FINAL PROFESSIONAL INFORMATION FOR HETVAGLAN

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

HETVAGLAN powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of constituted oral solution contains valganciclovir free base 50 mg equivalent to 55,15 mg of valganciclovir hydrochloride.

Preservative: Sodium benzoate 1 mg/mL.

Contains sugar (57,150 mg mannitol per mL).

Contains sweetener (0,300 mg saccharin sodium per mL).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

HETVAGLAN is white to slightly yellow coloured powder. The constituted solution is a colourless to brownish yellow tutti-frutti flavoured clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HETVAGLAN 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 HETVAGLAN is up to 10-fold higher than from ganciclovir capsules, therefore the dosage and administration of HETVAGLAN powder for oral solution should be closely followed.

The ganciclovir systemic exposure following administration of 900 mg valganciclovir oral solution is equivalent to a dose of 900 mg valganciclovir tablets (2 x 450 mg tablets).

Standard dosage in adults

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg HETVAGLAN 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 HETVAGLAN 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 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 he monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance, as shown in **table 1** 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.

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

CL_{CR} = creatinine clearance

S_{CR} = serum creatinine

Table 1: HETVAGLAN oral solution dose for renally impaired patients

CrCl (mL/min)	**Induction dose of HETVAGLAN oral solution**	**Maintenance/prevention dose of HETVAGLAN oral solution**

≥ 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	225 mg once daily
10 – 24	225 mg once daily	125 mg once daily
< 10	200 mg (3 x weekly after dialysis)	100 mg (3 x weekly after dialysis)

Patients undergoing haemodialysis

Dosage adjustment is necessary for patients on haemodialysis (CrCl < 10 mL/min) and a dosing recommendation for HETVAGLAN powder for oral solution is given in the above table.

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

Severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with HETVAGLAN (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 population

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

Method of administration

HETVAGLAN is administered orally and should be taken with food.

HETVAGLAN, powder for oral solution, preparation of solution:

1. Measure 91 mL of purified water in a graduated cylinder.

2. Add purified water to the bottle. Shake the closed bottle until the powder is dissolved.
3. Remove the child resistant cap and push the bottle adapter into the neck of the bottle.
4. Close bottle tightly with child resistant cap.

For further instructions on handling HETVAGLAN see section 6.6.

4.3 Contraindications

- HETVAGLAN is contraindicated in patients with hypersensitivity to valganciclovir, ganciclovir or any of the excipients listed in section 6.1.
- Due to the similarity of the chemical structure of HETVAGLAN and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these medicines is possible.
- HETVAGLAN is contraindicated during breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception

Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. HETVAGLAN should be considered a potential teratogen and carcinogen with the potential to cause birth defects and cancers. It is likely that valganciclovir causes temporary or permanent inhibition of spermatogenesis (see section 4.6). Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long-term.

Myelosuppression

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with HETVAGLAN (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 level is less than 8 g/dL.

HETVAGLAN 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 (see section 4.2).

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

HETVAGLAN cannot be substituted for ganciclovir capsules on a one-to-one basis.

Renal impairment

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) a tablet dose recommendation cannot be given. Thus HETVAGLAN powder for oral solution, should be used in these patients.

Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly.

Use with other medicines

HETVAGLAN should not be used concomitantly with imipenem-cilastatin (see section 4.5).

Zidovudine and HETVAGLAN 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 HETVAGLAN, 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 HETVAGLAN may result in added toxicity (see section 4.5).

Cross-hypersensitivity

Due to the similarity of the chemical structure of ganciclovir and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these drugs is possible. Caution should therefore be used when prescribing HETVAGLAN to patients with known hypersensitivity to aciclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Precautions to be taken before handling

Owing to the teratogenic character, the Valcyte powder and reconstituted solution should be handled with caution. Inhalation should be avoided. If the powder or solution make direct contact with skin, the area should be washed thoroughly with soap and water. If the solution gets into the eye, the eye should be thoroughly washed with water immediately.

Paediatric population

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

Excipients with known effects

HETVAGLAN powder for oral solution contains sodium benzoate. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

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).

HETVAGLAN is metabolised to ganciclovir. Therefore, medicine interactions associated with ganciclovir will be expected for HETVAGLAN.

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 increase exposure (40 %). These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore, patients taking probenecid and HETVAGLAN 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 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. 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 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 in which MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed and patients monitored carefully.

Zalcitabine

Zalcitabine increased the $AUC_{0\text{-}8h}$ 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 HETVAGLAN 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 $AUC_{0\text{-}8h}$ 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 medicine 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 those occurring 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, sulfamethoxazole-trimethoprim combinations, nucleoside analogues and hydroxyurea) therefore these medicines should be considered for concomitant use with HETVAGLAN only if the potential benefits outweigh the potential risks (see section 4.4).

Other antiretrovirals

Cytochrome P450 isoenzymes play no role in ganciclovir pharmacokinetics. As a consequence, pharmacokinetic interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are not anticipated.

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.

Pregnancy

HETVAGLAN should not be used in pregnancy.

The safety of HETVAGLAN for use in pregnant women has not been established. 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.

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Breastfeeding

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in the breastmilk and causing serious adverse reactions in the nursing infant cannot be discounted. Animal data indicate that ganciclovir is excreted in the milk of lactating rats Therefore, breast-feeding must be discontinued during treatment with valganciclovir (see section 4.3).

Fertility

A clinical study with renal transplant patients receiving valganciclovir for CMV prophylaxis for up to 200 days demonstrated an impact of valganciclovir on spermatogenesis, with decreased sperm density and motility measured after treatment completion. This effect appears to be reversible and approximately six months after valganciclovir discontinuation, mean sperm density and motility recovered to levels

comparable to those observed in the untreated controls.

