PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VALCYTE® 450 film-coated tablet

VALCYTE® 50 mg/mL powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALCYTE 450 film-coated tablet:

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

VALCYTE 50 mg/mL powder for oral solution:

Each bottle contains 5,5 g valganciclovir hydrochloride, in 12 g powder for oral solution. Following reconstitution with 91 mL purified water, 1 mL solution contains valganciclovir hydrochloride corresponding to 50 mg valganciclovir free base.

Excipients with known effect:

Contains sugar, i.e. mannitol (5,78 g per bottle). See section 4.4.

Contains sodium saccharin as sweetener (0.03 g per bottle).

Contains: Sodium benzoate 0,83 % m/m as preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VALCYTE 450 film-coated tablets: A pink, biconvex, oval, film-coated tablet with “VGC” embossed on one side and “450” on the other side.

VALCYTE 50 mg/mL powder for oral solution: The powder is a granulate with a white to slightly yellow colour. The reconstituted powder is a colourless to brownish-yellow clear solution. Each bottle contains

12 g of powder for oral solution. When reconstituted, the volume of the solution is 100 mL, providing a minimal usable volume of 88 mL.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

VALCYTE is indicated for

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

4.2. Posology and method of administration

Strict adherence to dosage recommendations is essential to avoid overdose.

VALCYTE is administered orally and should be taken with food.

The bioavailability of ganciclovir from VALCYTE is up to 10-fold higher than from ganciclovir capsules, therefore the dosage and administration of VALCYTE tablets or 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 (two VALCYTE 450 mg tablets).

An oral dosing dispenser with 0.5 mL graduations (25 mg) to 10 mL (500 mg) with 25 mg graduations up to 500 mg is provided with the powder for oral solution. It is recommended that this dispenser is used to measure and administer the dose.

Standard dosage

Treatment of cytomegalovirus (CMV) retinitis

Adult Patients

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg valganciclovir (two VALCYTE 450 mg tablets) twice a day for 21 days taken with food. 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 valganciclovir (two VALCYTE 450 mg tablets) once daily taken with food. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

The duration of maintenance treatment should be determined on an individual basis.

Paediatric Patients

The safety and efficacy of VALCYTE in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in paediatric patients.

Prevention of CMV disease in solid organ transplantation

Adult Patients

For kidney transplant patients, the recommended dose is 900 mg valganciclovir (two VALCYTE 450 mg tablets) 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 valganciclovir (two VALCYTE 450 mg tablets) once daily, starting within 10 days of transplantation until 100 days post transplantation.

Paediatric Patients

In paediatric solid organ transplant patients, aged from birth, who are at risk of developing CMV disease, the recommended once daily dose of VALCYTE is based on body surface area (BSA) and creatinine clearance (Clcr) derived from Schwartz formula (ClcrS), and is calculated using the equation below:

Paediatric Dose (mg) = 7 x BSA x ClcrS (see Mosteller BSA formula and Schwartz Creatinine Clearance formula below). If the calculated Schwartz creatinine clearance exceeds

150 mL/min/1,73 m^2, then a maximum value of 150 mL/min/1,73 m^2 should be used in the equation.

$$Mosteller\ BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (ml/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dl)}$$

Where k = 0,45 for patients aged < 2 years, 0,55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0,7 for boys aged 13 to 16 years.

Refer to adult dosing for patients older than 16 years of age.

- The k values provided are based on the Jaffe method of measuring serum creatinine and may require correction when enzymatic methods are used.
- * A lowering of k value may also be necessary for appropriate sub-populations.

For paediatric kidney transplant patients, the recommended once daily mg dose (7 x BSA x ClcrS) should start within 10 days post-transplantation and continue until 200 days post-transplantation.

