PROFESSIONAL INFORMATION FOR

VALGANCICLOVIR 450 mg Film-coated Tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VALVIR 450 Film-coated Tablets

Strength

Each Film-coated tablet contains 450 mg valganciclovir

Pharmaceutical form

Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 496,3 mg of valganciclovir hydrochloride, equivalent to 450 mg of valganciclovir.

Sugar free

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film-coated Tablets

VALVIR 450 is a pink coloured, capsule shaped, biconvex film coated tablet, that is plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VALVIR 450 is indicated for:

- The treatment of cytomegalovirus (CMV) retinitis in acquired immunodeficiency syndrome (AIDS) patients.
- The prevention of CMV disease in solid organ transplant patients who are at risk i.e. donor seropositive and recipient seronegative.

4.2 Posology and method of administration

Posology

Strict adherence to dosage recommendation is essential to avoid overdose.

Standard dosage in adults

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg VALVIR 450 twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity.

Maintenance treatment of CMV retinitis

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg VALVIR 450 once daily. Patients whose retinitis worsens may repeat induction treatment, however, consideration should be given to the possibility of viral medicine resistance.

Prevention of CMV disease in solid organ transplantation

For kidney transplant patients, the recommended dose is 900 mg once daily depending on creatinine clearance, starting within 10 days of transplantation until 200 days post-transplantation.

For patients who have received a solid organ transplant other than the kidney, the recommended dose is 900 mg once daily, starting within 10 days of transplantation until 100 days post transplantation.

Special populations

Patients with renal impairment

Serum creatinine levels or creatinine clearance should be monitored carefully.

Dosage adjustment is required for adult patients based on creatinine clearance, as shown in table 1. Creatinine clearance (mL/min) is calculated from serum creatinine by the following formulae:

CL_{CR} (mL/min)

$$= \frac{(140 - \text{age}) \times (\text{Wt [kg]}) \times \text{constant}^*}{S_{CR}\ [\mu\text{mol/L}]}$$

* Constant = 1,23 for males and 1,04 for females (0,85 x 1,23 = 1,04)

The South African Renal Society recommends simplifying the above formula by omitting the constant of 1,23 for males

CL_{CR} (mL/min)

$$= \frac{(140 - \text{age}) \times (\text{Wt [kg]}) \times 0{,}85 \text{ (if female)}}{S_{CR}\ [\mu\text{mol/L}]}$$

CL_{CR} = creatinine clearance

S_{CR} = serum creatinine

Table 1: VALVIR 450 film-coated dose for renally impaired patients

CrCl (mL/min)	**Induction dose of VALVIR 450 film-coated tablet**	**Maintenance/Prevention dose of VALVIR 450 film-coated tablet**
≥ 60	900 mg twice daily	900 mg once daily
40 - 59	450 mg twice daily	450 mg once
25 - 39	450 mg once daily	450 mg every 2 days
10 - 24	450 mg every 2 days (tablets)	450 mg twice weekly
< 10	Not recommended	Not recommended

Patients undergoing haemodialysis

For patients on haemodialysis (Clcr < 10 mL/min) a dose recommendation cannot be given. Thus VALVIR 450 film-coated tablets should not be used in these patients (see **sections 4.4 and 5.2**).

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia, and pancytopenia:

Severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with VALVIR 450 (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cell/µL or the platelet count is less than 25 000/µL or the haemoglobin is less than 8 g/dL.

Elderly

Safety and efficacy have not been established.

Paediatric population

Safety and efficacy have not been established in adequate and well-controlled clinical studies.

Method of Administration

VALVIR 450 is administered orally and should be taken with food.

The bioavailability of ganciclovir from VALVIR 450 is up to 10-fold higher than from ganciclovir capsules, therefore the dosage and administration of VALVIR 450 tablets should be closely monitored.

Patients should be advised that the tablets should be swallowed whole and not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets. Direct contact of broken or crushed tablets with skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.

4.3 Contraindications

- VALVIR 450 is contra-indicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any excipient of product.

  Due to the similarity of the chemical structure of VALVIR 450 and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these medicines is possible.

4.4 Special warnings and precautions for use

Prescribers must adhere to the antibiotic stewardship

Due to the similarity of the chemical structure of ganciclovir and that of acyclovir and penciclovir, a cross-hypersensitivity reaction between these medicines is possible. VALVIR 450 should not be prescribed to patients with known hypersensitivity to acyclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively), (see **section 4.3**).

