PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE

OLCICAN 450 MG (Film-coated Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 496,286 mg of valganciclovir hydrochloride equivalent to 450 mg of valganciclovir.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Pink oval biconvex film-coated tablets embossed with “450” on one side with dimensions 17,1 ± 0,3 mm in length, 8,2 ± 0,3 mm in width and 6,1 ± 0,3 mm in thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OLCICAN 450 MG 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 recommendations is essential to avoid overdose.

The bioavailability of ganciclovir from OLCICAN 450 MG is up to 10-fold higher than from ganciclovir

capsules, therefore the dosage and administration of OLCICAN 450 MG tablets should be closely followed.

Standard dosage in adults

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is
900 mg OLCICAN 450 MG 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 OLCICAN 450 MG once daily. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug 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 tables 2 and 3 below. Creatinine clearance (mL/min) is calculated from serum creatinine by the following formulae:

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

* 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:

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

CL_{CR} = creatinine clearance

S_{CR} = serum creatinine

OLCICAN 450 MG dose for renally impaired patients

CrCl (mL/min)	Induction Dose	Maintenance / Prevention Dose
≥ 60	900 mg twice daily	900 mg once daily
40 - 59	450 mg twice daily	450 mg once daily
25 - 39	450 mg once daily	450 mg every 2 days
10 - 24	450 mg every 2 days	450 mg twice weekly
< 10	Not recommended	Not recommended

Patients undergoing haemodialysis

Dosage adjustment is necessary for patients on haemodialysis (CrCl < 10 mL/min).

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

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with OLCICAN 450 MG (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 25 000/µL or the haemoglobin is less than 8 g/dL (see section 4.4).

Elderly

Safety and efficacy have not been established.

Paediatric patients

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

Method of administration

OLCICAN 450 MG is administered orally and should be taken with food.

The tablets should not be broken or crushed. Since OLCICAN 450 MG is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see section 4.4). 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, or plain water if sterile water is unavailable.

4.3 Contraindications

OLCICAN 450 MG is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any excipient of the product (see section 6.1).

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

OLCICAN 450 MG is contraindicated during breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Cross-hypersensitivity

Caution should therefore be used when prescribing OLCICAN 450 MG to patients with known hypersensitivity to aciclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Mutagenicity, teratogenicity, carcinogenicity, fertility, and contraception

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, carcinogenic, and a suppressor of fertility. OLCICAN 450 MG should therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 5.3).

Based on clinical and nonclinical studies it is also considered likely that OLCICAN 450 MG causes

temporary or permanent inhibition of spermatogenesis. Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long term.

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 OLCICAN 450 MG.

Myelosuppression

Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with valganciclovir as contained in OLCICAN 450 MG (and ganciclovir). Severe thrombocytopenia may be associated with potentially life-threatening bleeding. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µL, or the platelet count is less than 25 000/µL, or the haemoglobin level is less than 8 g/dL.

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 (see sections 4.2 and 4.8).
When extending prophylaxis beyond 100 days the possible risk of developing leukopenia and neutropenia should be taken into account (see sections 4.2, 4.8 and 5.1).
OLCICAN 450 MG 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. 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 (see section 4.2).

Safety and efficacy in children have not been established in adequate and well-controlled clinical studies (see section 4.2).

The bioavailability of ganciclovir from OLCICAN 450 MG is up to 10-fold higher than from ganciclovir

capsules. OLCICAN 450 MG cannot be substituted for ganciclovir capsules on a one-to-one basis. 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. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of OLCICAN 450 MG tablets (see section 4.2).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see section 4.2).

For patients on haemodialysis (CrCl < 10 mL/min), OLCICAN film-coated tablets should not be used.

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. OLCICAN 450 MG should not be used concomitantly with imipenem-cilastatin unless the potential benefit outweighs the potential risks (see section 4.5).

Zidovudine and OLCICAN 450 MG 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 OLCICAN 450 MG , 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 OLCICAN 450 MG may result in added toxicity (see section 4.5).

Since OLCICAN 450 MG is considered a potential teratogen and carcinogen in humans, the tablets should be handled with caution. If a broken tablet makes direct contact with skin, the area should be washed thoroughly with soap and water.

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 valganciclovir (rat *in-situ* model). OLCICAN 450 MG is metabolised to ganciclovir. Therefore, interactions associated with ganciclovir will be expected for OLCICAN 450 MG .

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 resulted in statistically significant decreased 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 OLCICAN 450 MG 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 (see section 4.4).

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 (see section 4.4).

Mycophenolate Mofetil

Based on the results 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 agents (which have the potential to compete for renal tubular secretion) will result in increases 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 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 OLCICAN 450 MG 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 significantly decreased the renal clearance of oral ganciclovir by 16,3 % and this 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 of ciclosporin based on the comparison of ciclosporin trough concentrations. 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 combinations, nucleoside analogues and hydroxyurea). Therefore, these medicines should not be considered for concomitant use with OLCICAN 450 MG (see section 4.4).

4.6 Fertility, pregnancy and lactation

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 sections 4.4 and 5.3).

Pregnancy

Ganciclovir was shown to be teratogenic and embryotoxic. The safety of OLCICAN 450 MG in pregnant and lactating women has not been established.

Breastfeeding

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

Fertility

Based on clinical and nonclinical studies, it is considered likely that ganciclovir (and valganciclovir) may cause temporary or permanent inhibition of human spermatogenesis (see sections 4.4 and 5.3).

