VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Cytomegalovirus (CMV), a member of the herpesvirus family, was a familiar cause of blindness and death in patients with advanced AIDS in Western countries prior to the introduction of highly active antiretroviral therapy (HAART). CMV retinitis then occurred in roughly one-third of patients with AIDS, and accounted for over 90% of cases of HIV-related blindness. In developing countries CMV infection is usually acquired in childhood, and nearly 100% of adults are seropositive. Like other herpesvirus infections, CMV may remain latent for life. Overt clinical disease occurs with waning immunity. Available data on the epidemiology of CMV retinitis in developing countries are difficult to interpret, as the patients are often not stratified by CD4 lymphocyte counts, and both the technique and quality of retinal examination are variable. From the limited data available, it appears that the extent of the problem in Southeast Asia is similar to that observed in the pre-HAART era in Europe and the United States. Ophthalmology centers in Chiang Mai, Thailand, and Chennai, India report prevalence rates of CMV retinitis in patients with HIV of 33% and 17%, respectively, although other Southeast Asian studies have reported lower figures. In Africa, the CMV problem appears to be less severe, with reported prevalence rates from cross-sectional surveys ranging from 0%–8.5%. However, a longitudinal study from Togo, which followed 200 patients for 20 months, found a cumulative CMV retinitis incidence of 21.4%. In that setting, mean survival after a diagnosis of CMV retinitis was 22 days. The short duration from diagnosis to death in this example suggests that cross-sectional surveys may underestimate the cumulative risk of CMV. Our screening studies in patients with CD4 counts below 50 cells/µl show a high

attack rate in Southeast Asia, and a lower prevalence in more limited studies from sub-Saharan Africa, where, nevertheless, CMV retinitis still represents a substantial problem due to the large absolute numbers of people infected with HIV. Our observations support the hypothesis that CMV retinitis is substantially under diagnosed. Ganciclovir, the traditional "gold standard" for treatment of CMV, can be administered systemically (daily or twice daily intravenous infusion), or locally (intraocular injection). Valganciclovir, a well-absorbed valine ester prodrug of ganciclovir, can achieve equivalent blood levels when given by mouth, and is equally effective as intravenous ganciclovir. [1]

VI.2.2 Summary of treatment benefits

Valganciclovir Aurobindo is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Valganciclovir Aurobindo is indicated for the prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.

Because valganciclovir Aurobindo is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Valcyte.

Because Valganciclovir Aurobindo is generic, it's beneficial treatment effects are taken as being the same as the reference medicines.

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns relating to treatment benefits that the MAH is aware of.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Use in patients with hypersensitivity to valganciclovir, ganciclovir, acyclovir and valaciclovir	Valganciclovir Aurobindo is contra-indicated in patients with hypersensitivity to valganciclovir, ganciclovir or to any of the excipients. Due to the similarity of the chemical structure of valganciclovir and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible. Therefore, valganciclovir is contra-indicated in patients with hypersensitivity to aciclovir and valaciclovir	Valganciclovir must be discontinued immediately and appropriate medical therapy instituted.

[1] Heiden D, Ford N, Wilson D, Rodriguez WR, Margolis T, et al. Cytomegalovirus Retinitis: The Neglected Disease of the AIDS Pandemic. PLoS Med 4(12): Dec 1;2007.

Risk	What is known	Preventability
Male infertility	Valganciclovir is a pro-drug of ganciclovir and therefore effects observed with ganciclovir apply equally to valganciclovir. Toxicity of valganciclovir in pre-clinical safety studies was the same as that seen with ganciclovir and was induced at ganciclovir exposure levels comparable to, or lower than, those in humans given the induction dose. These findings were gonadotoxicity (testicular cell loss) and nephrotoxicity (uraemia, cell degeneration), which were irreversible; myelotoxicity (anaemia, neutropenia, lymphocytopenia) and gastrointestinal toxicity (mucosal cell necrosis), which were reversible. Further studies have shown ganciclovir to be mutagenic, carcinogenic, teratogenic, embryotoxic, aspermatogenic (i.e. impairs male fertility) and to suppress female fertility.	Physician supervision and care
Blood and lymphatic system disorders (Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia)	Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with valganciclovir (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µl, or the platelet count is less than 25000/µl or the haemoglobin level is less than 8 g/dl. It is recommended that complete blood counts and platelet counts be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment. In patients developing severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered.	Physician supervision and care. Regular medical examinations with appropriate laboratory tests. Treatment with haematopoietic growth factors and/or dose interruption

