PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Valcyte® 450 film-coated tablet

Valcyte® 50 mg/mℓ powder for oral solution

COMPOSITION

Valcyte 450 film-coated tablet:

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

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

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.

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

Other ingredients: fumaric acid, mannitol (i.e. a sugar), povidone K30, saccharin sodium, tutti frutti flavour. Contains sodium saccharin as sweetener.

CATEGORY AND CLASS

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 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).

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 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.

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. See DOSAGE AND DIRECTIONS FOR USE.

Haemodialysis: For patients receiving haemodialysis (CrCl < 10 mℓ/min); it is recommended that *IV* ganciclovir is used. The individual dose of Valcyte required for these patients is less than the 450 mg tablet strength. Approximately half of the ganciclovir present at the start of dialysis is removed during dialysis. The mean intra-dialysis half-life and mean interdialysis half-life is estimated to be 3,47 h and 51,0 h respectively. However, for patients receiving haemodialysis (CrCl < 10 mℓ/min) Valcyte 50 mg/mℓ powder for oral solution is recommended to provide an individualised dose. See DOSAGE AND DIRECTIONS FOR USE.

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 $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg *IV* ganciclovir in liver transplant recipients.

Paediatric Patients

In a phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) valganciclovir was given once daily for up to 100 days. Pharmacokinetic parameters were similar across organ type and age range and comparable with adults. Population pharmacokinetic modelling suggested that bioavailability was approximately 60 %. Clearance was positively influenced by both body surface area and renal function. The mean total clearance was 5,3 ℓ /h (88,3 mℓ/min) for a patient with a creatinine clearance of 70,4 mℓ/min. The following table shows the mean C_{max}, $t_{½}$ and AUC values including standard deviations for the relevant paediatric age groups compared to adult data:

PK Parameter	**Adults***	**Paediatrics**		
	≥ 18 years (n = 160)	**≤ 2 years (n = 17)**	**> 2 - < 12 years (n = 21)**	**≥ 12 years (n = 25)**
AUC_{0-24h} (µg·h/mℓ)	46,3 ± 15,2	64,3 ± 29,2	59,2 ± 15,1	50,3 ± 15,0
C_{max} (µg/mℓ)	5,3 ± 1,5	10,3 ± 3,3	9,4 ± 2,7	8,0 ± 2,4
Clearance (ℓ /h)	12,7 ± 4,5	2,5 ± 2,4	4,5 ± 2,9	6,4 ± 2,9
$t_{½}$ (h)	6,5 ± 1,4	3,1 ± 1,4	4,1 ± 1,3	5,5 ± 1,1

* Extracted from study report PV 16000

The once daily dose of Valcyte was based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and was calculated using the equation below:

Paediatric Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula)

where

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

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

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.

The dose should not exceed the adult 900 mg dose. In addition, if the calculated Schwartz creatinine clearance exceeds 150 mℓ/min/1,73 m^2 should be used in the equation. It should be noted that the paediatric dosage algorithm was developed based on pharmacokinetic data only and has not been verified in efficacy and safety studies.

A phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) receiving valganciclovir once daily for up to 100 days according to a dosing algorithm produced exposures similar to that in adults. Follow up after treatment was 12 weeks. CMV D/R serology status at baseline was D+/R- in 40 %, D+/R+ in 38 %, D-/R+ in 19 % and D-/R- in 3 % of the cases. Presence of CMV virus was reported in 7 patients. The observed adverse drug reactions were of similar nature as those in adults (see SIDE EFFECTS). These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients.

The pharmacokinetics and safety of single dose valganciclovir (dose range 14-16-20 mg/kg/dose) was studied in 24 neonates (aged 8-34 days) with symptomatic congenital CMV disease. The neonates received 6 weeks of antiviral treatment, whereas 19 of the 24 patients received up to 4 weeks of treatment with oral valganciclovir, in the remaining 2 weeks they received i.v. ganciclovir. The 5 remaining patients received i.v. ganciclovir for the most time of the study period. This treatment indication is not recommended presently for valganciclovir. The design of the study and obtained results are too limited to allow appropriate efficacy and safety conclusions on valganciclovir.

Ganciclovir pharmacokinetics were also evaluated in 24 neonates aged 8 to 34 days with symptomatic congenital CMV disease. 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. The following table shows the mean AUC C_{max}, and $t_{½}$ values including standard deviations compared adult data:

PK Parameter	Adults	Neonates	
	5 mg/kg GAN Single dose (n = 8)	**6 mg/kg GAN Twice daily (n = 19)**	**16 mg/kg GAN Twice daily (n = 19)**
$AUC_{-\infty}$ (mg·h/ℓ)	25,4 ± 4,32	-	-
AUC_{12h} (mg·h/ℓ)	-	38,25 ± 42,7	30,1 ± 15,1
C_{max} (µg/mℓ)	9,03 ± 1,26	12,9 ± 21,5	5,44 ± 4,04
$t_{½}$ (h)	3,32 ± 0,47	2,52 ± 0,55	2,98 ± 1,26

GAN = Ganciclovir, i.v.

VAL = Valganciclovir, oral

The pharmacokinetic modelling suggested that the typical value of clearance (ℓ/h), volume of distribution (ℓ), and bioavailability of ganciclovir in neonates were 0,146 x Weight^{1,68}, 1,15 x Weight and 54 % respectively. These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients with congenital CMV infection.

INDICATIONS

Valcyte 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.

CONTRAINDICATIONS

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

WARNINGS AND SPECIAL PRECAUTIONS

Women of child bearing 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 Valcyte.

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression 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. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered. See DOSAGE AND DIRECTIONS FOR USE - *Special Dosage Instructions.*

Safety and efficacy in children have not been established in adequate and well-controlled clinical studies. See DOSAGE AND DIRECTIONS FOR USE - *Special Dosage Instructions*.

