SANDOZ

Valganciclovir hydrochloride

450 mg

Film-coated tablet

1.8.2 Safety Risk Management Plan

Active substance(s) (INN or common name):	Valganciclovir hydrochloride
Pharmacotherapeutic group (ATC Code):	Pharmacotherapeutic group: Anti-infectives for systemic use, antivirals for systemic use, direct acting antivirals, ATC Code: J05A B14
Name of Marketing Authorization Holder or Applicant:	Sandoz
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	
Version number	1.0
Data lock point for this RMP	17 Jul 2013
Date of final sign off	13 Jan 2014

Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of disease epidemiology

Cytomegalovirus (CMV) is a universally distributed pathogen with approximately 40-100% of the world's population having CMV antibody present in blood as evidence of infection, the highest prevalence being in countries in the developing world. Infection earlier in life is typical in developing countries, whereas up to 50% of young adults are seronegative in many developed nations. In the United States, >90% of healthy adults have become infected with CMV by the age of 80 years. Immunocompromised patients (AIDS patients or organ transplant recipients), premature infants, and newborns with congenital CMV are at a high risk of developing serious, life threatening illness with CMV infection. In the United States, approximately 30,000 children are born annually with congenital CMV infection, 20% of whom develop permanent disabilities. Transmission of infection has been reported to occur in day-care centers. Furthermore, the majority of these congenital infections result from recurrent infections in pregnant women. CMV is seldom associated with mortality in nonimmunocompromised hosts (< 1%). Substantial morbidity may occur in patients with a mononucleosis syndrome, as described in Adult Cytomegalovirus Infection in the Immunocompetent Host. In both solid organ and marrow transplant recipients, CMV causes substantial morbidity and mortality. CMV prevalence increases with age. Age has also been found to be a risk factor for CMV disease in certain transplant populations.(1)

Part VI.2.2 Summary of treatment benefits

Valganciclovir is an orally administered prodrug of the standard anti-cytomegalovirus (CMV) drug ganciclovir. Valganciclovir is as effective as intravenous ganciclovir for the treatment of AIDS-related CMV retinitis, and oral ganciclovir for the prophylaxis of CMV infection and disease in high-risk solid organ transplant recipients. The drug is generally well tolerated and has a similar tolerability profile to that of oral or intravenous ganciclovir, but is devoid of adverse events related to intravenous or indwelling catheter access associated with the use of intravenous ganciclovir, cidofovir and foscarnet. The simple and convenient once-daily valganciclovir regimen offers potential for improved patient compliance. It provides greater systemic ganciclovir exposure than oral ganciclovir, thus reducing the risk of viral resistance when used for prophylaxis in high-risk solid organ transplant recipients. Furthermore, the use of valganciclovir instead of intravenous ganciclovir may provide significant cost savings, based on data comparing oral versus intravenous regimens for the treatment of AIDS-related CMV retinitis. Overall, valganciclovir appears to have some advantages over ganciclovir. Therefore, when used as prophylaxis against CMV infection and disease in high-risk solid organ transplant recipients or as induction and maintenance therapy of CMV retinitis in patients with AIDS, oral valganciclovir is an attractive alternative to other available anti-CMV drugs (2)

Part VI.2.3 Unknowns relating to treatment benefits

None

Part VI.2.4 Summary of safety concerns

Table Fejl! Ingen tekst med den anførte typografi i dokumentet.**-1 Important identified risks**

Risk	What is known	Preventability

Risk	What is known	Preventability
Haemotopoietic cytopenias and associated infections and haemorrhages	Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with 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.
Male infertility	Male infertility has been reported as uncommon adverse drug reaction.	Not applicable.
Hypersensitivity	Valganciclovir is contra-indicated in patients with hypersensitivity to valganciclovir, ganciclovir or to any of the excipients listed in section 6.1. 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.	Valganciclovir is contra-indicated in patients with hypersensitivity to aciclovir and valaciclovir.
Identified interactions: seizures associated with co-administration with Imipenem-cilastatin	Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir.	Valganciclovir should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks.

Table Fejl! Ingen tekst med den anførte typografi i dokumentet.**-2 Important potential risks**

Risk	What is known (Including reason why it is considered a potential risk)
Carcinogenicity	Valganciclovir has a potential to cause carcinogenicity. Toxicity of valganciclovir in preclinical safety studies was the same as that seen in ganciclovir. Preclinical safety studies have shown ganciclovir to be carcinogenic.
Reproductive toxicity	In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and suppressor of female fertility. 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
Adverse pregnancy outcomes	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.
Potential for overdose in patients with renal impairment	In patients with impaired renal function, dosage adjustments based on creatinine clearance are required Serum creatinine levels or creatinine clearance should be monitored carefully.
Enhanced toxicity during co-	Since ganciclovir is excreted through the kidney, toxicity

Risk	What is known (Including reason why it is considered a potential risk)
administration with drugs that might reduce the renal clearance of ganciclovir	may also be enhanced during co-administration of valganciclovir with drugs that might reduce the renal clearance of ganciclovir and hence increase its exposure. The renal clearance of ganciclovir might be inhibited by two mechanisms: (a) nephrotoxicity, caused by drugs such as cidofovir and foscarnet, and (b) competitive inhibition of active tubular secretion in the kidney by, for example, other nucleoside analogues. Therefore, all of these drugs should be considered for concomitant use with valganciclovir only if the potential benefits outweigh the potential risks.
Risk of added toxicity in combination with other myelosuppressive drugs	Patients treated with Valganciclovir hydrochloride and drugs that are known to be myelosuppressive (e.g. zidovudine) should be closely monitored for signs of added toxicity. No clinically significant pharmacokinetic interaction was observed when trimethoprim and oral ganciclovir were given in combination. However, there is a potential for toxicity to be enhanced since both drugs are known to be myelosuppressive and therefore both drugs should be used concomitantly only if the potential benefits outweigh the risks.

Table Fejl! Ingen tekst med den anførte typografi i dokumentet.**-7 Important missing information**

Risk	What is known
Patients with severe uncontrolled diarrhoea or with evidence of malabsorption	There are no data on Patients with severe uncontrolled diarrhoea or with evidence of malabsorption. Currently available data do not support the need for risk minimization.

Part 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 package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post authorisation development plan

None

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

None