prospective viral monitoring programme	Pros-pective study	HSCT	40 (0.1-19.4 yrs)	At start of conditioning, all pts received antiviral prophylaxis with acyclovir. IV IgG was administered on day -1, day +21 and thereafter if the Ig level dropped below normal levels. Recurrent viral DNAemia for CMV, EBV and HHV6 prompted initiation of pre-emptive GCV at induction dose of 5 mg/kg/12 hours continued until viral load dropped below the PCR thresholds.	Efficacy: Viral DNA detected in 25/40 pts (63%) over median follow-up period of 3.7 years. Most pts tested positive for CMV (11/40 patients) or EBV (19/40 patients). Median time to first detection of viral DNA 77 days (range 12-919 days) and median duration of GCV therapy 25 days (range 12-147 days). Risk for recurrent DNAemia and viral disease significantly higher in pts with non-malignant disease. In non-malignant disease cohort 6/10 patients developed viral disease compared to 3/30 patients in the malignant disease cohort. CMV occurred in 4/10 patients in the non-malignant disease group compared to 1/30 in the malignant disease group. During the course of the study most patients tested positive for viral DNA at least once but pre-emptive GCV therapy limited the extent of viral DNAemia and the manifestations of viral disease and no deaths from viral DNAemia or viral disease occurred. Safety: No toxicities were observed during pre-emptive therapy.	PCR-guided viral monitoring is critically important and prophylactic acyclovir and pre-emptive GCV is adequate to prevent viral disease in paediatric HSCT recipients
Shin et al. 2013	Evaluation of pre-emptive CMV therapy with half-dose IV GCV	Retros pective analysis	HSCT	155 (age not specified)	Pre-emptive IV ganciclovir 5 mg/kg once daily following positive CMV antigenemia in < 10/200 000 cells or 5 mg/kg twice daily daily following positive CMV antigenemia in ≥ 10/200 000 cells	Efficacy: CMV antigenemia was detected in 73 (47.1%) patients. 59 patients received half dose pre-emptive GCV therapy. Of these 16 (31.4%) showed an increase of CMV antigenemia necessitating initiation of full dose GCV. None of the patients developed CMV disease. Safety: None of the patients receiving half dose therapy developed significant neutropenia.	Pre-emptive GCV effectively prevented CMV following HSCT. Initiating treatment with a half dose was safe in patients with positive CMV antigenemia in < 10/200000 cells

Treatment guidelines recommend that in general, the principles guiding CMV prophylaxis in adults apply also to children.

The safety and efficacy of ganciclovir in children under 12 years of age has not been established. The use of Cymevene in the paediatric population warrants extreme caution due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should be carefully weighed against the risks.

Clinical trials include only patients with haematological malignancy. MAH state that other oncology patients receiving chemotherapy do not routinely require CMV prophylaxis but certain high-risk patients, such as Asian patients, particularly those receiving rituximab or hyper-CVAD, may benefit. As there is a lack of clinical trial data, the indication for prevention of CMV in patients receiving cancer therapy seems not justified. The wording can be changed to only include patients with haematological malignancies.

The use of ganciclovir in paediatric transplant recipients and patients with AIDS/HIV is recommended in current authoritative treatment guidelines, but the clinical data in trials are scarce. However the benefit-risk conclusion and posology can, in the CHMP view, be extrapolated to adolescents of 12 years and older considering the very serious nature of the disease it is indicated for.

The British Transplantation Society in the third edition (2011) of their guidelines for the prevention and management of CMV disease in SOT recipients, recommend treatment of CMV disease with i.v. ganciclovir (or valganciclovir) until resolution of symptoms (1B), with foscarnet and cidofovir as second line treatment options (Not graded, B).

The MAH has not conducted formal studies in the paediatric patient population. The proposed therapeutic indication (and posology) for children from 12 years of age is based on non-company sponsored ganciclovir studies and treatment guidelines[1]. The inclusion criteria regarding the age of eligible patients in ganciclovir studies are variable. Some of the studies are conducted predominantly in adults, but also included children.

