VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Cytomegalovirus Retinitis (CMVR) is an AIDS-related opportunistic infection that can lead to blindness. CMVR is a neglected disease, largely undiagnosed and untreated. Available data on the epidemiology of CMVR 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. The age of most individuals developing CMVR is 20-50 years. Although the incidence of CMVR is the same among men and women, the prevalence is higher in men than in women because of the higher prevalence of AIDS in men. Highly active antiretroviral therapy (HAART) for HIV infection has revolutionized the treatment of CMVR by allowing immune reconstitution in many individuals. In a prospective cohort study, Sugar et al estimated the incidence of CMVR in the post-HAART era among 1600 AIDS patients without CMVR at enrollment. They found an incident rate of 0.36/100 person-years, with the highest rate observed among patients with CD4 counts below 50 cells/μL.

CMV disease is associated with increased morbidity, mortality, and poor long-term outcomes after **system organ transplantation (SOT)**. CMV disease occurs most commonly during the first 4 months after SOT. The widespread use of antiviral prophylaxis, implemented during the past decade, has reduced the incidence of CMV disease during the early period after SOT. The 1-year incidence rates of CMV infection varied depending on the type of transplantation (heart [19 %], liver [7 %], kidney [6.2 %], double transplant [5.5 %]), likely influenced by the type of prevention strategy and the baseline immune characteristics of the population.

VI.2.2 Summary of treatment benefits

Valganciclovir is used to treat CMVR (eye infection that can cause blindness) in people who have AIDS. Valganciclovir is also used to prevent CMV disease in people who have received a heart, kidney, or kidney-pancreas transplant and who have a chance of getting CMV disease. Valganciclovir is in a class of medications called antivirals. It works by preventing the spread of CMV disease or slowing the growth of CMV.

VI.2.3 Unknowns relating to treatment benefits

- There is no experience of valganciclovir use in patients with hepatic impairment;
- There is no experience of valganciclovir use in elderly patients;
- The safety and efficacy of valganciclovir in the treatment of CMVR have not been established in adequate and well-controlled clinical studies in paediatric patients;

- There is no experience of valganciclovir use during breast feeding.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Haematological toxicity *(Hematopoietic cytopenias and associated infections and hemorrhage)*	Valganciclovir can cause a reduction in the number of white blood cells in the blood (neutropenia) - which will make you more likely to get infections, a reduction in the pigment in the blood that carries oxygen (anaemia) - which can cause tiredness and breathlessness when you exercise.	Yes, by using valganciclovir with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy. Complete blood counts and platelet counts should be monitored during therapy by your treating physician.
Allergy to valganciclovir *(Hypersensitivity)*	Up to 1 in every 100 people may have a sudden and severe allergic reaction to valganciclovir (anaphylactic shock). The drug should not be used in patients with known hypersensitivity to valganciclovir or ganciclovir. Valganciclovir is contra-indicated in patients with hypersensitivity to aciclovir and valaciclovir due to the similarity of the chemical structure of valganciclovir.	Yes, by informing your doctor in case of hypersensitivity to aciclovir, valaciclovir, valganciclovir or ganciclovir. If you experience any of the following (a raised, itchy skin rash (hives), sudden swelling of the throat, face, lips and mouth which may cause difficulty swallowing or breathing, sudden swelling of the hands, feet or ankles) you should seek for immediate medical advice.
Convulsions (fits) associated with imipenem-cilastatin concomitant use *(Seizures associated with co-administration with imipenem-cilastatin)*	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 risks.	Yes, by informing your doctor about your current medication. Valganciclovir should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks.
Males inability to cause pregnancy in a fertile female *(Male infertility)*	No human data on the effect of valganciclovir on fertility are available. Fertility studies have not been repeated with valganciclovir because of the rapid and extensive	Yes, by advising men to practice barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female

	conversion of valganciclovir to ganciclovir in the body. Valganciclovir is associated with impaired fertility in animal studies.	partner is not at risk of pregnancy.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Adverse pregnancy outcomes	There is no data from the use of valganciclovir in pregnant women. Its active metabolite, ganciclovir, readily diffuses across the human placenta which can cause pregnancy complications. If patients are pregnant or breast-feeding, or are planning to have a baby, they are advised to ask doctor or pharmacist for advice before taking this medicine. Taking Valganciclovir when pregnant could harm unborn baby.
Carcinogenicity	In animal studies, ganciclovir was found to be carcinogenic. Valganciclovir should, therefore, be considered a potential carcinogen in humans with the potential to cause cancers especially in the long-term. Since valganciclovir is considered a potential carcinogen in humans, caution should be observed in handling broken tablets. Avoid direct contact of broken or crushed tablets with skin or mucous membranes.
Potential for overdose in patients with kidney problems (renal impairment)	It is expected that an overdose of valganciclovir could also possibly result in kidney damage. Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during post-marketing experience. As per current available data, strict adherence to dosage recommendations is essential to avoid overdose.
Potential interactions with other drugs that cause myelosuppression	Patients treated with valganciclovir and drugs that are known to be myelosuppressive are at risk of added toxicity. Caution is needed when valganciclovir is used with other haematotoxic drugs (such as zidovudine, mycophenolate mofetil, trimethoprim, dapsone, pentamidine, vincristine etc.). Valganciclovir and other (potentially) myelosuppressive drugs should be used concomitantly only if the potential benefits outweigh the potential risks.
Potential interaction with drugs which are excreted through the kidneys	Since ganciclovir is excreted through the kidney, co-administration of valganciclovir with drugs that are also excreted by kidney may change the concentrations of valganciclovir and/or the co-administered drug in the blood. These patients are at risk of added toxicity. Valganciclovir and other drugs that might reduce the renal clearance or alter renal function should be used concomitantly only if the potential benefits outweigh the potential risks.

Missing information

Risk	What is known
Long term safety and	Valganciclovir is associated with a higher risk of diarrhoea compared

clinical outcomes data	to intravenous ganciclovir. There is no safety data available in patients with severe uncontrolled diarrhoea or with evidence of malabsorption.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the PL. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	08.09.2017	**Important identified risks** • Hematopoietic cytopenias and associated infections and hemorrhage • Hypersensitivity • Seizures associated with co-administration with imipenem-cilastatin • Male infertility **Important potential risks** • Adverse pregnancy outcomes • Carcinogenicity • Potential for overdose in patients with renal impairment • Potential interactions with other drugs that cause myelosuppression • Potential interaction with drugs which are excreted through the kidneys **Missing information** • Safety in patients with severe uncontrolled diarrhea or with evidence of malabsorption	Initial version
1.0	**16.04.2018**		SmPC and PL updated.