Women of childbearing potential must be advised to use effective contraception during treatment. Male patients should be advised to practice barrier contraception during, and for at least 90 days following treatment with VALVIR 450.

Severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with VALVIR 450 (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µL, or if the platelet count is less than 25 000/µL, or the haemoglobin levels than 8 g/dL.

VALVIR 450 should be used with caution in patients with pre-existing haematological cytopenia or a history of medicine-related haematological cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood counts and platelet counts be monitored during therapy.

In patients with severe leukopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered.

Safety and efficacy in children have not been established in adequate and well-controlled clinical studies.

The bioavailability of ganciclovir from VALVIR 450 is up to 10-fold higher than from ganciclovir capsules.

VALVIR 450 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 VALVIR 450 tablets. (See **section 4.2**).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required. (See **section 4.2**)-Adjustment of dose in special populations.

For patients on haemodialysis (CrCl < 10 mL/min) a tablet dose recommendation cannot be given.

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These medicines should not be used concomitantly

Zidovudine and VALVIR 450 each have the potential to cause neutropenia and anaemia. Some patients may not tolerate concomitant therapy at full dosage. (See **section 4.5**).

Didanosine plasma concentrations may increase during concomitant use with VALVIR 450, therefore, patients should be closely monitored for didanosine toxicity. (See **section 4.5**).

Concomitant use of other medicines that are known to be myelosuppressive or associated with renal impairment with VALVIR 450 may result in added toxicity. (See **section 4.5**).

4.5 Interaction with other medicines and other forms of interaction

The following medicines, valaciclovir, didanosine, nelfinavir, ciclosporin, omeprazole and mycophenolate mofetil did not affect the permeability of VALVIR 450 (rat in-situ model).

VALVIR 450 is metabolised to ganciclovir. Therefore, interactions associated with ganciclovir will be expected for VALVIR 450**.**

Interactions with ganciclovir

Imipenem-cilastatin: Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These medicines should not be used concomitantly.

Probenecid: Probenecid given with oral ganciclovir may reduce renal clearance of ganciclovir (20 %) leading to statistically significantly increased exposure (40 %). These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore, patients taking probenecid and VALVIR 450 should be closely monitored for ganciclovir toxicity.

Zidovudine: When zidovudine was given in the presence of oral ganciclovir there was a small (17 %) but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage.

Didanosine: Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6 g/day, an increase in the AUC of didanosine ranging from 84 to 124 % has been observed, and likewise at intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67 % has been observed. This increase cannot be explained by competition for renal tubular secretion, as there was an increase in the percentage of didanosine dose excreted. This increase could arise from either increased bioavailability or decreased metabolism. There was no clinically significant effect on ganciclovir concentrations. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity.

Mycophenolate Mofetil: Based on the result of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co-administration of these medicines (which have the potential to compete for renal tubular secretion) will result in increase in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid

(MPA) pharmacokinetics is anticipated, and MMF dose adjustment is not required. In patients with renal impairment and in which MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed, and patients monitored carefully.

Zalcitabine: Zalcitabine increased the AUC_{0-8h} of oral ganciclovir by 13 %. There were no statistically significant changes in any of the other pharmacokinetic parameters assessed. Additionally, there were no clinically relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir although a small increase in the elimination rate constant was observed.

Both VALVIR 450 and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events.

Stavudine: No statistically significant pharmacokinetic interactions were observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim: Trimethoprim statistically decreased the renal clearance of oral ganciclovir by 16,3 % and was associated with a statistically significant decrease in the terminal elimination rate and the corresponding increase in half-life by 15 %. However, these changes are unlikely to be clinically significant, as AUC_{0-8h} and C_{max} were unaffected.

The only statistically significant change in trimethoprim pharmacokinetic parameters when co-administered with ganciclovir was a 12 % increase in C_{min}. However, this is unlikely to be of clinical significance and no dose adjustment is recommended.

Ciclosporin: There was no evidence that introduction of ganciclovir affects the pharmacokinetics. However, there was some evidence of increases in the maximum serum creatinine value observed following initiation of ganciclovir therapy.