For paediatric patients who have received a solid organ transplant other than kidney, the recommended once daily mg dose (7 x BSA x ClcrS) should start within 10 days post-transplantation and continue until 100 days post-transplantation.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. The oral dispenser is graduated in mL. A 50 mg dose is equivalent to 1 mL:

Valganciclovir dose	**VALCYTE for Oral Solution to be administered**
50 mg	1 mL
75 mg	1,5 mL
100 mg	2 mL
500 mg	10 mL

If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, VALCYTE tablets may be used if the calculated doses are within 10 % of available tablet doses, and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. It is

recommended to monitor serum creatinine levels regularly and consider changes in height and body weight and adapt the dose as appropriate during prophylaxis period.

Special Dosage Instructions

Paediatric Patients

Dosing of paediatric SOT patients is individualised based on a patient's renal function and size (see section 4.2).

A higher risk of haematological cytopenias in neonates and infants warrants careful monitoring of blood counts in these age groups. Monitoring of liver function abnormalities, renal function and gastrointestinal fluid loss is also recommended in paediatric patients.

Elderly Patients

Safety and efficacy have not been established in this patient population. No studies have been conducted in adults older than 65 years of age. Since renal clearance decreases with age, VALCYTE should be administered to elderly patients with special consideration of their renal status (see Table 1 and section 5.2).

Adult patients with renal impairment

Serum creatinine levels or estimated creatinine clearance should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance, as shown in tables 1 and 2 below.

Estimated 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)

= (140 – age) x (Wt [kg]) x 0,85 (if female)

S_{CR} [µmol/L]

CL_{CR} = creatinine clearance

S_{CR} = serum creatinine

Table 1 VALCYTE 450 film-coated tablet dose for renally impaired patients

CrCl (mL/min)	Induction dose of VALCYTE 450 film-coated tablet	Maintenance/Prevention dose of VALCYTE 450 film-coated tablet
≥ 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 (tablets)	450 mg twice weekly
< 10	Not recommended	Not recommended

Table 2 VALCYTE 50 mg/mL oral solution dose for renally impaired patients

CrCl (mL/min)	Induction dose of VALCYTE 50 mg/mL oral solution	Maintenance/Prevention dose of VALCYTE 50 mg/mL 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 VALCYTE 50 mg/mL Powder for oral solution is given in the above table.

Hepatic impairment

The safety and efficacy of VALCYTE have not been established in patients with hepatic impairment (see section 5.2).

Paediatric patients

Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

VALCYTE 50 mg/mL 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.

4.3. Contraindications

VALCYTE is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any of the excipient.

4.4. Special warnings and precautions for use

Cross hypersensitivity

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

Caution should therefore be used when prescribing VALCYTE to patients with known hypersensitivity to acyclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Contraception

Prior to initiation of VALCYTE treatment, patients should be advised of the potential risks to the foetus and to use contraceptive measures (see section 4.6).

Women of child bearing potential must use effective contraception during treatment. Male patients must practice barrier contraception during, and for at least 90 days following treatment with VALCYTE.

Myelosuppression

VALCYTE 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.

Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anaemia have been observed in patients treated with VALCYTE (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.

It is recommended that complete blood counts and platelet counts be monitored during therapy, particularly in patients with renal impairment and in neonates and infants (see section 4.8). In patients with severe leukopenia, neutropenia, anaemia and/or thrombocytopenia treatment with haematopoietic growth factors and/or interruption of therapy is recommended.

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 VALCYTE is up to 10-fold higher than from ganciclovir capsules.

VALCYTE 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 VALCYTE 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) a tablet dose recommendation cannot be given. Thus VALCYTE 50 mg/mL Powder for oral solution, should be used in these patients.

Use with other medicines

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. VALCYTE should not be used concomitantly with imipenem-cilastatin unless the potential benefit outweighs the potential risks. See section 4.5.

Zidovudine and VALCYTE 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 VALCYTE, 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 VALCYTE may result in added toxicity. See section 4.5.