Clinical trials have been conducted in children with congenital CMV, HIV/AIDS, or following organ transplantation, and treatment guidelines recommend its use. However, studies or clinical treatment guidelines that specifically address the use of ganciclovir in children receiving cancer chemotherapy are lacking.

Safety and efficacy data from valganciclovir studies conducted in children were also presented as relevant to the safety and efficacy of ganciclovir (clinical use of valganciclovir, the pro-drug of ganciclovir, has been approved in EU for paediatric SOT recipients for prevention of CMV disease.)

Overall the CHMP accepted the justifications and the data presented by the MAH for the use of ganciclovir in the paediatric population of 12 year and above. The CHMP also noted the worksharing (Art 45) with data on the paediatric population including children below 12 years of age. All the existing data that is collected by the MAH may be submitted after the finalisation of this Article 30 referral procedure, in a separate procedure at national level to support any changes to the use in the paediatric population.

Following all the above data assessment the CHMP concluded that the final harmonised indication wording in the treatment and prevention of CMV disease is:

Cymevene is indicated in adults and adolescents from 12 years of age for the:

- *treatment of cytomegalovirus (CMV) disease in immunocompromised patients;*
- *prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).*

Consideration should be given to official guidance on the appropriate use of antiviral agents.

[1] Department of Health and Human Services. Panel on Opportunistic Infections in HIV-exposed and HIV-Infected Children. 2013 [cited April 2014].

Section 4.2 - Posology and Method of Administration

The harmonised information on posology was presented by the MAH per indication, i.e. standard dosage for treatment of CMV disease in adults and children from 12 years of age with normal renal function and standard dosage for prevention of CMV disease in adults and children from 12 years of age with normal renal function using prophylaxis or pre-emptive therapy.

Special dosage instructions are provided for older people and patients with renal impairment. The dosage recommendations proposed by MAH are in line with the indications. Cymevene is indicated for use in adults and children from 12 years of age. Clinical studies, pharmacodynamics data, and treatment guidelines are provided to support the use of the same dose in adults and children from 12 years of age for treatment and prevention of CMV disease.

Posology for treatment of CMV disease

The MAH proposed the following dosage recommendation for treatment of CMV disease.

Standard dosage for treatment of CMV disease in adults and children from 12 years of age with normal renal function.

- Induction treatment: 5 mg/kg given as an i.v. infusion over one hour, every 12 hours for 14 - 21 days.

- Maintenance treatment: For immunocompromised patients at risk of relapse maintenance therapy may be given. 5 mg/kg given as an i.v. infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of maintenance treatment should be determined on an individual basis, local treatment guidelines should be consulted.

- Treatment of disease progression: Any patient, in whom CMV disease progresses, either while on maintenance treatment or because treatment with Cymevene has been withdrawn, may be re-treated using the induction treatment regimen.

The proposed dose of 5 mg/kg every 12 hours for induction treatment reflects current local SmPCs, clinical studies, and clinical treatment guidelines.

Clinical studies conducted by MAH about 20 years ago assessed the efficacy of Cymevene in the treatment of CMV in patients with HIV or AIDS and transplant recipients. The induction doses of Cymevene in most of the studies were 5 mg/kg i.v. b.i.d. and duration of therapy employed in those studies varied from 1 to 3 weeks for induction therapy and from 14 weeks to 6 month for maintenance treatment. The duration of induction treatment shows some variability in current local SmPCs, clinical studies, and clinical treatment guidelines, but the proposed duration of 14-21 days is recommended in the majority of these sources.

The proposed dose for maintenance treatment of 5 mg/kg daily for 7 days a week or 6 mg/kg daily for 5 days a week reflects current local SmPCs and is supported by clinical studies and treatment guidelines. The duration of maintenance therapy is variable and should be determined on an individual basis according to disease severity, viral load, and, in patients with AIDS, according to immune response to HAART. The proposal reflects this variability and refers clinicians to local treatment guidelines for advice.

Several E.U. Member States include advice that disease progression may be managed by reintroducing the induction regimen; this advice is reflected in clinical treatment guidelines and is proposed for inclusion in the harmonised SmPC.