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 DOSAGE AND DIRECTIONS FOR USE.

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required. See DOSAGE AND DIRECTIONS FOR USE - *Special Dosage Instructions*.

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.

Convulsions 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 INTERACTIONS.

Zidovudine and Valcyte each have the potential to cause neutropenia and anaemia. Some patients may not tolerate concomitant therapy at full dosage. See INTERACTIONS.

Didanosine plasma concentrations may increase during concomitant use with Valcyte, therefore patients should be closely monitored for didanosine toxicity. See INTERACTIONS.

Concomitant use of other medicines that are known to be myelosuppressive or associated with renal impairment with Valcyte may result in added toxicity. See INTERACTIONS.

Valcyte 50 mg/mℓ powder for oral solution contains sodium benzoate. Benzoates cause mild irritation to the skin, eyes and mucous membranes.

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.

Effects on ability to drive and use machines

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

INTERACTIONS

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

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

Interactions with ganciclovir

Imipenem-cilastatin: Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These medicines should not be used concomitantly unless the potential benefit outweighs the potential risks. See WARNINGS AND SPECIAL PRECAUTIONS.

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.

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 WARNINGS AND SPECIAL PRECAUTIONS.

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 WARNINGS AND SPECIAL PRECAUTIONS.

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 clinical relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir although a small increase in the elimination rate constant was observed.

Both Valcyte 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 be considered for concomitant use with Valcyte only if the potential benefits outweigh the potential risks. See WARNINGS AND SPECIAL PRECAUTIONS.

HUMAN REPRODUCTION

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

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. Women using Valcyte should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

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 Valcyte tablets (2 x Valcyte 450 tablets).

Standard dosage in adults

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg Valcyte 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 Valcyte 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 Dosage Instructions

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)

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

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

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

CL_{CR} (mℓ/min)

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

CL_{CR} = creatinine clearance

S_{CR} = serum creatinine

Table 2: 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 3 : 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.

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

Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, bone marrow depression 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 is less than 8 g/dℓ. See WARNINGS AND SPECIAL PRECAUTIONS.

Elderly: Safety and efficacy have not been established.

Paediatric patients*:*

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

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.

SIDE 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.

Clinical trials

All of the undesirable effects observed in Valcyte clinical studies have been previously observed with ganciclovir. The most commonly reported adverse drug reactions following administration of Valcyte in adults are neutropenia, anaemia and diarrhoea.

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

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

The frequency of adverse reactions reported in clinical trials with either Valcyte, oral ganciclovir, or intravenous ganciclovir is presented in the table below. The adverse reactions listed were reported in clinical trials in patients with AIDS for the induction of maintenance treatment of CMV retinitis, or in liver, kidney or heart transplant patients for the prophylaxis of CMV disease. The term (severe) in parenthesis in the table indicates that the adverse reaction has been reported in patients at both

mild/moderate intensity and severe/life-threatening intensity and severe/life-threatening intensity at that specific frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body System	**Very Common (≥ 1/10)**	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1 000, < 1/100)**	**Rare (≥ 1/10 000, < 1/1 000)**
Infections and infestations		Oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection		
Blood and lymphatic system disorders	(Severe) neutropenia, anaemia	(Severe) anaemia, (severe) thrombocytopenia, (severe) leucopenia, (severe) pancytopenia	Bone marrow depression	Aplastic anaemia
Immune system disorders			Anaphylactic reaction	
Metabolic and nutrition disorders		Decreased appetite, anorexia		
Psychiatric disorders		Depression, anxiety, confusion, abnormal thinking	Agitation, psychotic disorder, hallucination	
Nervous system disorders		Headache, insomnia, dysgeusia (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness (excluding	Tremor	

Body System	Very Common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1 000, < 1/100)	Rare (≥ 1/10 000, < 1/1 000)
		vertigo), convulsion		
Eye disorders		Macular oedema, retinal detachment, vitreous floaters, eye pain	Visual disturbance, conjunctivitis	
Ear and labyrinth disorders		Ear pain	Deafness	
Cardiac disorders			Dysrhythmias	
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Cough		
Gastrointestinal disorders	Diarrhoea	Nausea, vomiting, abdominal pain, upper abdominal pain, dyspepsia, constipation, flatulence, dysphagia,	Abdominal distension, mouth ulcerations, pancreatitis	
Hepatobiliary disorders		(Severe) abnormal hepatic function, increased blood alkaline phosphatase, increased aspartate aminotransferase	Increased alanine aminotrans-ferase	
Skin and subcutaneous tissue disorders		Dermatitis, night sweats, pruritus	Alopecia, urticaria, dry skin	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia, arthralgia, muscle cramps		
Renal and		Decreased	Haematuria, renal	

Body System	Very Common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1 000, < 1/100)	Rare (≥ 1/10 000, < 1/1 000)
urinary disorders		creatinine renal clearance, renal impairment	failure	
Reproductive system and breast disorders			Male infertility	
General disorders and administration site conditions		Fatigue, pyrexia, rigors, pain, chest pain, malaise, asthenia		
Investigations		Decreased weight, increased blood creatinine		

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

Paediatrics

There are very limited paediatric data on the exposure of Valcyte. The following is a summary of all adverse events which occurred in more than 10 % (very common) of the total paediatric population on treatment:

Body system	Very common adverse events reported in clinical trials
Blood and lymphatic system disorders	Anaemia, neutropenia
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, constipation
General disorders and administration site conditions	Pyrexia, transplant rejection

Post-Marketing

Experience with ganciclovir

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 Valcyte is rapidly and extensively converted to ganciclovir, such adverse events might also occur with Valcyte.