VALCYTE 50 mg/mL powder for oral solution contains 1 mg/mL sodium benzoate in each bottle. Benzoates cause mild irritation to the skin, eyes and mucous membranes. Sodium benzoate may

increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). VALCYTE 50 mg/mL powder for oral solution contains less than 1 mmol sodium (23 mg) per bottle, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

Medicine interactions with VALCYTE

VALCYTE is the pro-drug of ganciclovir. Therefore, interactions associated with ganciclovir are expected.

Imipenem-cilastatin

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two medicines cannot be discounted. These medicines should not be used concomitantly unless the potential benefit outweighs the potential risks. See section 4.4.

Potential medicine interactions

Toxicity may be enhanced when ganciclovir/valganciclovir 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. This includes nucleoside analogues (e.g. zidovudine, didanosine, stavudine), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and anti-infective agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these medicines should only be considered for concomitant use with VALCYTE only if the potential benefits outweigh the potential risks. See section 4.4.

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, a pharmacodynamic interaction may occur during concomitant administration of these medicines, 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 IV ganciclovir. 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 confirming a pharmacokinetic interaction during the concomitant administration of these medicines. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis). See section 4.4.

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 VALCYTE should be closely monitored for ganciclovir toxicity.

4.6. Fertility, pregnancy and lactation

Contraception in males and females

Women of reproductive potential should use effective contraception during and for at least 30 days after treatment. Sexually active men should use condoms during and for at least 90 days after cessation of treatment with VALCYTE, unless it is certain that the female partner is not at risk of becoming pregnant (see section 4.4).

Pregnancy

In animal studies, ganciclovir was shown to be embryotoxic and was associated with reproductive toxicity and teratogenicity. The safety of VALCYTE in pregnant and lactating women has not been established. However, VALCYTE readily diffuses across the human placenta.

The safe use of VALCYTE during labour and delivery has not been established

Lactation

Women using VALCYTE should not breastfeed their infants.

Peri- and postnatal development has not been studied with VALCYTE, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breast-fed infant cannot be discounted. Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats.

Fertility

In animal studies ganciclovir was found to impair fertility. In a clinical study, renal transplant patients receiving VALCYTE for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with VALCYTE. At follow-up, approximately six months after treatment discontinuation, the mean sperm density in treated patients was comparable to that observed in the untreated control group. In VALCYTE treated patients, all patients with normal sperm density (n = 7) and 8/13 patients with low sperm density at baseline, had normal density after treatment cessation. In the control group, all patients with normal sperm density (n = 6) and 2/4 patients with low sperm density at baseline, had normal density at the end of follow-up.

4.7. Effects on ability to drive and use machines

Adverse reactions such as seizures, dizziness and confusion have been reported with the use of VALCYTE and/or ganciclovir (see section 4.8). If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

4.8. Undesirable effects

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 VALCYTE administration.

a.) Summary of the safety profile

Clinical trials

All of the undesirable effects observed in VALCYTE clinical studies have been previously observed with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with VALCYTE are included in the table of adverse reactions (Table 3).

In patients treated with VALCYTE/ganciclovir the most serious and frequent adverse drug reactions are haematological reactions and include neutropenia, anaemia and thrombocytopenia.

The frequencies presented in the table of adverse reactions are derived from a pooled population of patients (n = 1704) receiving maintenance therapy with ganciclovir (GAN 1697, GAN 1653, GAN 2304, GAN 1774, GAN 2226, AVI 034, GAN 041) or valganciclovir (WV15376, WV15705). Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia the frequencies of which are derived from post-marketing experience. Frequencies are presented as percentages and as CIOMS frequency categories defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000).