In animal studies, ganciclovir impaired fertility in male and female mice and has shown to inhibit spermatogenesis and induce testicular atrophy in mice, rats and dogs at doses considered clinically relevant.

Based on clinical and nonclinical studies, it is considered likely that ganciclovir (and valganciclovir) may cause temporary or permanent inhibition of human spermatogenesis (see section 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 valganciclovir 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) Summary of the safety profile

Valganciclovir 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 valganciclovir administration.

All of the undesirable effects observed in valganciclovir have been previously observed with ganciclovir. The most frequently reported adverse medicine reactions following administration of valganciclovir in adults are neutropenia, anaemia and diarrhoea.

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

Severe neutropenia (< 500 ANC/µL) has been seen more frequently in CMV retinitis patients undergoing treatment with valganciclovir than in solid organ transport patients receiving valganciclovir.

b) Tabulated summary of adverse reactions

System organ class	Frequency	Adverse event
Infections and Infestations	Frequent	Oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection, upper respiratory tract infection,
Blood and lymphatic system disorders	Frequent	Severe neutropenia, anaemia, thrombocytopenia, leucopenia, pancytopenia
	Less frequent	Bone marrow depression, aplastic anaemia
	Frequent unknown	Agranulocytosis, granulocytopenia
Immune system disorders	Frequent	Hypersensitivity
	Less frequent	Anaphylactic reaction
Metabolism and nutrition disorders	Frequent	Decreased appetite, anorexia
Psychiatric disorders	Frequent	Depression, anxiety, confusion, abnormal thinking
	Less frequent	Agitation, psychotic disorder, hallucinations,
Nervous system disorders	Frequent	Headache, insomnia, dysgeusia, hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness (excluding vertigo), convulsion
	Less frequent	Tremor
Eye disorders	Frequent	Macular oedema, retinal detachment, vitreous floaters, eye pain, visual disturbance, conjunctivitis
Ear and labyrinth disorders	Frequent	Ear pain
	Less frequent	Deafness
Cardiac disorders	Less frequent	Dysrhythmias
Vascular disorders	Frequent	Hypotension, hypertension
Respiratory, thoracic and	Frequent	Dyspnoea, cough

mediastinal disorders		
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, abdominal pain, upper abdominal pain, dyspepsia, constipation, flatulence, dysphagia,
	Less frequent	Abdominal distension, mouth ulcerations, pancreatitis
Hepato-biliary disorders	Frequent	Severe abnormal hepatic function, increased blood alkaline phosphatase, increased aspartate aminotransferase
	Less frequent	Increased alanine aminotransferase
Skin and subcutaneous tissue disorders	Frequent	Dermatitis, pruritus, rash, night sweats
	Less frequent	Alopecia, urticaria, dry skin
Musculoskeletal and connective tissue 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 administrative site conditions	Frequent	Fatigue, pyrexia, rigors, pain, malaise, asthenia, chest pain, transplant rejection
Investigations	Frequent	Decreased weight, increased blood creatinine

c) Description of selected adverse reactions

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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.

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 via the Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem- reporting-form/ or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

It is expected that an overdose of HETVAGLAN, 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 HETVAGLAN.

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 PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors. **ATC code:** J05A B14

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 HSMV-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 virus 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 IC_{50} 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} 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:

Table 2:

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)	28,0 ± 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:

Table 3:

Parameter	Ganciclovir (1000 mg three 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 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 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 (see section 4.2).

Haemodialysis:

For patients receiving haemodialysis (CrCl < 10 mL/min) valganciclovir oral solution is recommended to provide an individualised dose (see section 4.2).

Patients with hepatic impairment:

The pharmacokinetics of valganciclovir in suitable 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_{0-24} was comparable to that achieved by 5 mg/kg IV ganciclovir in liver transplant recipients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Anhydrous citric acid
- Mannitol
- Povidone
- Sodium benzoate
- Saccharin sodium
- Purified water
- Tutti-frutti flavor 051880 AP0551 contains maize maltodextrin, flavourings, INS 1520 polypropylene glycol, INS 307 c dl-alpha-tocopherol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Powder for oral solution: 24 months.

Reconstituted solution: 49 days stored in a refrigerator in 2 °C – 8 °C.

6.4 Special precautions for storage

- Store at or below 25 °C. Protect from light and moisture.
- Bottle must be kept tightly-closed.
- Reconstituted solution to be stored not longer than 49 days at 2 °C to 8 °C (see section 6.3).
- This medicine does not require any special storage conditions.

6.5 Nature and contents of container

HETVAGLAN powder for oral solution:

12 grams of powder in 120 mL moulded amber coloured type I glass bottle with 28 mm screw type neck finish with white opaque polypropylene, ribbed, child resistant plastic caps with opening illustrations embossed on top. The bottles come with 2 10 mL oral dosing syringes with a white opaque tip cap and

clear adapter with printed graduation marks from 1 mL to 10,0 mL and each 0,5 mL on barrel.

Bottle is enclosed in an outer carton until required for use.

6.6 Special precautions for disposal and other handling

Since **HETVAGLAN** is considered a potential teratogen and carcinogen in humans, powder for oral solution and reconstituted solution should be handled with caution. If a powder or solution makes direct contact with skin, the area should be washed thoroughly with soap and water. If the solution gets into the eye, the eye should immediately be thoroughly washed with water.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

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8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION

05 September 2023

10 DATE OF REVISION OF THE TEXT

N/A