- Anaphylaxis

Adverse events that have been reported during the post-marketing period are consistent with those seen in clinical trials with Valcyte and ganciclovir.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

It is expected that an overdose of Valcyte, 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 Valcyte.

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.

IDENTIFICATION

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.

PRESENTATION

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 dispensers are graduated with 25 mg graduations up to 500 mg.

STORAGE INSTRUCTIONS

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.

REGISTRATION NUMBERS

Valcyte 450: 37/20.2.8/0296

Valcyte 50 mg/mℓ: 43/20.2.8/0433

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

Roche Products (Pty) Ltd

24 Fricker Road

Illovo

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

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PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

Valcyte® 450 film-coated tablet

Valcyte® 50 mg/mℓ powder for oral solution

Read all of the leaflet carefully before you start using Valcyte

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- Valcyte has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

WHAT VALCYTE CONTAINS

Each Valcyte film-coated tablet contains 450 mg valganciclovir as valganciclovir hydrochloride.

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

Each Valcyte powder for oral solution, 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.

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

Excipients: Fumaric acid, Mannitol (a sugar), povidone K30, tutti-frutti flavour.

Contains sodium saccharin as sweetener.

WHAT VALCYTE IS USED FOR

Valcyte 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 at risk

After taking Valcyte, the valganciclovir is quickly changed in your body to release ganciclovir, which is the active medicine. Ganciclovir prevents the growth and the increase in numbers of a virus called Cytomegalovirus (CMV).

BEFORE YOU TAKE VALCYTE

Please take special note of the advice regarding taking Valcyte during pregnancy below.

Do not take Valcyte if:

- you have ever had an allergic reaction to valganciclovir, or to ganciclovir, or to any of the other ingredients of Valcyte.
- you have ever had an allergic reaction to aciclovir or valaciclovir.
- if you are breastfeeding.

Take special care with Valcyte:

- If you have (or have recently had) low numbers of white blood cells, red blood cells or platelets (small cells involved in blood clotting) in your blood. Your doctor will perform blood tests before you start taking Valcyte and more tests will be done while you are taking Valcyte.
- If you have problems with your kidneys. Your doctor may need to prescribe a reduced dose for you and may need to check your blood frequently during treatment.
- If you are on haemodialysis or receiving radiotherapy. Valcyte 450 film-coated tablets are not suitable for people on haemodialysis, however, Valcyte 50 mg/mℓ oral solution may be used. If your doctor decides to give you Valcyte 50 mg/mℓ oral solution, your blood will need to be checked frequently.
- If you are currently taking ganciclovir capsules and your doctor wants you to switch to Valcyte. It is important that you do not take more than the dose prescribed by your doctor or you could risk an overdose.

Safety and efficacy - studies of Valcyte use in children are limited.

Taking Valcyte with food and drink:

Valcyte should be taken with food. If you are unable to eat for any reason,

you should still take your dose of Valcyte as usual.

Pregnancy and breastfeeding:

Pregnancy

If you are pregnant or breastfeeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before taking this medicine.

Valcyte is not usually given to pregnant women because it is possible that this could lead to the loss of the baby or to the birth of a malformed baby or to problems in the baby after birth.

If you are already pregnant before starting to take Valcyte, or if you think you may possibly be pregnant, you **must** tell your doctor before you take Valcyte.

Your doctor will only advise you to take Valcyte if it is clearly needed and only after discussing the risks to the unborn baby with you. If you have any questions, ask your doctor.

It is also extremely important that both men and women of child-bearing age use effective contraception during treatment with Valcyte. If you need advice on contraception, ask your doctor before you start to take Valcyte. Men should use condoms while taking Valcyte and should continue to use condoms for 90 days after treatment has finished (see section *Possible Side Effects*).

Breastfeeding

Valcyte must not be used if you are breastfeeding. The active ingredient, ganciclovir, may pass into the milk and may harm your baby.

Driving and operating machinery:

If you feel dizzy, sleepy or confused while taking Valcyte, do not drive or operate machinery. Other side effects that can occur with Valcyte and may cause problems if you drive or operate machinery are fits and loss of co-ordination (see *Possible Side Effects* below for details).

Taking other medicines with Valcyte:

Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines).

Special care is needed when some other medicines are taken with Valcyte. Make sure that you tell your doctor about ALL the medicines that you are taking before you take Valcyte, including all medicines that have been prescribed for you and any medicines that you have bought without a prescription.

Your doctor may still advise you to take Valcyte, but may ask to see you more often during treatment and it may be necessary to check your blood more often if you are taking the medicines listed below.

Taking Valcyte with these medicines may increase the number and severity of any side effects.

Tell your doctor if you are already taking medicines that contain the following:

- Imipenem-cilastatin. There may be an increased risk of fits when this antibiotic is taken with Valcyte.
- Trimethoprim with or without sulphonamides, pentamidine, flucytosine, amphotericin B and dapsone taken for the treatment of infections.
- Adriamycin, vincristine, vinblastine and hydroxyurea used in the treatment of cancer.
- Zidovudine, didanosine, zalcitabine, stavudine or other medicines used in the treatment of HIV. Your doctor may reduce the dose of didanosine that you need to take.
- Probenecid taken for the treatment of gout may increase your blood levels of ganciclovir.
- Mycophenolate mofetil, a medicine that is used in patients who have received an organ transplant.
- Cidovir, foscarnet, or nucleoside analogues used against viral infections.

HOW TO TAKE VALCYTE

Do not share medicines prescribed for you with any another person.

Always take Valcyte exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure.

Whenever possible, Valcyte should be taken with food. If you are unable to eat for any reason, you should still take the dose when it is due.