The overall safety profile of ganciclovir/VALCYTE is consistent in HIV and transplant populations except that retinal detachment has only been reported in patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. VALCYTE is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC < 500/µL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

b.) Tabulated list of adverse drug reactions

Table 3 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704)

ADR (MedDRA) System Organ Class	**Percentage**	**Frequency Category**
Infections and infestations:		
Candida infections including oral candidiasis.	22,42 %	Very common
Upper respiratory tract infection	16,26 %	
Sepsis	6,92 %	Common
Influenza	3,23 %	
Urinary tract infection	2,35 %	
Cellulitis	1,47 %	
Blood and lymphatic disorders:		
Neutropenia	26,12 %	Very common
Anaemia	19,89 %	
Thrombocytopenia	7,34 %	Common

Leukopenia	3,93 %	
Pancytopenia	1,06 %	
Bone marrow failure	0,29 %	Uncommon
Aplastic anaemia	0,06 %	Rare
Agranulocytosis*	0,02 %	
Granulocytopenia*	0,02 %	
Immune system disorders:		
Hypersensitivity	1,12 %	Common
Anaphylactic reaction*	0,02 %	Rare
Metabolic and nutrition disorders:		
Decreased appetite	12,09 %	Very common
Weight decreased	6,46 %	Common
Psychiatric disorders:		
Depression	6,69 %	Common
Confusional state	2,99 %	
Anxiety	2,64 %	
Agitation	0,59 %	Uncommon
Psychotic disorder	0,23 %	
Thinking abnormal	0,18 %	
Hallucinations	0,18 %	
Nervous system disorders:		
Headache	17,37 %	Very common
Insomnia	7,22 %	Common
Neuropathy peripheral	6,16 %	
Dizziness	5,52 %	
Paraesthesia	3,58 %	
Hypoaesthesia	2,58 %	
Seizures	2,29 %	
Dysgeusia (taste disturbance)	1,35 %	
Tremor	0,88 %	Uncommon
Eye disorders:		
Visual impairment	7,10 %	Common
Retinal detachment**	5,93 %	
Vitreous floaters	3,99 %	
Eye pain	2,99 %	
Conjunctivitis	1,58 %	

Macular oedema	1,06 %	
Ear and labyrinth disorders:		
Ear pain	1,17 %	Common
Deafness	0,65 %	Uncommon
Cardiac disorders:		
Dysrhythmia	0,47 %	Uncommon
Vascular disorders:		
Hypotension	2,05 %	Common
Respiratory, thoracic and mediastinal disorders:		
Cough	18,31 %	Very common
Dyspnea	11,80 %	
Gastrointestinal disorders:		
Diarrhoea	34,27 %	Very common
Nausea	26,35 %	
Vomiting	14,85 %	
Abdominal pain	10,97 %	
Dyspepsia	4,81 %	Common
Flatulence	4,58 %	
Abdominal pain upper	4,58 %	
Constipation	3,70 %	
Mouth ulceration	3,17 %	
Dysphagia	2,93 %	
Abdominal distention	2,41%	
Pancreatitis	1,64%	
Hepato-biliary disorders:		
Blood alkaline phosphatase increased	3,58 %	Common
Hepatic function abnormal	3,23 %	
Aspartate aminotransferase increased	1,88 %	
Alanine aminotransferase increased	1,23 %	
Skin and subcutaneous tissues disorders:		
Dermatitis	11,80 %	Very common
Night sweats	7,92 %	Common
Pruritus	4,58 %	
Rash	2,52 %	
Alopecia	1,29 %	
Dry skin	0,94 %	Uncommon

Urticaria	0,70 %	
Musculo-skeletal and connective tissue disorders:		
Back pain	4,46 %	Common
Myalgia	3,52 %	
Arthralgia	3,35 %	
Muscle spasms	2,99 %	
Renal and urinary disorders:		
Renal impairment	2,52 %	Common
Decreased renal creatinine clearance	2,35 %	
Serum creatinine increased	1,88 %	
Renal failure	0,76 %	Uncommon
Haematuria	0,70 %	
Reproductive system and breast disorders:		
Infertility male	0,23 %	Uncommon
General disorders and administration site conditions:		
Pyrexia	33,51 %	Very common
Fatigue	18,96 %	
Pain	5,81 %	Common
Chills	5,40 %	
Malaise	2,11 %	
Asthenia	2,00 %	
Chest pain	0,88 %	Uncommon

* 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

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 normalizes 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 HIV infection (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 (16 %) undergoing treatment with VALCYTE than in solid organ transplant patients receiving VALCYTE or oral ganciclovir. In patients receiving VALCYTE or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5 % and 3 % respectively, whilst in patients receiving VALCYTE until Day 200 posttransplant the incidence of severe neutropenia was 10 %.

