VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Most people come into contact with Cytomegalovirus (CMV) in their lifetime. CMV infection most commonly develops between ages 10 - 35. However, typically only individuals with weakened immune systems become ill from CMV infection and develop a more severe form of the disease.

CMV retinitis occurs mostly in patients with acquired immunodeficiency syndrome (AIDS). Highest rate observed were among patients with CD4 counts below 50 cells/µL.

CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor depend on the type of the transplant (heart [one-year incidence 19%], liver [17%], kidney [6.2%] and double transplant [5.5%]).

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, valganciclovir represents an effective drug in the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) and for the prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, valganciclovir can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to tratment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Haematological toxicity (such as neutropenia, anemia, thrombocytopenia, leucopenia, pancytopenia, bone marrow failure and aplastic anemia)	Valganciclovir has effects on the blood: a reduction in the number of white blood cells that fight infection, platelets in the blood (thrombocytopenia) - which can cause bruising and bleeding, anaemia - which can cause tiredness and breathlessness, a reduction in the number of several types of blood cells at the same time (pancytopenia), failure of the production of all types of blood cells in the bone marrow	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. 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.
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.	Treating physician and patient should be aware of risk stated in the SPC and PL. 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.
Hypersensitivity	Anaphylactic reaction is a known uncommon adverse event. Drug should not be used in patients with known hypersensitivity to valganciclovir or ganciclovir.	Treating physician and patient should be aware of risk stated in the SPC and PL. In the PL it is stated that the product should not be used if there is known hypersensitivity to valganciclovir, ganciclovir, acyclovir or valaciclovir; furthermore the patients are warned to stop taking valganciclovir and report to the hospital immediately if they experience any symptoms of an allergic reaction.
Renal toxicity	Creatinine clearance renal decreased, renal impairment, haematuria and renal failure are known adverse events. The product should not be used in patients undergoing haemodialysis.	Treating physician and patient should be aware of risk stated in the SPC and PL. In patients with impaired renal function, dosage adjustments based on creatinine clearance are required.
Interactions with drugs which are	Patients treated with valganciclovir and substances	Treating physician and patient should be aware of risk stated in the SPC and PL.

Risk	What is known	Preventability
excreted through the kidneys	affecting renal function are at risk of added toxicity.	Caution is needed when valganciclovir is used with other drugs which are excreted through the kidneys reducing the renal clerance and that are affecting renal function (such as probenicicde, mycophenolate mofetil, cidofovir, foscarnet and other nucleoside analogues). 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.
Reproductive toxicity	In animal studies, ganciclovir was found to be mutagenic, teratogenic, spermatogenic and carcinogenic, and a suppressor of female fertility. It is also considered likely that valganciclovir causes temporary or permanent inhibition of spermatogenesis.	Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. 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. You have to be careful when handling your tablets. Do not break or crush them. You should swallow them whole and with food whenever possible.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Carcinogenicity	Valganciclovir has the potential to cause carcinogenicity in the long term. You have to be careful when handling your tablets. Do not break or crush them. You should swallow them whole and with food whenever **possible.**
Drug interaction with imipenem-ciliastatin	Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. Therefore, this interaction is also possible with valganciclovir.
Drug interaction with didanosine	Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir. Therefore, this interaction is also possible with valganciclovir.

Important missing information

Risk	What is known
Use in patients undergoing haemodialysis	For patients receiving haemodialysis dose recommendations for Valganciclovir 450 mg film-coated tablets cannot be given. This is because an individual dose of valganciclovir required for these patients is less than the 450 mg tablet strength. Thus, valganciclovir should not be used in these patients.
Use in patients with hepatic	The safety and efficacy of valganciclovir have not been studied in

Risk	What is known
impairment	patients with hepatic impairment. Hepatic impairment should not affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made.
Use in elderly patients	Safety and efficacy have not been established in this patient population.
Use in paediatric patients	Two studies in paediatric patients were performed. The data in these studies are too limited to allow conclusions regarding safety, efficacy or posology recommendations for paediatric patients.
Use in pregnancy and lactation	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. It is unknown if ganciclovir is excreted in breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, breast-feeding must be discontinued.
Patients with severe uncontrolled diarrhea or with evidence of malabsorption	In the originators studies on valganciclovir use in AIDS patients one of the exclusion criteria was severe, uncontrolled diarrhoea or evidence of malabsorption and therefore there is missing information on this patient group.

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

No additional risk minimisation measures are proposed.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

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

Table 2. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	23 Nov 2012	Identified Risks: Haematological toxicity, hypersensitivity, renal toxicity and reproductive toxicity Potential Risks: None Missing information: None	-
2.0 (internal version)	(30 May 2013)	Carcinogenicity added as a potential risk; Drug interaction with imipenem-ciliastatin and drug interaction with didanosine added as potential risks.	Based on the RMS Day 70 Assessment Report - UK, applicant agreed to add these safety concerns

Version	Date	Safety Concerns	Comment
		Use in patients undergoing haemodialysis, use in patients with hepatic impairment, use in elderly patients, use in paediatric patients, and use in pregnancy and lactation added as missing information	
2.1	12 July 2013	Interactions with other drugs that cause myelosuppression and interactions with drugs which are excreted through the kidneys added as identified risks. Use in patients with severe uncontrolled diarrhea or with evidence of malabsorption added as missing information	Based on the RMS Day 70 Assessment Report - NL, applicant agreed to add these safety concerns. This version combines comments from UK and NL Assessment Reports.