Valcyte 450 tablets should be handled with care and should not be broken or crushed. You should swallow them whole and with food whenever possible.

Valcyte 50 mg/mℓ Oral Solution should be handled with care. You should avoid getting the solution on your skin or in your eyes.

If you do accidentally get the solution on your skin, or touch damaged tablets, wash the area thoroughly with soap and water. If you accidentally get any solution or powder in your eyes, rinse your eyes thoroughly with water.

It is important that you use the syringe provided in the pack to measure your dose of Valcyte 50 mg/mℓ oral solution.

The usual dose is:

Adults:

Standard dosage

Prevention of CMV disease in transplant patients:

You should start to take Valcyte within 10 days of your transplant. The usual dose is 900 mg Valcyte taken ONCE daily. You should continue with this dose for up to 100 days following your transplant. If you have received a kidney transplant, your doctor may advise you to take the dose for 200 days.

Treatment of very active CMV retinitis in AIDS patients (called induction treatment):

The usual dose is 900 mg (450 mg x 2 tablets/amounts) (2 full syringes) taken TWICE a day for 21 days (three weeks). That is, two 450 mg tablets/amounts (i.e. 2 full syringes) of the Valcyte in the morning and two 450 mg tablets/ amounts (i.e. 2 full syringes) in the evening.

Do not continue with this dose for more than 21 days unless your doctor tells you to as this may increase your risk of possible side effects.

Longer term treatment to prevent recurrence of active inflammation in AIDS patients with CMV retinitis (called maintenance treatment):

The usual dose is 900 mg (450 mg x 2 tablets/amounts) (2 full syringes) Valcyte taken ONCE a day. You should try to take Valcyte at the same time each day. Your doctor will advise you how long you should continue to take Valcyte. If your retinitis worsens while you are on this dose, your doctor may tell you to repeat the induction treatment (as above) or may decide to give you a different medicine to treat the CMV infection.

Patients with kidney disorders:

If your kidneys are not working properly, your doctor may instruct you to take a lower dose of the Valcyte each day or may ask you to take Valcyte only on some days of the week.

It is VERY IMPORTANT that you follow these special dose instructions from your doctor.

Your doctor will tell you how long your treatment with Valcyte will last. Do not stop treatment early. If you have the impression that the effect of Valcyte is too strong or weak, tell your doctor or pharmacist.

If you take more Valcyte than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

Contact your doctor or hospital immediately if you have taken, or think you have taken more Valcyte than you should. Taking too much Valcyte can cause serious side effects, particularly affecting your blood or kidneys. You may need hospital treatment.

If you forget to take/missed a dose of Valcyte:

It is important that you continue to take your medicine according to the instructions on the label and that you do not miss any doses. However, if you do miss a dose, take it as soon as you remember and take the next dose at the normal time. Do not take a double dose to make up for a forgotten dose.

Effects when treatment with Valcyte is stopped:

You must not stop taking Valcyte unless your doctor tells you to. If you have any further questions on the use of Valcyte, ask your doctor or pharmacist.

POSSIBLE SIDE EFFECTS

Valcyte can have side effects. Although Valcyte can help fight CMV infection, it can have some serious side effects. Your doctor may advise stopping your treatment either temporarily or permanently depending on your condition.

Not all side effects reported for Valcyte are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking Valcyte, consult your doctor, pharmacist or other health care professional for advice.

Allergic reactions

Infrequently, people may have a sudden and severe allergic reaction to Valcyte (anaphylactic shock). STOP taking Valcyte and go to the nearest hospital emergency room if you experience any of the following:

- **A raised, itchy skin (hives)**
- **Sudden swelling of the throat, face, lips and mouth which may cause difficulty swallowing or breathing**
- **Sudden swelling of the hands, feet or ankles**

Frequent side effects:

- Effects on the blood: a reduction in the number of white blood cells in the blood (neutropenia) - which will make you more likely to get infections, a reduction in the pigment in the blood that carries oxygen (anaemia) - which can cause tiredness and breathlessness when you exercise
- Effects on breathing: feeling short of breath or having trouble breathing (dyspnoea)
- Effects on the stomach and digestive system: diarrhoea
- Effects on the blood: a reduction in the number of leucocytes (blood cells that fight infection) in the blood (leucopenia) a reduction in the number of platelets in the blood (thrombocytopenia) - which can cause bruising and bleeding, a reduction in several types of blood cells at the same time (pancytopenia)
- Effects on the nervous system: headache, difficulty sleeping (insomnia), strange tastes (dysgeusia), becoming less sensitive to touch (hypoaesthesia), prickly or tingling skin (paraesthesia), loss of feeling in the hands or feet (peripheral neurophathy), dizziness, fits (convulsions)
- Effects in the eye: eye pain, swelling within the eye (oedema), separation of the back of the eye (detached retina), seeing floaters
- Effects in the ear: earache
- Effects on breathing: coughing
- Effects on the stomach and digestion: feeling and being sick, stomach ache, constipation, wind, indigestion (dyspepsia), difficulty swallowing (dysphagia)
- Effects on the skin: inflamed skin (dermatitis), itching (pruritus), sweating at night
- Effects on the muscles, joints or bones: back pain, pain in the muscles (myalgia) or joints (arthralgia), stiff muscles (rigor), muscle cramps
- Infections: fungal infection in the mouth (oral candidiasis), infections caused by bacteria or viruses in the blood, inflammation of cellular tissue (cellulitis), inflammation or infection of the kidneys or bladder
- Effects in the liver: a rise in some liver enzymes, which will only be seen during blood tests
- Effects in the kidney: changes to the normal working of the kidneys
- Effects on eating: loss of appetite (anorexia), weight loss