There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both VALCYTE and oral ganciclovir when compared to CMV retinitis patients. However, impaired renal function is a feature more frequent in solid organ transplantation patients. The overall safety profile of VALCYTE did not change with the extension of prophylaxis up to 200 days in high-risk kidney transplant patients. Leukopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia were similar in both arms.

Laboratory abnormalities

Laboratory abnormalities reported in adult CMV retinitis patients and SOT patients receiving valganciclovir until Day 100 post-transplant are listed in Table 4. The incidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high-risk kidney transplant patients. Laboratory abnormalities reported in paediatric SOT patients are listed in Table 5.

The incidence of severe neutropenia (ANC < 500/µL) was higher in paediatric kidney transplant patients treated until Day 200 as compared to paediatric kidney transplant patients treated until Day 100 and to adults kidney transplant patients treated until Day 100 or Day 200

Table 4 Laboratory Abnormalities in Adult Patients

Laboratory abnormalities	**CMV Retinitis Patients**	**Solid Organ Transplant Patients (Dosing until Day 100 Post-Transplant)**	
	Valganciclovir (n = 370)	**Valganciclovir (n = 244)**	**Oral ganciclovir (n = 126)**
	%	**%**	**%**
Neutropenia (ANC/μL)			
< 500	16	5	3
500 - < 750	17	3	2
750 - < 1000	17	5	2
Anaemia (haemoglobin g/dL)			
< 6,5	7	1	2
6,5 - < 8,0	10	5	7
8,0 - < 9,5	14	31	25
Thrombocytopenia (platelets/μL)			
< 25 000	3	0	2
25 000 - < 50 000	5	1	3
50 000 - <10 0000	21	18	21
Serum creatinine (mg/dL)			
> 2,5	2	14	21
> 1,5 – 2,5	11	45	47

Table 5 Laboratory Abnormalities in Paediatric Solid Organ Transplant patients

Laboratory abnormalities	**VALCYTE in Paediatric SOT patients**	
	Dosing until Day 100 Post-Transplant n=63	**Dosing until Day 200 Post-Transplant n=56**
	%	**%**
Neutropenia (ANC/μL)		
< 500	**5**	**30**
500 - < 750	**8**	**7**
750 - < 1 000	**5**	**11**
Anaemia (haemoglobin g/dL)		

Laboratory abnormalities	VALCYTE in Paediatric SOT patients	
< 6,5	**0**	**0**
6,5 - < 8.0	**14**	**5**
8.0 - < 9,5	**38**	**29**
Thrombocytopenia (platelets/μL)		
< 25 000	**0**	**0**
25 000 - < 50 000	**10**	**0**
50 000 - <10 0000	**3**	**4**
Serum creatinine (mg/dL)		
> 2,5	**2**	**5**
> 1,5 – 2,5	**11**	**20**

Paediatric patients

Neutropenia was also reported with slightly higher incidence in the two paediatric studies as compared to adults but neutropenia and infectious adverse events were generally not correlated in the paediatric populations.

In kidney transplant paediatric patients, prolongation of VALCYTE exposure to 200 days was not associated with increased incidence of adverse events.

