**WARNING: To be sold on the prescription of Nephrologist/Specialist only**

# Valganciclovir Tablets and Powder for Oral Solution

**VALCYTE®**

वेल्साइट

## 1. DESCRIPTION

### 1.1 Therapeutic / Pharmacologic Class of Drug

Antiviral

ATC code: J05AB14

### 1.2 Type of Dosage Form and strength

Film-coated tablet: 450mg

Powder for Oral Solution: 50mg/mL

### 1.3 Route of Administration

Oral

### 1.4 Sterile / Radioactive Statement

*Not applicable.*

### 1.5 Qualitative and Quantitative Composition

*Active ingredien*t: valganciclovir (as valganciclovir hydrochloride).

Film-coated tablets: 450 mg.

Each film-coated tablet contains Valganciclovir Hydrochloride equivalent to Valganciclovir 450mg

Powder for Oral Solution: 50 mg/mL.

A bottle of 12 g powder contains 5.5 g valganciclovir hydrochloride corresponding to 5 g of valganciclovir (free base).

1 ml of constituted solution contains 55 mg of valganciclovir hydrochloride corresponding

to 50 mg of valganciclovir (free base).

*List of Excipients*

Film-coated tablet:

*Tablet* core: povidone K-30, crospovidone, microcrystalline cellulose, stearic acid.

*Tablet coat (*in form of Opadry Pink 15B24005)*:* hypromellose, titanium dioxide, polyethylene glycol, synthetic red iron oxide and polysorbate 80.

Powder for Oral Solution:

Sodium benzoate, fumaric acid, povidone K-30, saccharin sodium, mannitol and tutti-frutti flavor.

## 2. CLINICAL PARTICULARS

### 2.1 Therapeutic Indication(s)

Valcyte is indicated for the treatment of cytomegalovirus (CMV) retinitis in acquired immunodeficiency syndrome (AIDS) patients and for prevention of CMV disease in solid organ transplant patients at high risk.

### 2.2 Dosage and Administration

Caution – Strict adherence to dosage recommendations is essential to avoid overdose.

**Standard Dosage**

Valcyte is administered orally, and should be taken with food (see Sections 3.2.5, *Pharmacokinetics in Special Populations,* and 3.2.1, *Absorption*).

Valcyte is rapidly and extensively converted into the active ingredient ganciclovir. The bioavailability of ganciclovir from Valcyte is up to 10-fold higher than from oral ganciclovir.

The dosage and administration of Valcyte tablets or powder for oral solution as described below should be closely followed (see Sections 2.4, *Warnings and Precautions* and 2.7, *Overdose*).

The ganciclovir systemic exposure following administration of 900 mg Valcyte powder for oral solution is equivalent to a 900 mg Valcyte dose administered as two 450 mg tablets.

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

**Treatment of cytomegalovirus (CMV) retinitis**

*Adult Patients*

*Induction treatment of CMV retinitis*

For patients with active CMV retinitis, the recommended dose is 900 mg twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see Section 2.4, *Warnings and Precautions*).

*Maintenance treatment of CMV retinitis*

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg once daily. Patients whose retinitis worsens may repeat induction treatment (see *Induction treatment of CMV retinitis*).

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

**Prevention of CMV disease in transplantation**

*Adult Patients*
For kidney transplant patients, the recommended dose is 900 mg once daily starting within 10 days post-transplantation and continuing until 200 days post-transplantation.

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

### 2.2.1 Special Dosage Instructions

*Geriatric Use*

Safety and efficacyunshave 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 *3.2.5 Pharmacokinetics in special populations, Geriatric Population*).

*Adult Patients with renal impairment*

Serum creatinine or estimated creatinine clearance levels should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance as shown in Table 1 and Table 2 below (see Sections 3.2.5, *Pharmacokinetics in Special Populations* and 2.4, *Warnings and Precautions*).

**Table 1 Valcyte Tablets Dose for Renally Impaired Patients**

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

**Table 2 Valcyte Powder for Oral Solution Dose for Renally Impaired Patients**

| CrCl (mL/min) | Induction Dose of Valcyte Oral Solution | Maintenance/Prevention Dose of Valcyte 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) |

Estimated creatinine clearance is calculated from serum creatinine by the following formulae:

For males:

$$\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/L]})}$$

For females:

0.85 x male value

*Hepatic impairment*

The safety and efficacy of Valcyte have not been established in patients with hepatic impairment. (see section 3.2.5 *Pharmacokinetics in special populations, hepatic impairment*).