- General effects: tiredness, fever, pain, chest pain, loss of energy (asthenia), generally feeling unwell (malaise)
- Effects on mood or behaviour: depression, feeling anxious, confused, having unusual thoughts

Less frequent side effects:

- Effects in the heart: changes to the normal heartbeat (dysrhythmia)
- Effects on circulation: low blood pressure (hypotension), which can cause you to feel light headed or faint
- Effects on the blood: a decrease in the production of blood cells in the bone marrow
- Effects in the nerves: shaking or trembling (tremor)
- Effects in the eyes: red, swollen eyes (conjunctivitis), abnormal vision
- Effects in the ears: deafness
- Effects on the stomach or digestion: swollen stomach, mouth ulcers, inflammation of the pancreas (pancreatitis) where you may notice severe pain in the stomach and back
- Effects on the skin: hair loss (alopecia), itchy rash or swellings (urticaria), dry skin
- Effects in the kidneys: blood in the urine (haematuria), kidney failure
- Effects in the liver: a rise in the liver enzyme called alanine aminotransferase (which will only be seen during blood tests)
- Effects on fertility: infertility in men
- Effects on mood or behaviour: having unusual changes in mood and behaviour, losing contact with reality such as hearing voices or seeing things that are not there, feeling agitated
- Effects on the blood: failure of the production of all types of blood cells (red blood cells, white blood cells and platelets) in the bone marrow

STORING AND DISPOSING OF VALCYTE

Store all medicines out of reach of children.

Valcyte 450 film-coated tablets: Store at or below 25 °C.

Do not use after the expiry date stated on the pack.

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. Return any unused solution in the original container to your pharmacist for safe disposal.

PRESENTATION OF VALCYTE

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

Valcyte 50 mg/mℓ 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 dispensers are graduated with 25 mg graduations up to 500 mg.

IDENTIFICATION OF VALCYTE

Valcyte 450 film-coated tablets: The tablets are pink, oval film-coated tablets marked “VGC” on one side and “450” on the other side.

Valcyte 50 mg/mℓ oral solution: The reconstituted powder is a colourless to brownish-yellow clear solution.

REGISTRATION NUMBERS

Valcyte 450 film-coated tablet: 37/20.2.8/0296

Valcyte 50 mg/mℓ oral solution: 43/20.2.8/0433

NAME AND BUSINESS ADDRESS OF REGISTRATION HOLDER

Roche Products (Pty) Ltd

24 Fricker Road

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South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

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PASIËNT INLUGTINGSTUK

SKEDULERINGSTATUS

S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM

VALCYTE® 450 filmbedekte tablet

VALCYTE® 50 mg/mℓ poeier vir mondelikse oplossing

Lees hierdie hele inligtingstuk noukeurig duer voordat u Valcyte begin gebruik

- Hou hierdie inligtingstuk. U sal dit dalk weer moet lees.
- Indien u verdere vrae het, vra asseblief u dokter of u apteker.
- Valcyte is vir u voorgeskryf. Moenie dit met ander deel nie. Dit kan hulle kwaad aandoen, selfs al het hulle dieselfde simptome as u.
- Indien enige van die newe-effekte vererger of indien u newe-effekte waarneem wat nie in hierdie inligtingstuk gemeld word nie, verwittig asseblief u dokter.

WAT VALCYTE BEVAT

Elke Valcyte filmbedekte tablet bevat 450 mg valgansiklovir as valgansiklovirhidrochloried.

Hulpstowwe: Krospovidoon, mikrokristallyne sellulose, povidoon K-30, stearіensuurpoeier, Opadry pienk wat bestaan uit: Hipromellose, makrogol, polisorbaat 80, rooi-ysteroksied (E172), titaniumdioksied (E171).

Elke Valcyte poeier vir mondelikse oplossing bevat 5,5 g valgansiklovirhidrochloried, in 12 g poeier vir mondelikse oplossing. Ná vermenging met 91 mℓ gesuiwerde water, bevat elke 1 mℓ oplossing valgansiklovirhidrochloried gelykstaande aan 50 mg valgansiklovir vrybasis.

Bevat: Natriumbensoaat 0,83 % m/m as preserveermiddel.

Ander bestanddele: fumariese suur, mannitol (‘n suiker), povidoon K30, tutti-frutti geursel.

Bevat natriumsaggarien as versoeter.

WAARVOOR VALCYTE GEBRUIK WORD

Valcyte word gebruik vir:

- die behandeling van sitomegalovirus (SMV) retinitis by pasiënte met verworwe immuungebreksindroom (VIGS)
- die voorkoming van SMV-siekte in soliede orgaanoorplantingspasiënte wat ’n risiko loop

Nadat VALCYTE geneem is, word die valgansiklovir vinnig in die liggaam verander om gansiklovir vry te stel, wat die aktiewe medisyne is. Gansiklovir verhoed die groei en toename in die aantal van ’n virus genaamd Sitomegalovirus (SMV).

VOORDAT U VALCYTE NEEM

Neem asseblief kennis van die spesiale kennisgewing hieronder rakende die neem van Valcyte tydens swangerskap.

Moenie Valcyte neem indien:

- u al ooit ’n allergiese reaksie teenoor valgansiklovir of gansiklovir, of enige van die bestanddele van Valcyte gehad het nie.
- u al ooit ’n allergiese reaksie teenoor asiklovir of valasiklovir gehad het nie.
- u borsvoed nie.