4.7 Effects on ability to drive and use machines

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of valganciclovir as contained in OLCICAN 450 MG and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Frequent*	Oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection, upper respiratory tract infection, influenza
Blood and lymphatic system disorders	*Frequent*	(Severe) neutropenia, anaemia, (severe) thrombocytopenia, (severe) leukopenia, (severe) pancytopenia
	Less frequent	Bone marrow depression, aplastic anaemia, agranulocytosis, granulocytopenia
Immune system disorders	*Less frequent*	Hypersensitivity, Anaphylactic reaction
Metabolic and nutrition disorders	*Frequent*	Decreased appetite, anorexia

Psychiatric disorders	*Frequent*	Depression, anxiety, confusion, abnormal thinking
	Less frequent	Agitation, psychotic disorder, hallucination
Nervous system disorders	*Frequent*	Headache, insomnia, dysgeusia (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness (excluding vertigo), convulsion, seizure
	Less frequent	Tremor
Eye disorders	*Frequent*	Macular oedema, retinal detachment, vitreous floaters, eye pain
	Less frequent	Visual disturbance, conjunctivitis
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	*Frequent*	Diarrhoea, nausea, vomiting, abdominal pain, upper abdominal pain, dyspepsia, constipation, flatulence, dysphagia
	Less frequent	Abdominal distension, mouth ulcerations, pancreatitis
Hepatobiliary disorders	*Frequent*	(Severe) abnormal hepatic function, increased blood alkaline phosphatase, increased aspartate aminotransferase
	Less frequent	Increased alanine aminotransferase
Skin and	*Frequent*	Dermatitis, night sweats, pruritus, rash

subcutaneous tissue disorders		
	Less frequent	Alopecia, urticaria, dry skin
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Back pain, myalgia, arthralgia, muscle cramps
Renal and urinary disorders	*Frequent*	Decreased creatinine renal clearance, renal impairment
	Less frequent	Haematuria, renal failure
Reproductive system and breast disorders	*Less frequent*	Male infertility
General disorders and administration site conditions	*Frequent*	Fatigue, pyrexia, rigors, pain, chest pain, malaise, asthenia, chills
Investigations	*Frequent*	Decreased weight, increased blood creatinine

b. 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

Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

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 drugs are at greater risk of thrombocytopenia than patients with AIDS (see section 4.4).

c. Post-marketing experience

Adverse events from post-marketing spontaneous reports with intravenous and oral ganciclovir not mentioned in any section above, and for which a causal relationship cannot be excluded are listed below. As OLCICAN 450 MG is rapidly and extensively converted to ganciclovir, such adverse events might also occur with OLCICAN 450 MG.

System Organ Class	Frequency	Undesirable effect
Immune system disorders	*Frequency unknown*	Anaphylactic reaction

d. 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

It is expected that an overdose of OLCICAN 450 MG , 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 OLCICAN 450 MG .

Overdose experience with IV ganciclovir:

The majority of patients experienced one or more of the following adverse events:

- Haematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia.
- Hepatotoxicity: hepatitis, liver function disorder.
- Renal toxicity: worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine.
- Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting.
- Neurotoxicity: generalised tremor, convulsion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase
inhibitors, ATC code: J05A B14.
Classification: 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 include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6,-7 and -8 (HHV-6, HHV-7, HHV-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 deoxyguanosine- 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-viral 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

Systemic 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, once daily) 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 patients to ganciclovir after daily oral administration of ganciclovir and valganciclovir is:

Parameter	**Ganciclovir (1 000 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 was similar after oral administration of valganciclovir according to the renal function dosing algorithm. Following the administration of valganciclovir as an oral solution, equivalent systemic ganciclovir exposures were obtained compared to the tablet formulation.

Food

When valganciclovir was given with food at the recommended dose of 900 mg, increases were seen in both mean ganciclovir AUC24 (± 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.

Metabolism

Valganciclovir is rapidly and extensively metabolised to ganciclovir, no other metabolites have been detected. No metabolite of orally administered radiolabelled ganciclovir (1 000 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 populations

Patients with renal impairment

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with an increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients

Haemodialysis

For patients receiving haemodialysis (CrCl < 10 mL/min); it is recommended that IV ganciclovir is used. The individual dose of OLCICAN 450 MG 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 inter-dialysis half-life is estimated to be 3,47 h and 51,0 h respectively.

Patients with 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 conditions was approximately 60 %, in agreement with estimates obtained in other patient populations. Ganciclovir AUC_{0-24h} 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

Cellulose, Microcrystalline

Povidone (K 30)

Crospovidone

Stearic Acid 50

Coating medium (Pink)

Hypromellose Titanium dioxide (E171)

Macrogol 400

Red Iron Oxide (E172)

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

A cardboard box containing white opaque HDPE bottle with child-resistant polypropylene (PP) screw cap and induction seal liner. Pack size: One bottle containing 60 film-coated tablets.

6.6 Special precautions for disposal and other handling

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

7 HOLDERS OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

3 Gwen Lane, Fourth Floor

Sandton

South Africa

2031

8 REGISTRATION NUMBER(S)

56/20.2.8/0175

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

15 July 2025

10 DATE OF REVISION OF THE TEXT

15 July 2025