## 2.3 Contraindications

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

## 2.4 Warnings and Precautions

### 2.4.1 General

*Cross hypersensitivity*

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

*Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception*

In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. Valcyte should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Prior to initiation of valganciclovir treatment, patients should be advised of the potential risks to the fetus and to use contraceptive measures. Based on clinical and nonclinical studies, Valcyte may cause temporary or permanent inhibition of spermatogenesis (see Sections 2.5.1 *Females and Males of Reproductive Potential*, 2.5.2 *Pregnancy, 2.5.3Lactation,* 2.6 *Undesirable Effects,* 3.3 *Nonclinical Safety and* 4.2*, Special Instructions for Use, Handling and Disposal*).

*Myelosuppression*

Valcyte should be used with caution in patients with pre-existing hematological cytopenia or a history of drug-related hematological cytopenia and in patients receiving radiotherapy.

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia 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 25000/μL or the hemoglobin is less than 8 g/dL (see Sections 2.2.1, *Special Dosage Instructions*, 2.4, *Warnings and Precautions*, and 2.6, *Undesirable Effects*).

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment and in neonates and infants (see Section *2.2.4 Laboratory Tests*).

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see Section 2.6 *Undesirable Effects*).

*Use with other medicines*

Seizures have been reported in patients taking imipenem- cilastatin and ganciclovir. Valcyte should not be used concomitantly with imipenem-cilastatin unless the potential benefits

outweigh the potential risks (see Section 2.8, *Interactions with other Medicinal Products and other Forms of Interaction*).

Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage (see Section 2.8, *Interactions with other Medicinal Products and other Forms of Interactions*).

Didanosine plasma concentrations may increase during concomitant use with Valcyte; therefore patients should be closely monitored for didanosine toxicity (see Section 2.8, *Interactions with other Medicinal Products and other Forms of Interactions*).

Concomitant use of other drugs that are known to be myelosuppressive or associated with renal impairment with Valcyte may result in added toxicity (see Section 2.8, *Interactions with other Medicinal Products and other Forms of Interactions*).

The bioavailability of ganciclovir from Valcyte tablets is up to 10-fold higher than from ganciclovir capsules. Valcyte tablets 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 Sections 2.2, *Dosage and Administration and 2.7, Overdose*).

### 2.4.2 Drug Abuse and Dependence

No information is available for drug abuse and dependence with Valcyte.

### 2.4.3 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 2.6 *Undesirable Effects*). If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

## 2.5 Use in Special Populations

### 2.5.1 Females and Males of Reproductive Potential

*Fertility*

In animal studies ganciclovir was found to impair fertility (see section 3.3.3 *Impairment of 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.

*Contraception*

Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment. Sexually active men are recommended to 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 Sections 2.4, *Warnings and Precautions* and 3.3.4, *Reproductive Toxicity*).

### 2.5.2 Pregnancy

The safety of Valcyte for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of Valcyte should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity (see Section 3.3.4, *Reproductive Toxicity*).

The safe use of Valcyte during labor and delivery has not been established.

### 2.5.3 Lactation

Peri- and postnatal development has not been studied with valganciclovir or with ganciclovir but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Therefore, a decision should be made to discontinue the drug or discontinue nursing taking into consideration the potential benefit of Valcyte to the nursing mother.

### 2.5.4 Geriatric Use

Safety and efficacy have not been established in this patient population (see Section 2.2.1, *Special Dosage Instructions* and 3.2.5. *Pharmacokinetics in Special Populations*).

### 2.5.5 Renal Impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see Sections 2.2.1, *Special Dosage Instructions* and 3.2.5, *Pharmacokinetics in Special Populations*).

### 2.5.6 Hepatic Impairment

Safety and efficacy have not been established in this patient population (see Section 2.2.1 *Special Dosage Instructions* and 3.2.5 *Pharmacokinetics in Special Populations*).

## 2.6 Undesirable Effects

### 2.6.1 Clinical Trials

Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte. All of the adverse drug reactions 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 valganciclovir are included in the table of adverse reactions (see Table 3).

In patients treated with valganciclovir/ganciclovir the most serious and frequent adverse drug reactions are hematological reactions and include neutropenia, anemia 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, 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/valganciclovir 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. Valganciclovir is associated with a higher risk of diarrhea 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 dysfunctions are reported more frequently in organ transplant recipients.