Other potential interactions: Toxicity may be enhanced when ganciclovir is co-administered with, or is given immediately before or after, other medicines that inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, tested and germinal layers of the skin and gastrointestinal mucosa, or that are associated with renal impairment (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulfa combination, nucleoside analogues and hydroxyurea.) These medicines should not be used concomitantly with VALVIR 450.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential / Contraception in males and females

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 valganciclovir unless it is certain that the female partner is not at risk of pregnancy (see **section 4.4**).

Pregnancy

In animal studies, ganciclovir was shown to be teratogenic and embryotoxic. The safety of VALVIR 450 in pregnant women has not been established.

VALVIR 450 should not be used in pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the foetus.

Breastfeeding

Peri- and postnatal development has not been studied with VALVIR 450, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be discounted. Women using VALVIR 450 should not breastfeed their infants.

Fertility

Based on clinical and nonclinical studies, it is considered likely that VALVIR 450 may cause temporary or permanent inhibition of human spermatogenesis (see **sections 4.4**)

4.7 Effects on ability to drive and use machines

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of VALVIR 450. This may affect the patient's ability to drive and operate machinery.

4.8 Undesirable effects

a) Summary of the safety profile

VALVIR 450 is a prodrug of ganciclovir. It is rapidly converted to ganciclovir after oral administration. The side effects known to be associated with ganciclovir usage can therefore be expected to occur with VALVIR 450 administration.

The most frequently reported adverse reactions following administration of VALVIR 450 in adults are neutropenia, anaemia, and diarrhoea.

VALVIR 450 is associated with a higher risk of diarrhoea compared to intravenous ganciclovir.

Severe neutropenia (< 500 ANC/µL) is seen more frequently in CMV retinitis patients undergoing treatment with VALVIR 450 than in solid organ transplant patients receiving VALVIR 450.

b) Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Adverse reaction**
Infections and Infestations	*Frequent*	Oral candidiasis, sepsis (bacteraemia, viremia), urinary tract infection, upper respiratory tract infection, influenza, cellulitis
Blood and lymphatic system disorders	*More Frequent*	Severe neutropenia, severe anaemia
	Frequent	Severe leukopenia, severe thrombocytopenia, severe pancytopenia,
	Less Frequent	Bone marrow failure, aplastic anaemia, agranulocytosis*, granulocytopenia*
Immune system disorder	*Frequent*	Hypersensitivity
	Less Frequent	Anaphylactic reaction*
Metabolism and nutrition disorders	*Frequent*	Anorexia, decreased appetite, decreased weight
Psychiatric disorders	*Frequent*	Depression, anxiety, confusion, abnormal thinking
	Less Frequent	Agitation, psychotic disorder, hallucinations
Nervous system disorders	*Frequent*	Headache, insomnia, dysgeusia (taste disturbance), hypoesthesia, paraesthesia, peripheral neuropathy, dizziness (excluding vertigo), convulsions
	Less Frequent	Tremor
Eye disorders	*Frequent*	Macular oedema, retinal detachment**, vitreous floaters, eye pain, conjunctivitis
	Less Frequent	Visual disturbance,
Ear and labyrinth disorders	*Frequent*	Ear pain
	Less Frequent	Deafness
Cardiac disorders	*Less Frequent*	Dysrhythmias
Vascular disorders	*Less Frequent*	Hypotension

Respiratory, thoracic, and mediastinal disorders	*Frequent*	Dyspnoea, cough
Gastrointestinal disorders	*More Frequent*	Nausea, diarrhoea, vomiting, abdominal pain,
	Frequent	Dysphagia, flatulence, mouth ulceration, constipation, abdominal distension, upper abdominal pain, dyspepsia,
Hepato-biliary disorder	*Frequent*	Severe abnormal hepatic function, increased blood alkaline phosphatase, increased aspartate aminotransferase, increased alanine aminotransferase
Skin and subcutaneous tissue disorders	*More Frequent*	Dermatitis,
	Frequent	Night sweat, pruritus rash, alopecia, urticaria, dry skin
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia, myalgia, back pain, muscle cramps
Renal and urinary disorders	*Frequent*	Decreased creatinine renal clearance, renal impairment, increased blood creatinine
	Less frequent	Haematuria, renal failure
Reproductive system and breast disorder	*Less frequent*	Male infertility
General disorders and administration site conditions	*More Frequent*	Fatigue, pyrexia,
	Frequent	Chills, rigors, pain, malaise, asthenia
	Less Frequent	Chest pain
Investigations	*Frequent*	Decreased weight, increased blood creatinine
Injury and poisoning	*Less Frequent*	Contusion, radiation recall phenomenon, radiation pneumonitis

*The frequencies of these adverse reactions are derived from post marketing experience
** Retinal detachment has only been reported in HIV patients treated for CMV retinitis

c) Description of selected adverse reactions

Neutropenia

The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalises within 2 to 5 days after discontinuation of the medicine or dose reduction (see **section 4.4**).