Congenital CMV

Congenital CMV is not an approved indication for VALCYTE. However, studies conducted in neonates and infants with congenital CMV do provide safety data in this patient population. Studies suggest that the safety of VALCYTE and CYMEVENE appear consistent with the known safety profile of VACYTE/ganciclovir. The primary toxicity is neutropenia, in one study 9 of 24 subjects (38 %) developed Grade 3 or 4 neutropenia while on ganciclovir therapy (one patient required treatment cessation). Most events were manageable with continuation of antiviral therapy. Growth (head circumference, weight and height) of all neonates, who had growth measurements recorded, increased over time in this non-comparative study. The most frequent treatment-related AEs associated with oral valganciclovir were neutropenia, anaemia, liver function abnormality and diarrhoea, all seen more frequently in the placebo group. The only treatment-related SAEs were neutropenia and anaemia, both seen more frequently in the placebo arm. No statistically or clinically

significant differences were observed in the rate of growth (average head circumference, body weight and length) over time at each time point between the two treatment groups.

Post Marketing

Safety reports from the post-marketing setting are consistent with safety data from clinical trials with ganciclovir and VALCYTE (see section 4.8).

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

It is expected that an overdose of VALCYTE, could also possibly result in increased renal toxicity.

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, leukopenia, 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 tremors, seizures.

Haemodialysis and hydration may be of benefit in reducing valganciclovir and mainly ganciclovir blood plasma levels in patients who receive an overdose of VALCYTE.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor, ATC code: J05AB14.

Mechanism of action

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). UL97 mutations arise earlier and more frequently than mutations in UL54. Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, with M460V/I, H520Q, C592G, A594V, L595S, C603W being the most frequently reported ganciclovir resistance-associated substitutions. Mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target the viral polymerase.
Amino acid substitutions in UL54 conferring cross-resistance to ganciclovir and cidofovir are generally located within the exonuclease domains and region V, however amino acid substitutions conferring cross resistance to foscarnet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805-845).

Prevention of CMV disease in transplantation

Resistance was evaluated in a study that extended valganciclovir CMV prophylaxis from 100 days to 200 days post-transplant in adult kidney transplant patients at high risk for CMV disease (D+/R-). Five subjects from the 100 day group and four subjects from the 200 day group meeting the resistance analysis criteria had known ganciclovir resistance-associated amino acid substitutions detected. In six subjects, the following resistance associated amino acid substitutions were detected within pUL97: 100 day group: A440V, M460V, C592G; 200 day group: M460V, C603W. In three subjects, the following resistance-associated amino acid substitutions were detected within pUL54: 100day group: E315D, 200 day group: E315D, P522S. Overall, the detection of known ganciclovir resistance-associated amino acid substitutions was observed more frequently in patients during prophylaxis therapy than after the completion of prophylaxis therapy (during therapy: 5/12 [42 %] versus after therapy: 4/58 [7 %]). The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

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} 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, IV) 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 adult renal function dosing algorithm and paediatric dosing algorithm (see section 4.2).

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 %). Also, the inter-individual variation in exposure (AUC) of ganciclovir decreases when taking valganciclovir with food. It is recommended that valganciclovir be administered with food. See section 4.2.

Distribution: The steady state volume of distribution of ganciclovir after IV administration was 0,680 ± 0,161 L/kg. For IV ganciclovir, the volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0,54 - 0,87 L/kg. Ganciclovir penetrates the cerebrospinal fluid. Binding to plasma proteins was 1 % - 2 % over ganciclovir concentrations of 0,5 and 51 µg/mL.

Metabolism: Valganciclovir is rapidly and extensively metabolised to ganciclovir, no other metabolites have been detected. Ganciclovir itself is not metabolised to a significant extent.

Elimination: Following dosing with oral valganciclovir, the medicine is rapidly hydrolysed to ganciclovir. Ganciclovir is eliminated from the systemic circulation by glomerular filtration and active tubular secretion. In patients with normal renal function greater than 90 % of IV administered ganciclovir was recovered un-metabolised in the urine within 24 hours. In patients with normal renal function the post-peak plasma concentrations of valganciclovir decline with a half-life ranging from 0,4 h to 2,0 h. In these patients, ganciclovir concentrations decline with a half-life ranging from 3,5 to 4,5 hours similarly to that observed after direct IV administration of ganciclovir.