**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 |
| Anemia | 19.89% | |
| Thrombocytopenia | 7.34% | Common |
| Leukopenia | 3.93% | |
| Pancytopenia | 1.06% | |
| Bone marrow failure | 0.29% | Uncommon |
| Aplastic anemia | 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 edema | 1.06% | |
| ***Ear and labyrinth disorders:*** | | |
| Ear pain | 1.17% | Common |
| Deafness | 0.65% | Uncommon |
| ***Cardiac disorders****:* | | |
| Arrhythmia | 0.47% | Uncommon |
| ***Vascular disorders****:* | | |
| Hypotension | 2.05% | Common |
| ***Respiratory, thoracic and mediastinal disorders:*** | | |
| Cough | 18.31% | Very common |
| Dyspnea | 11.80% | |
| ***Gastrointestinal disorders:*** | | |
| Diarrhea | 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 |
| Creatinine clearance renal decreased | 2.35% | |
| Blood creatinine increased | 1.88% | |
| Renal failure | 0.76% | Uncommon |
| Hematuria | 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*
*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 drug or dose reduction (see Section 2.4, Warnings and Precautions).

*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 drugs are at greater risk of thrombocytopenia than patients with HIV (see Section 2.4, Warnings and Precautions). 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 valganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant 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 valganciclovir 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 pediatric SOT patients are listed in Table 5. The incidence of severe neutropenia (ANC<500/μL) was higher in pediatric kidney transplant patients treated until Day 200 as compared to pediatric 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** | |
|---|---|---|---|
| | **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 |
| Anemia (hemoglobin g/dL) | | | |
| <6.5 | 7 | 1 | 2 |
| 6.5 - <8.0 | 10 | 5 | 7 |

| **Laboratory abnormalities** | **CMV Retinitis Patients** | **Solid Organ Transplant Patients** | |
|---|---|---|---|
| | **Valganciclovir (n=370)** | **Valganciclovir (n=244)** | **Oral ganciclovir (n=126)** |
| | **%** | **%** | **%** |
| 8.0 - <9.5 | 14 | 31 | 25 |
| Thrombocytopenia (platelets/μL) | | | |
| <25000 | 3 | 0 | 2 |
| 25000 - <50000 | 5 | 1 | 3 |
| 50000 - <100000 | 21 | 18 | 21 |
| Serum creatinine (mg/dL) | | | |
| >2.5 | 2 | 14 | 21 |
| >1.5 – 2.5 | 11 | 45 | 47 |

**Table 5 Laboratory Abnormalities in Pediatric Solid Organ Transplant Patients**

| **Laboratory abnormalities** | **Valganciclovir in Pediatric 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 - <1000 | 5 | 11 |
| Anemia (hemoglobin g/dL) | | |
| <6.5 | 0 | 0 |
| 6.5 - <8.0 | 14 | 5 |
| 8.0 - <9.5 | 38 | 29 |

| | | |
|---|---|---|
| Thrombocytopenia (platelets/μL) | | |
| <25000 | 0 | 0 |
| 25000 - <50000 | 10 | 0 |
| 50000 - <100000 | 3 | 4 |
| Serum creatinine (mg/dL) | | |
| >2.5 | 2 | 5 |
| >1.5 – 2.5 | 11 | 20 |

***Pediatric Patients***

Valcyte has been studied in 179 pediatric solid organ transplant patients who were at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days.

The overall safety profile was similar in pediatric patients as compared to adults. Neutropenia was also reported with slightly higher incidence in the two pediatric studies as compared to adults but neutropenia and infectious adverse events were generally not correlated in the pediatric populations.

In kidney transplant pediatric patients, prolongation of valganciclovir 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 valganciclovir/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 diarrhea, all seen more frequently in the placebo

group. The only treatment-related SAEs were neutropenia and anemia, both seen more frequently in the placebo arm. No statistically or clinically significant differences were observed in the rate of growth (average head circumference, weight and length) over time at each time point between the two treatment groups.

### 2.6.2 Postmarketing Experience

Safety reports from the postmarketing setting are consistent with safety data from clinical trials with valganciclovir and ganciclovir (see Section 2.6.1 *Undesirable Effects* - Table 3).

## 2.7 Overdose

***Overdose experience with valganciclovir and intravenous ganciclovir***

It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see Sections 2.4, *Warnings & Precautions* and 2.2, *Dosage and Administration*).

Reports of overdoses with intravenous ganciclovir some with fatal outcomes, have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

– Hematological toxicity: myelosuppression including pancytopenia, bone marrow failure, leukopenia , neutropenia, granulocytopenia.

– Hepatotoxicity: hepatitis, liver function disorder

– Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine.

– Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting.

– Neurotoxicity: generalized tremor, seizure.

Hemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see Section 3.2.5 *Pharmacokinetics in Special Populations*).