Neem spesiale voorsorg met Valcyte:

- Indien u (of u onlangs) lae aantal witbloedselle, rooibloedselle of plaatjies (klein selle wat betrokke is by bloedstolling) in u bloed gehad het. U dokter sal bloedtoetse uitvoer voor u Valcyte begin neem en nog toetse sal gedoen word terwyl u Valcyte neem.
- Indien u nierprobleme het. U dokter kan dit nodig vind om ’n laer dosis vir u voor te skryf en dit kan nodig wees om u bloed dikwels tydens behandeling te toets.
- Indien u op hemodialise is of radioterapie ontvang. Valcyte 450 filmbedekte tablette is nie geskik vir pasiënte op hemodialise nie, Valcyte 50 mg/mℓ mondelikse oplossing kan egter gebruik word. Indien u dokter besluit om u Valcyte 50 mg/mℓ mondelikse oplossing te gee, sal dit nodig wees om u bloed dikwels te toets.
- Indien u tans gansiklovir kapsules neem en u dokter wil u oorskakel na Valcyte 50 mg/mℓ mondelikse oplossing, is dit belangrik dat u nie meer as die voorgeskrewe dosis neem nie aangesien u ’n oordosis kan neem.

Veiligheid en doeltreffendheid – studies oor die gebruik van Valcyte by kinders is beperk.

Neem van Valcyte met voedsel en drank:

Valcyte moet saam met voedsel geneem word. Indien u om een of ander rede nie kan eet nie, moet u steeds u dosis Valcyte soos gewoonlik neem.

Swangerskap en borsvoeding:

Swangerskap

Indien u swanger is of u baba borsvoed, bespreek dit asseblief met u dokter, apteker of ander gesondheidsorgdeskundige voordat u hierdie medisyne neem.

Valcyte word gewoonlik nie aan swanger vroue gegee nie, aangesien dit kan lei tot 'n miskraam of die geboorte van 'n misvormde baba of tot probleme by die baba na geboorte.

Indien u reeds swanger is voordat u begin met Valcyte, of indien u dink dat u moontlik swanger kan wees, **moet** u dokter vertel voordat u Valcyte neem.

U dokter sal slegs aanbeveel dat u Valcyte neem indien dit duidelik nodig blyk te wees en na bespreking van die risiko's vir die ongebore baba. Indien u enige vrae het, vra u dokter.

Dit is uiters belangrik dat beide mans en vrouens van vrugbare lewe doeltreffende geboortebeperking sal gebruik tydens behandeling met Valcyte. Indien u advies benodig rakende geboortebeperking, vra u dokter voor u begin om Valcyte te neem. Mans behoort kondome te gebruik terwyl hulle Valcyte neem en behoort voort te gaan om kondome te gebruik vir 90 dae nadat behandeling voltooi is (kyk afdeling *Moontlike newe-effekte*).

Borsvoeding

Valcyte moet nie gebruik word indien u borsvoed nie. Die aktiewe bestanddeel, gansiklovir, kan in die borsmelk voorkom en die baba kwaad aandoen.

Motorbestuur en hantering van masjinerie:

Indien u duiselig, slaperig of verward voel terwyl u Valcyte neem, moet u nie bestuur of masjinerie hanteer nie. Ander newe-effekte wat met Valcyte kan voorkom en wat probleme met motorbestuur en hantering van masjinerie kan veroorsaak, is toevalle en verlies van koördinasie (kyk *Moontlike newe-effekte* hieronder vir besonderhede).

Gebruik van ander middels saam met Valcyte:

Vertel altyd u gesondheidsorgdeskundige indien u enige ander middels neem (dit sluit komplementêre of tradisionele middels in).

Spesiale voorsorg is nodig wanneer sommige ander middels saam met Valcyte geneem word. Maak seker dat u u dokter inlig oor AL die medisyne wat u neem, voordat u Valcyte neem, insluitende alle medisyne wat vir u voorgeskryf is en enige ander medisyne wat u sonder 'n voorskrif gekoop het.

U dokter kan u steeds adviseer om Valcyte te neem, maar kan versoek om u meer dikwels te sien tydens behandeling en dit kan nodig wees om u bloed meer dikwels te toets indien u die medisynes neem wat hieronder gelys word.

Die neem van Valcyte saam met hierdie middels kan die aantal en erns van newe-effekte verhoog.

Vertel u dokter indien u reeds medisyne neem wat die volgende bevat:

- Imipenem-silastatien. Daar kan 'n verhoogde risiko van toevalle wees wanneer hierdie antibiotikum saam met Valcyte geneem word.
- Trimetopriem met of sonder sulfonamiede, pentamidien, flusitosien, amfoterisien B en dapsoon vir die behandeling van infeksies.
- Adriamisien, vinkristien, vinblastien en hidroksi-urea by die gebruik van kankerbehandeling.
- Sidovudien, didanosien, salsitabien, stavudien of ander middels vir gebruik by die behandeling van VIGS. U dokter mag die dosis van didanosien wat u neem, verlaag.
- Probenesied wat vir die behandeling van jig geneem word, kan u bloedvlakke van gansiklovir verhoog.

- Mikofenolaat mofetiel, ’n middel wat gebruik word by pasiënte wat ’n orgaanoorplanting ontvang het.
- Sidovir, foskarnet of nukleosiede analoë wat teen virale infeksies gebruik word.

HOE OM VALCYTE TE NEEM

Moenie medisyne wat vir u voorgeskryf is met iemand anders deel nie.

Valcyte moet altyd geneem word soos deur u dokter voorgeskryf. U moet by u dokter of apteker seker maak indien u nie seker is nie.

Waar moontlik moet Valcyte saam met voedsel geneem word. Indien u vir enige rede nie kan eet nie, moet u steeds die dosis neem wanneer dit vereis word.

Valcyte 450 tablette moet met omsigtigheid hanteer word en moet nie gebreek of verbrokkel word nie. U moet dit heel insluk en saam met voedsel waar moontlik.

Valcyte 50 mg/mℓ mondelikse oplossing moet met omsigtigheid hanteer word. U moet verhoed dat die oplossing aan u vel of in u oë kom.