Risk	What is known	Preventability
Convulsions in patients taking ganciclovir and imipenem-cilastatin concomitantly	Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential	Aviod co-adminstration of drugs that effects in patients taking ganciclovir and imipenem-cilastatin concomitantly Physician supervision and care. Requiring alertness and appropriate medical therapy instituted.

Important potential risks

Risk	What is known	Preventability
Risk of carcinogenicity	Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long term	Valganciclovir must be discontinued immediately and appropriate medical therapy instituted. Physician supervision and care.
Use in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia	Valganciclovir should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.	Physician supervision and care. Regular medical examinations with appropriate laboratory tests. Treatment with haematopoietic growth factors and/or dose interruption
Risk of overdosage in	One adult developed fatal bone marrow	Physician

Risk	What is known	Preventability
patients with renal impairment (including those on hemodyalisis)	depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance). It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity. Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir .	supervision and care.
Potential interaction with drugs that are excreted through the kidneys	Valganciclovir should not be used in patients on haemodialysis	Valganciclovir must be discontinued immediately and appropriate medical therapy instituted.
Potential interactions with drugs that cause myelosupression	Patients treated with valganciclovir and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity	Dosage adjustment and avoid co-adminstration of didanosine, drugs that are known to be myelosuppressive (e.g. zidovudine). Physician supervision and care. Regular medical examinations with appropriate laboratory tests
Suppressed female fertility	Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies, ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic, and a suppressor of female fertility. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential	Valganciclovir must be discontinued immediately and appropriate medical therapy instituted. Practise of contraception measures

Risk	What is known	Preventability
	to cause birth defects and cancers. It is also considered likely that valganciclovir causes temporary or permanent inhibition of spermatogenesis. Women of child bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy.	
Medication error	The bioavailability of ganciclovir after a single dose of 900 mg valganciclovir is approximately 60 %, compared with approximately 6 % after administration of 1000 mg oral ganciclovir (as capsules). Excessive exposure to ganciclovir may be associated with life-threatening adverse reactions. Therefore, careful adherence to the dose recommendations is advised when instituting therapy, when switching from induction to maintenance therapy and in patients who may switch from oral ganciclovir to valganciclovir as valganciclovir cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valganciclovir Aurobindo tablets.	Physician supervision and care.
Risk of teratogenicity	Precautions to be taken before handling or administering the medicinal product The tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets. Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water,	Valganciclovir must be discontinued immediately and appropriate medical therapy instituted. Physician supervision and care.

Risk	What is known	Preventability
	or plain water if sterile water is unavailable. Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies, ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic, and a suppressor of female fertility. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. It is also considered likely that valganciclovir causes temporary or permanent inhibition of spermatogenesis. Women of child bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy. There are no data from the use of valganciclovir in pregnant women. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir there is a theoretical risk of teratogenicity in humans. Valganciclovir should not be used in pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the child.	

Missing information

Risk	What is known
Use in patients with severe uncontrolled diarrhoea or with evidence of malabsorption	The most commonly reported adverse drug reactions following administration of valganciclovir in adults are neutropenia, anaemia and diarrhoea**.** Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation
None

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	22 April 2014	List of safety concerns in RMP have been updated in line with assessor comments.	Version 01 has been updated in line with GPvP Module V – Risk Management Systems.