Pharmacokinetics in special populations:

Paediatric Population:

Prevention of CMV disease in transplantation

The pharmacokinetics of ganciclovir following the administration of valganciclovir were characterised using a population PK model based on data from four studies in paediatric solid organ transplant (SOT) patients aged 3 weeks to 16 years. PK data were evaluable from 119 of the 123 patients enrolled. In these studies, patients received daily intravenous doses of ganciclovir to produce exposure equivalent to an adult 5 mg/kg intravenous dose (70 kg reference body weight) and/or received oral doses of valganciclovir to produce exposure equivalent to an adult 900 mg dose.

The model indicated that clearance is influenced by body weight and creatinine clearance while the central and peripheral volumes of distribution were influenced by body weight (see section 4.2).

Table 6 summarises the model estimated GCV $AUC_{0\text{-}24h}$, and C_{max} across different age groups.

Table 6 Summary of Model-Estimated GCV Steady-State $AUC_{0\text{-}24h}$ for Different Age Groups for Study NP22523 and Pooled Previous Studies

PK Parameter	NP22523[a] (< 4 Months)	Pooled Studies (< 2 years)	Pooled Studies (2–6 years)	Pooled Studies (6–12 years)	Pooled Studies (> 12 years)
$AUC_{0\text{-}24h}$ (µg•h/mL)	n = 18	n = 102	n = 48	n = 63	n = 101
Mean	68,1	54,5	50,3	46,1	46,9
Median	64,6	56,4	49,6	46,5	47,3
%CV	29,0	37,4	37,6	32,8	37,7
C_{max} (µg/mL)	n = 14	n = 28	n = 14	n = 20	n = 43
Mean	10,5	11,1	9,09	8,87	8,38
Median	10,7	11,1	9,62	9,25	8,65

%CV	31,9	38,2	27,8	40,5	36,9

$AUC_{0\text{-}24h}$ = area under the concentration−time curve over the dosing interval;

n = number of observations; CV = coefficients of variation; PK = pharmacokinetic.

[a] n = 14 patients

Congenital CMV

Ganciclovir pharmacokinetics parameters following valganciclovir administration were also evaluated in 133 neonates aged 2 to 31 days with symptomatic congenital CMV disease in two studies.

In the first study, all patients received 6 mg/kg intravenous ganciclovir twice daily. Patients were then treated with oral valganciclovir, where the dose of valganciclovir powder for oral solution ranged from 14 mg/kg to 20 mg/kg twice daily. A dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided comparable ganciclovir exposure as 6 mg/kg intravenous ganciclovir twice daily in neonates, and also achieved ganciclovir exposure similar to the effective adult 5 mg/kg intravenous dose. In the second study, all patients received valganciclovir powder for oral solution at a dose of 16 mg/kg twice daily for 6 weeks and subsequently 96 out of 109 enrolled patients were randomized to continue receiving valganciclovir or placebo for 6 months.

The mean ganciclovir $AUC_{0\text{-}12hr}$ after oral dose administration of valganciclovir was approximately 23,2 µg·h/mL (equivalent to 46,4 µg·h/mL in $AUC_{0\text{-}24hr}$) in the first study. Similar exposure was also observed in the second study.

Elderly Population

No investigations on valganciclovir or ganciclovir pharmacokinetics in adults older than 65 years of age have been undertaken. However, as valganciclovir is a pro-drug of ganciclovir and because ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in elderly (see section 4.2).

Patients with renal impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir were evaluated in 24 otherwise healthy adult individuals with renal impairment.

Table 7 Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg VALCYTE tablets in patients with various degrees of renal impairment

Estimated Creatinine Clearance (mL/min)	N	Apparent Clearance (mL/min) Mean ± SD	$AUC_{0-\infty}$ (µg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51 - 70	6	249 ± 99	50,5 ± 23	4,9 ± 1.4
21 - 50	6	136 ± 64	100 ± 54	10,2 ± 4.4
11 - 20	6	45 ± 11	252 ± 64	21,8 ± 5.2
≤ 10	6	12.8 ± 8	407 ± 83	68,1 ± 35

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see sections 4.2 and 4.4).