Indien u per abuis die oplossing op u vel kry of aan gebreekte tablette raak, was die area deeglik met seep en water. Indien u die oplossing of poeier per abuis in u oë kry, spoel die oë deeglik met water.

Dit is belangrik dat u die spuit wat in die pak voorsien word gebruik om u dosis Valcyte 50 mg/mℓ mondelikse oplossing af te meet.

Die gewone dosis is:

Volwassenes:

Standaarddosis

Voorkoming van SMV-siekte in oorplantingspasiënte:

U behoort te begin om Valcyte te neem 10 dae ná u oorplanting. Die gewone dosis is Valcyte 900 mg EENKEER per dag. U behoort met hierdie dosis voort te gaan tot by 100 dae ná u oorplanting. Indien u ’n nieroorplanting ontvang het, sal u dokter dalk voorstel dat u die dosis vir 200 dae neem.

Behandeling van baie aktiewe SMV retinitis by VIGS-pasiënte (wat induksie behandeling genoem word):

Die gewone dosis is 900 mg (450 x 2 tablette/hoeveelhede) (2 vol spuite) TWEEKEER per dag vir 21 dae (drie weke). Dit is, twee 450 mg tablette/hoeveelhede (d.w.s. 2 vol spuite) Valcyte in die oggend en twee 450 mg tablette/hoeveelhede (d.w.s. 2 vol spuite) in die aand.

Moenie met hierdie dosis langer as 21 dae voortgaan nie, tensy u dokter so aanbeveel, aangesien dit u risiko vir newe-effekte kan verhoog.

Langer termyn behandeling om herhaling van aktiewe inflammasie by VIGS-pasiënte met SMV retinitis te voorkom (sogenaamde instandhoudingsbehandeling):

Die gewone dosis is 900 mg (450 x 2 tablette/hoeveelhede) (2 vol spuite) Valcyte EENKEER per dag. U moet probeer om Valcyte elke dag op dieselfe tyd te neem. U dokter sal u vertel vir hoe lank u moet aanhou om Valcyte te neem. Indien u retinitis versleg terwyl u op hierdie dosis is, mag u dokter u vra om die induksiebehandeling te herhaal (soos hierbo) of kan besluit om u ’n ander middel te gee om die SMV-infeksie te behandel.

Pasiënte met nierafwykings:

Indien u niere nie behoorlik funksioneer nie, kan u dokter u vra om ’n laer dosis van Valcyte elke dag te neem of kan ook vra dat u Valcyte net op sekere dae van die week moet neem.

Dit is BAIE BELANGRIK dat u hierdie spesiale dosisaanbevelings van u dokter stiptelik volg.

U dokter sal u inlig hoe lank u behandeling met Valcyte sal duur. Moenie behandeling vroeg staak nie.

Indien u van mening is dat die effek van Valcyte te sterk of te swak is, vertel u dokter of apteker.

Indien u meer Valcyte neem as wat u moes:

Raadpleeg u dokter of apteker in die geval van oordosering. Indien nie een van die twee beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

Kontak dadelik u dokter of hospitaal indien u meer Valcyte geneem het as wat u moes, of vermoed dat u te veel geneem het. Om te veel Valcyte te neem, kan ernstige newe-effekte veroorsaak, veral in u bloed of niere. U sal dalk hospitaalbehandeling benodig.

Indien u vergeet om Valcyte te neem/'n dosis oorslaan:

Dit is belangrik dat u aanhou om u medisyne te neem volgens die instruksies op die etiket en dat u nie 'n dosis oorslaan nie. Indien u wel 'n dosis oorgeslaan het, neem dit sodra u onthou en neem die volgende dosis op die gewone tyd. Moenie 'n dubbel dosis neem om op te maak vir 'n oorgeslane dosis nie.

Effekte wanneer behandeling met Valcyte gestaak word:

U moenie ophou om Valcyte te neem tensy u dokter u aansê om dit te doen nie. Indien u enige verdere vrae oor die gebruik van Valcyte het, vra u dokter of apteker.

MOONTLIKE NEWE-EFFEKTE

Valcyte kan newe-effekte veroorsaak. Ten spyte daarvan dat Valcyte kan help om SMV-infeksie te beveg, kan dit erge newe-effekte veroorsaak. U dokter mag aanbeveel dat u behandeling tydelik of permanent staak, afhangende van u toestand.

Nie alle newe-effekte wat vir Valcyte aangemeld is, word by hierdie inligtingstuk ingesluit nie. Indien u algemene gesondheid verswak of u enige newe-effekte ervaar terwyl u Valcyte neem, raadpleeg u dokter, apteker of ander gesondheidsorgdeskundige.

Allergiese reaksies

In seldsame gevalle kan mense dalk skielike en erge allergiese reaksie op Valcyte ervaar (anafilaktiese skok). HOU OP om Valcyte te neem en gaan na die naaste hospitaal se noodeenheid indien u enige van die volgende ervaar:

- **Opgeswelde, jeukerige vel (galbulte)**

- **Skielike swelling van die gesig, lippe, mond en keel wat moeisame sluk en asemhaling kan veroorsaak**
- **Skielike swelling van die hande, voete of enkels**

Algemene newe-effekte:

- Effekte op die bloed: ’n verlaging in die aantal witbloedselle in die bloed (neutropenie) – wat sal veroorsaak dat u dalk meer infeksies kry, ’n verlaging in die pigment in die bloed wat suurstof dra (anemie) – wat moegheid en asemnood kan veroorsaak wanneer u oefeninge doen
- Effekte op asemhaling: voel kortasem of sukkel om asem te haal (dispnee)
- Effekte op die maag en verteringstelsel: diarree
- Effekte op die bloed: ’n verlaging in die aantal leukosiete (bloedselle wat infeksie beveg) in die bloed, (leukopenie) ’n verlaging in die aantal plaatjies in die bloed (trombositopenie) – wat kneusing en bloeding kan veroorsaak, ’n verlaging in verskeie tipes bloedselle terselfdertyd (pansitopenie)
- Effekte op die senuweestelsel: hoofpyn, slaaploosheid (insomnie), snaakse smake (disgeusie), verlies van gevoel (hipoëstesie), spelde en naalde (parestesie), verlies van gevoel in die hande of voete (perifere neuropatie), duiseligheid, stuipe (stuiptrekkings)
- Effekte in die oog: oogpyn, swelling binne die oog (edeem), loskom van die agterkant van die oog (retinale loslating), abnormale visie
- Effekte in die oor: oorpyn
- Effekte op asemhaling: hoes
- Effekte op maag en vertering: siekgevoel en opgooi, maagpyn, hardlywigheid, winderigheid, slegte spysvertering (dispepsie), sukkel om te sluk (disfagie)
- Effekte op die vel: inflammasie van die vel (dermatitis), jeukerigheid (pruritus), nagsweet
- Effekte op die spiere, gewrigte of bene: rugpyn, pyn in die spiere (mialgie) of gewrigte (artralgie), stywe spiere (rigor), spierkrampe
- Infeksies: swaminfeksie in die mond (mondelikse kandidiase), infeksies wat veroorsaak word deur bakterieë of virusse in die bloed, inflammasie van sellulêre weefsel (sellulitis), inflammasie of infeksie van die niere of blaas

- Effekte in die lewer: ’n toename in sommige lewerensieme wat slegs met bloedtoetse waargeneem kan word
- Effekte in die nier: veranderings aan die normale werking van die niere
- Effekte op eet: eetlusverlies (anoreksie), gewigsverlies
- Algemene effekte: moegheid, koors, pyn, borspyn, energieverlies (astenie), algemene gevoel van onwel (malaise)
- Effekte op gemoed of gedrag: depressie, angstigheid, verwardheid, abnormale denke

Minder algemene newe-effekte:

- Effekte in die hart: veranderinge aan die normale hartklopping (disritmieë)
- Effekte op bloedsomloop: lae bloeddruk (hipotensie), wat u lighoofdig of duiselig kan laat voel
- Effekte op die bloed: ’n verlaging in die vervaardiging van bloedselle in die beenmurg
- Effekte in die senuwees: bewerasie
- Effekte in die oë: rooi, opgeswelde oë (konjunktivitis), abnormale visie
- Effekte in die ore: doofheid
- Effekte op die maag of vertering: geswolle buik, mondsere, inflammasie van die pankreas (pankreatitis) waar u dalk erge pyn in die maag en rug sal waarneem
- Effekte op die vel: haarverlies (alopesie), jeukerige uitslag of swelsels (urtikarie), droë vel
- Effekte in die niere: bloed in die niere (hematurie), nierversaking
- Effekte in die lewer: ’n toename in die lewerensieme genaamd alanien aminotransferase (wat slegs met bloedtoetse waargeneem kan word)
- Effekte op vrugbaarheid: onvrugbaarheid in mans
- Effekte op gemoed en gedrag: ongewone veranderings in gemoed en gedrag, verloor gevoel met realiteit soos om stemme te hoor of dinge te sien wat nie daar is nie, voel angstig
- Effekte op die bloed: mislukking van die vervaardiging van alle tipes bloedselle (rooibloedselle, witbloedselle en plaatjies) in die beenmurg

BEWARING EN WEGDOENING VAN VALCYTE

Bêre alle medisyne buite bereik van kinders.

Valcyte 450 filmbedekte tablette: Bêre by of onder 25 °C.

Moenie ná die vervaldatum soos op die verpakking aangebring is, gebruik nie.

Moenie die tablette breek of verbrokkel nie. Vermy vel- of slymvlieskontak met gebreekte of verbrokkelde tablette.

Valcyte 50 mg/mℓ Poeier vir mondelikse oplossing: Bêre by of onder 30 °C.

Hersaamgestelde oplossing: Bêre in die yskas by 2 °C tot 8 °C.

Bêre in die oorspronklike bottel. Hou die bottel dig toe. Enige oorblywende oplossing moet ná 49 dae mee weggedoen word. Neem enige ongebruikte oplossing in die oorspronklike houer terug na u apteker vir veilige wegdoening.

AANBIEDING VAN VALCYTE

Valcyte 450 filmbedekte tablette: 60 filmbedekte tablette in ’n wit plastiekbottel met ’n kinderbestande skroefprop.

Valcyte 50 mg/mℓ mondelikse oplossing: ’n Karton wat ’n amberkleurige glasbottel met ’n kinderbestande wit deurskynende plastiese skroefprop, ’n bottelaanpasser en ’n stulpverpakking wat 2 mondelikse toedieners bevat. Die toedieners is gegradeer volgens 25 mg graderings tot op 500 mg.

IDENTIFIKASIE VAN VALCYTE

Valcyte 450 filmbedekte tablette: Die tablette is pienk, ovaalvormige, filmbedekte tablet met “VGC” aan die een kant ingedruk en “450” aan die ander kant.

Valcyte 50 mg/mℓ Poeier vir mondelikse oplossing: Die hersaamgestelde poeier is kleurloos tot ’n bruinerige geel helder oplossing.

REGISTRASIENOMMERS

Valcyte 450 filmbedekte tablet: 37/20.2.8/0296

Valcyte 50 mg/mℓ mondelikse oplossing: 43/20.2.8/0433

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE

Roche Products (Pty) Ltd

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Suid-Afrika

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

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