Posology for prevention of CMV disease

The majority of current local SmPCs reflect the dose and duration of Cymevene for the prevention of CMV disease. The exceptions are Belgium, Finland, France, Germany, the Netherlands, Norway, and Slovakia.

The proposed doses and duration of treatment is based on the data of clinical studies and clinical treatment guidelines.

Clinical studies conducted or supported by MAH assessed the efficacy of Cymevene in the prophylaxis of CMV in patients with AIDS and transplant recipients.

A number of clinical treatment guidelines provide information on the prevention of CMV disease. Guidelines in Europe and the United States advise that CMV prophylaxis is not generally required in HIV-positive patients.

CMV prophylaxis is recommended in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. In SOT recipients, both universal prophylaxis and pre-emptive therapy are considered viable forms of prophylaxis. However, pre-emptive therapy can only be undertaken in centers able to accommodate the stringent monitoring required and universal prophylaxis is still preferred for high-risk patients. In HSCT recipients, universal prophylaxis and pre-emptive therapy are both acceptable but a pre-emptive approach may be preferred[2].

In oncology patients, the highest rates of CMV infection are seen in those with chronic lymphocytic leukaemia (CLL). At particularly high risk are patients receiving alemtuzumab, in whom reactivation rates range from 15%-66%. Reactivation of CMV tends to occur between the first and third months of alemtuzumab therapy when CD4 and CD8 cell counts are at their lowest. Pre-emptive therapy is recommended in these patients with monitoring for CMV reactivation during and for at least 2 months after completion of alemtuzumab therapy. Routine prophylaxis, or pre-emptive therapy for patients with haematological malignancies who do not receive alemtuzumab, is not routinely recommended.

The doses of ganciclovir proposed for prevention of CMV disease as prophylaxis (5 mg/kg daily for 7 days per week or 6 mg/kg daily for 5 days per week) or pre-emptive therapy (5 mg/kg twice daily induction therapy then 5 mg/kg daily for 7 days per week or 6 mg/kg daily for 5 days per week as maintenance therapy) reflect recent clinical trials and clinical treatment guidelines.

The duration of CMV prophylaxis varies according to individual risk and will be determined on a case-by-case basis by the treating physician with reference to current treatment guidelines. Therefore duration of prophylaxis in the proposed harmonised SmPC is not specified. However, for pre-emptive therapy, where the treatment regimen comprises an induction phase followed by maintenance phase, there is a well-established duration of 7-14 days therapy for the induction phase which is reflected in the proposed harmonised SmPC. For the maintenance phase, the duration is again determined by the individual level of risk and no recommendation can be made on the duration of maintenance therapy in the proposed harmonised SmPC.

Special populations

[2] Kotton CN, Kumar D, Caliendo AM, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation, 2013; 96:333-60.

Clarification was given for the special populations, patients with renal impairment, patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, and elderly patients. Re-organisation has been performed of that section with clear subheadings.

Method of administration

Cymevene is a powder for solution for infusion. The infusion should be given into a vein with adequate blood flow, preferably via a plastic cannula.

The CHMP agreed that ganciclovir must be administered by i.v. infusion over 1 hour at a concentration not exceeding 10 mg/mL and not to be administered by rapid or bolus i.v. injection because the resulting excessive plasma levels may increase the toxicity of ganciclovir. Ganciclovir should not be administered by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.

The majority of approved SmPCs included already some precautionary information related to the precautions to be taken before handling or administering ganciclovir as it is considered a potential teratogen and carcinogen in humans. However the used wording differs in Member States.

The CHMP agreed the harmonised wording for this section.

Section 4.3 – Contraindications

Hypersensitivity to the active substance was harmonised as a contraindication in the SmPC. In addition information link on breast-feeding by cross-reference to section 4.6 was made.

Section 4.4 - Special Warnings and Precautions for Use

There were differences in this section approved across Member States regarding the information on paediatric population and patients with psychosis, information on monitoring for blood disorders, teratogenic, aspermatogenic and carcinogenic effects as well as altering the female fertility, inhibition of spermatogenesis.

The CHMP has recommended the rearrangement of the information and agreed on a common wording regarding mainly cross-hypersensitivity, mutagenicity, teratogenicity, carcinogenicity, fertility, and contraception and myelosuppression.