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000 /µL) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive medicines are at greater risk of thrombocytopenia than patients with AIDS (see **section 4.4**). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Influence of treatment duration or indication on adverse reactions

Severe neutropenia (ANC <500/µL) is seen more frequently in CMV retinitis patients (14 %) undergoing treatment with valganciclovir, intravenous or oral ganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia is 5 % and 3 % respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia is 10 %.

There is a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both valganciclovir and oral ganciclovir when compared to CMV retinitis patients. However, impaired renal function is a feature common in solid organ transplantation patients.

The overall safety profile of VALVIR 450 does not change with the extension of prophylaxis up to 200 days in high risk kidney transplant patients. Leukopenia is reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia is similar in both arms.

d) Paediatric population

The most frequently reported adverse reactions on treatment in paediatric population are diarrhoea, nausea, neutropenia, leukopenia, and anaemia.

In solid organ transplant patients, the overall safety profile is similar in paediatric patients as compared to adults. A higher risk of cytopenia in neonates and infants warrants careful monitoring of blood counts in these age groups (see **section 4.4**).

In kidney transplant paediatric patients, prolongation of valganciclovir exposure up to 200 days is not associated with an overall increase in the incidence of adverse events. The incidence of severe neutropenia (ANC < 500/µL) is higher in paediatric kidney patients treated until Day 200 as compared to paediatric

patients treated until Day 100 and as compared to adult kidney transplant patients treated until Day 100 or Day 200 (see **section 4.4**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or drugsafetysa@cipla.com

4.9 OVERDOSE

It is expected that an overdose of VALVIR 450 could also result in increased renal toxicity. Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of VALVIR 450.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.8 Antiviral agents

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, Valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases.

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and inhibits replication of herpes viruses *in vitro* and *in vivo*. *In vitro* Sensitive human viruses included human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus-6,-7 and -8 (HHV-6, HH-7, HH-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus (HBV).

Ganciclovir requires phosphorylation to its triphosphate form for antiviral activity. In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intercellularly. Triphosphate metabolism has been shown to occur in HSV- and HCMV-infected cells with half-lives of 18 and between 6 and 24 hours respectively, after the removal of extracellular ganciclovir. As phosphorylation is largely dependent on the viral kinase, phosphorylation of Ganciclovir occurs preferentially in virus-infected cells.

The virus static activity of ganciclovir is due to inhibition of viral DNA synthesis by:

(a) ganciclovir triphosphate competitively inhibiting the incorporation of deoxy guanosine-triphosphate (dGTP) into DNA by viral DNA polymerase, and

(b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, further viral DNA elongation.

Viral resistance

Viral resistance to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in either the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and /or the viral polymerase gene (UL54). Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas viruses with mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target the viral polymerase.

Antiviral Activity

The in vitro anti-activity, measured as IC50 of ganciclovir against CMV, is in the range of 0, 08 µM (0, 02 µg/mL) to 14 µM (3, 5 µg/mL).

5.2 Pharmacokinetic properties

Absorption

Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolised in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60 %. Systemic exposure to valganciclovir is transient and low. Valganciclovir allows systemic exposure of ganciclovir similar to that achieved with recommended doses of IV ganciclovir.

AUC_{24} and C_{max} values for valganciclovir are approximately 1% and 3 % of those of ganciclovir, respectively. For comparison, the bioavailability of ganciclovir after administration of 1 000 mg oral ganciclovir (as capsules) is 6 - 8 %.