Patients undergoing haemodialysis

Ganciclovir is readily removable by haemodialysis. Data obtained during intermittent haemodialysis in adult patients dosed with valganciclovir showed estimated dialysis clearance as 138 mL/min ± 9,1 % (N = 3) and intra-dialysis half-life estimated to 3,47 h (N = 6).

55 % of ganciclovir was removed during a 3-hour dialysis session.

Stable liver transplant patients

The pharmacokinetic parameters of ganciclovir from valganciclovir in stable liver transplant adult patients were investigated in one open label 4-part crossover study (N = 28). The absolute bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60 %. Ganciclovir AUC_{0-24h} was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant adult patients.

Hepatic impairment

The safety and efficacy of valganciclovir have not been studied in patients with hepatic impairment.

Patients with cystic fibrosis [CF]

In a phase I pharmacokinetic study, steady state systemic exposure to ganciclovir was assessed in adult lung transplant recipients with or without cystic fibrosis (N = 31 [16 CF/15 non-CF]) who were receiving 900 mg/day of VALCYTE as part of their post-transplant prophylaxis. The study indicated that cystic fibrosis had no statistically significant influence on the overall average systemic exposure to ganciclovir in lung transplant recipients. Ganciclovir exposure in lung transplant recipients was comparable to that shown to be efficacious in the prevention of CMV disease in other solid organ transplant recipients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

VALCYTE 450 film-coated tablet:

Crospovidone, microcrystalline cellulose, povidone K-30, stearic acid powder (1 % w/w), Opadry Pink which consists of: hypromellose, macrogol, polysorbate 80, red iron oxide (E172), titanium dioxide (E171).

VALCYTE 50 mg/mL powder for oral solution:

Fumaric acid, mannitol *(5,78 g per bottle), povidone K30, saccharin sodium, tutti frutti flavour.

**Mannitol may be used to compensate the amount of valganciclovir HCl, if adjusted for assay.*

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Tablets – 36 months

Powder for Oral Solution – 36 months

6.4. Special precautions for storage

VALCYTE 450 film-coated tablets:

Store at or below 25 °C.

Do not break or crush the tablets. Avoid contact of broken or crushed tablets with skin or mucous membranes.

VALCYTE 50 mg/mL powder for oral solution:

Store at or below 30 °C.

Reconstituted solution: Store in the refrigerator at 2 °C to 8 °C.

Store in the original bottle. Keep the bottle tightly closed. Any remaining solution should be discarded after 49 days. Store all medicines out of reach of children.

6.5. Nature and contents of container

VALCYTE 450 film-coated tablets: 60 film-coated tablets in a white plastic bottle with a child resistant screw closure.

VALCYTE 50 mg/mL powder for oral solution: Carton containing an amber glass bottle with child-resistant white opaque plastic screw-cap, a bottle adapter and a blister pack containing 2 oral dispensers. The oral dosing dispensers have 0.5 mL graduations (25 mg) to 10 mL (500 mg).

6.6. Special precautions for disposal and other handling

Since VALCYTE is considered a potential teratogen and carcinogen in humans, the tablets, 50 mg/mL powder for oral solution and reconstituted solution should be handled with caution. If a broken tablet, 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.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd

3 Sandown Valley Crescent

South Tower, First Floor

Sandton 2196, Gauteng

South Africa

Ethical assistance Line: +27 (0)11 784 00 77

8. REGISTRATION NUMBER(S)

VALCYTE 450: 37/20.2.8/0296

VALCYTE 50 mg/mL: 43/20.2.8/0433

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: Tablets – 17 Sep 2004; Powder for Oral Solution – 27 Jul 2012

10. DATE OF REVISION OF THE TEXT

Last revision: 31 July 2024