For cross-hypersensitivity reaction the information on possible interaction with aciclovir and penciclovir was emphasised.

Especially in the paediatric population due to the potential for long-term carcinogenicity and reproductive toxicity special warning is mentioned and the benefits of treatment should be carefully considered in each case and should clearly outweigh the risks with reference to treatment guidelines.

In patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy the use of the product should be done with caution as severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia and bone marrow depression have been observed in patients treated with ganciclovir. The complete blood counts including platelet counts should be monitored during therapy; increased haematological monitoring may be warranted in patients with renal impairment.

Section 4.6 - Fertility, pregnancy and lactation

The information on pregnancy and breastfeeding was different in the individual Member States. The CHMP agreed on a common wording.

In animal studies ganciclovir impaired fertility in male and female mice. Based on the occurrence of aspermatogenesis at ganciclovir exposures below therapeutic levels in animal studies, it is considered likely that ganciclovir may cause temporary or permanent inhibition of human spermatogenesis (see section 4.4).

The safety of ganciclovir for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. In animals studies ganciclovir was associated with reproductive toxicity and teratogenicity. Therefore, ganciclovir should not be used in pregnant women unless the clinical need for treatment of the woman outweighs the potential teratogenic risk to the foetus.

Ganciclovir is found to be mutagenic, teratogenic, aspermatogenic and carcinogenic in animal reproduction studies. A review of the use of ganciclovir and valganciclovir in pregnancy, undertaken by the MAH in 2014, revealed 68 pregnancy-related cases of concerning patients who had received ganciclovir or valganciclovir either before or during pregnancy. Of these 68 reports, 24 contained serious or fatal AEs, of which 10 concerned birth defects/congenital malformations. Even though no specific pattern of malformations was identified in the reviewed cases of AEs related with exposure to ganciclovir or valganciclovir, the association between congenital malformations and treatment with ganciclovir or valganciclovir cannot be ruled out. As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir unless it is certain that the female partner is not at risk of pregnancy.

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be excluded. Therefore, breastfeeding must be discontinued during treatment with ganciclovir. This is also reflected in the section 4.3.

Section 4.8 – Adverse events

Safety and efficacy data from valganciclovir studies conducted in children were also presented as relevant to the safety and efficacy of ganciclovir (clinical use of valganciclovir, the pro-drug of ganciclovir, has been approved in EU for paediatric SOT recipients for prevention of CMV disease). These additions to the safety information were considered relevant and were accepted by the CHMP.

Other sections

Several other sections of the SmPC have been harmonised to include the relevant available information, or amend wording according to the attest QRD template.

Labelling

The labelling was reviewed during this procedure. No changes were introduced.

Package Leaflet

Following all the changes in the SmPC there were amendments made to the package leaflet (PL). The final PL wording was agreed by the CHMP.

2.3. Quality aspects - Module 3

The MAH submitted a CMC (Chemistry, Manufacturing and Controls) package with a view of harmonising the Quality dossier. The proposed harmonisations concerned the overall Module 3.

Based on the review of data on quality and the MAH responses the CHMP considers that all issues raised with regards to the harmonisation of the Module 3 are resolved.

2.4. Recommendation

In conclusion, the CHMP recommended the revision and harmonisation of the product information for Cymevene i.v. and associated names and recommended changes in several sections of the PI. For the therapeutic indication more specifically, the CHMP adopted the following harmonised indication,

Cymevene is indicated in adults and adolescents from 12 years of age for the:

- *treatment of cytomegalovirus (CMV) disease in immunocompromised patients;*
- *prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).*

Consideration should be given to official guidance on the appropriate use of antiviral agents.

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet.

In conclusion, based on the assessment of the MAHs' proposals and responses and following the discussions of the Committee, the CHMP adopted harmonised sets of product information documents of Cymevene and associated names.

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet;
- the summary of products characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee;

the CHMP was of the opinion that the benefit/risk ratio of Cymevene and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the variation to the terms of the marketing authorisations for which the summary of products characteristics, labelling and

package leaflet as set out in Annex III of the CHMP opinion for Cymevene and associated names (see Annex I).