Valganciclovir in HIV+, CMV+ patients

System exposure of HIV+, CMV+ patients after twice daily administration of ganciclovir and valganciclovir for one week is:

Parameter	**Ganciclovir (*5 mg/kg, i.v.*) n = 18**	**Valganciclovir (900 mg, p.o.) n = 25**	
		Ganciclovir	**Valganciclovir**
$AUC_{(0 - 12\ h)}$ (µg.h/mL)	28,6 ± 9,0	32,8 ± 10,1	0,37 ± 0,22

C_{max} (µg/mL)	10,4 ± 4,9	6,7 ± 2,1	0,18 ± 0,06

The efficacy of ganciclovir in increasing the time-to-progression of CMV retinitis has been shown to correlate with systemic exposure (AUC).

Valganciclovir in solid organ transplant patients

Steady state systemic exposure of solid organ transplant to ganciclovir after daily oral administration of ganciclovir and valganciclovir is

Parameter	**Ganciclovir (1000 mg three times daily) n = 82**	**Valganciclovir (900 mg, once daily) n = 161 Ganciclovir**
$AUC_{(0 - 24\ h)}$ (µg.h/mL)	28,0 ± 10,9	46,3 ± 15,2
C_{max} (µg/mL)	1,4 ± 0,5	5,3 ± 1,5

The systemic exposure of ganciclovir to heart, kidney and liver transplant recipients is similar after oral administration of valganciclovir according to renal function dosing algorithm.

Food

When valganciclovir was given with food at the recommendation dose of 900 mg, increases were seen in both mean ganciclovir AUC_{24} (± 30 %) and mean ganciclovir C_{max} values (± 14 %). It is recommended that valganciclovir be administered with food.

Distribution

Plasma protein binding of ganciclovir was 1-2 % over concentrations of 0,5 and 51 µg/mL. The steady state volume of distribution of ganciclovir after IV administration was 0,680 ± 0,161 L/kg.

Biotransformation

Valganciclovir is rapidly and extensively metabolised to ganciclovir, no other metabolites have detected. No metabolite of orally administered radiolabelled ganciclovir (1000 mg single dose) accounted for more than 1-2 % of the radioactivity recovered in the faeces and urine.

Elimination

The major route of elimination of valganciclovir as ganciclovir is renal excretion, by glomerular filtration and active tubular secretion. Renal clearance accounts for 81,5 % ± 22 % of the systemic clearance of valganciclovir. The half-life of ganciclovir from valganciclovir is 4,1 ± 0,9 hours in HIV- and CMV-seropositive patients.

Pharmacokinetics in special clinical situations

a) *Renal impairment*

Decreasing renal function resulted in decreasing clearance of ganciclovir from valganciclovir with an increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients. (See **section 4.2**).

b) *Haemodialysis*

For patients receiving haemodialysis (CrCl< 10mL/min); it is recommended that IV ganciclovir is used. The individual dose of valganciclovir required for these patients is less than the 450 mg tablet strength. Approximately half of the ganciclovir present at the start of dialysis is removed during dialysis. The mean intra-dialysis half-life and mean interdialysis half-life is estimated to be 3,47 h and 51,0 h respectively.

c) *Hepatic impairment*

The pharmacokinetics of valganciclovir in stable liver transplant recipients were investigated in one open-label 4-crossover study. The absolute bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed condition was approximately 60 % in agreement with estimates obtained in other patient populations. Ganciclovir AUC0-24 was comparable to that achieved by 5 mg/kg IV ganciclovir in liver transplant recipients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Crosprovidone (Kollidon CLM)

Microcrystalline cellulose (Avicel pH 101),

Povidone (PVP K 30),

Stearic acid.

Tablet coating:

Hypromellose,

Iron oxide,

Macrogol,

Titanium dioxide.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24-months

6.4 Special precaution for storage

Store at or below 25 °C.

Do no break or crush the tablets. Avoid contact of broken or crushed tablets with skin or mucous membrane.

6.5 Nature and contents of container

HDPE Container: One bottle containing 60 film-coated tablets packed in a white opaque high-density polyethylene (HDPE) bottle with a 38 mm child resistant polypropylene white opaque cap (with liner).

Blister pack: 6 x 10 film-coated tablets packed in 0,2 mm PVC/ 90 GSM PVDC coated clear transparent film and 0,025 mm Aluminium foil with NC coating 6-8 GSM VMCH.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Cipla Medpro (Pty) Ltd.

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Company Contact Details

Customer Care: 080 222 6662

8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 September 2020

10 DATE OF RIVISION OF THE TEXT