## 2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

***Drug 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 drugs cannot bediscounted. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see Section 2.4 *Warnings and Precautions*).

*Potential drug interactions*
Toxicity may be enhanced when ganciclovir / valganciclovir is co-administered with other drugs known to be myelosuppressive or 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 drugs should only be considered for concomitant use with valganciclovir if the potential benefits outweigh the potential risks (see Section 2.4 *Warnings and Precautions*).

*Zidovudine*
Both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, a pharmacodynamic interaction may occur during concomitant administration of these drugs, some patients may not tolerate concomitant therapy at full dosage (see Section 2.4 *Warnings and Precautions*).

*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 ofdidanosine ranging from 38 to 67% has been observed confirming a pharmacokinetic interaction during the concomitant administration of these drugs. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see Section 2.4 *Warnings and Precautions*).

*Probenecid*
Probenecid given with oral ganciclovir resulted in statistically significantly 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 valganciclovir should be closely monitored for ganciclovir toxicity.

# 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

## 3.1 Pharmacodynamic Properties

### 3.1.1 Mechanism of Action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpesviruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpesvirus 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly. This has been shown to occur in HSV- and HCMV-infected cells with half-lives of 18 and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate 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. Typical anti-viral $IC_{50}$ against CMV *in vitro* is in the range 0.08 μM (0.02 μg/mL) to 14 μM (3.5 μg/mL).

The clinical antiviral effect of Valcyte has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis (clinical trial WV15376). CMV shedding was decreased from 46% (32/69) of patients at study entry to 7% (4/55) of patients following four weeks of Valcyte treatment.

### 3.1.2 Clinical / Efficacy Studies

***Adult Patients***

*Treatment of CMV retinitis*

Clinical studies of Valcyte have been conducted in patients with AIDS and CMV retinitis. Valcyte has shown comparable efficacy for induction treatment of CMV retinitis to intravenous ganciclovir.

Patients with newly diagnosed CMV retinitis were randomized in one study to induction therapy with either Valcyte or intravenous ganciclovir. The proportion of patients with progression of CMV retinitis at week 4 was the same in both treatment groups.

Following induction treatment dosing, patients in this study received maintenance treatment with Valcyte given at the dose of 900 mg daily. The mean (median) time from randomization to progression of CMV retinitis in the group receiving induction and maintenance treatment with Valcyte was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with Valcyte was 219 (125) days.

Valcyte allows systemic exposure of ganciclovir similar to that achieved with recommended doses of intravenous ganciclovir, which has been shown to be efficacious in the treatment of CMV retinitis. Ganciclovir AUC has been shown to correlate with time to progression of CMV retinitis.

*Prevention of CMV disease in transplantation*

A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver, and kidney transplant patients at high risk of CMV disease (D+/R-) who received either Valcyte (900 mg od) or oral ganciclovir (1000 mg tid) starting within 10 days of transplantation until Day 100 post-transplant. The incidence of CMV disease (CMV syndrome + tissue invasive disease), as adjudicated by an independent Endpoint Committee, during the first 6 months post-transplant was 12.1% in the Valcyte arm (n=239) compared with 15.2% in the oral ganciclovir arm (n=125). The majority of cases occurred following cessation of prophylaxis (post Day 100) with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm. The incidence of acute rejection in the first 6 months was 29.7% in patients randomized to valganciclovir compared with 36.0% in the oral ganciclovir arm.

Extending CMV prophylactic therapy with Valcyte until Day 200 post-transplant demonstrated superiority in preventing CMV disease within the first 12 months post-transplant in high risk kidney transplant patients compared to the 100 day dosing regimen.

A double-blind, placebo controlled study has been conducted in 326 kidney transplant patients at high risk of CMV disease (D+/R-) to assess the efficacy and safety of extending Valcyte CMV prophylaxis from 100 to 200 days post-transplant. Patients were randomized (1:1) to receive Valcyte tablets (900 mg od) within 10 days of transplantation either until Day 200 post-transplant or until Day 100 post-transplant followed by 100 days of placebo.

The proportion of patients who developed CMV disease during the first 12 months post-transplant is shown in Table 6.

**Table 6 Percentage of Kidney Transplant Patients with CMV Disease[1], 12 Month ITT Population**

| | **Valganciclovir 900 mg od 100 Days** | **Valganciclovir 900 mg od 200 Days** | **Cochran-Mantel-Haenszel p-value** |
|---|---|---|---|
| Patients with confirmed or | 71/163 | 36/155 | 0.0001 |

| | | | |
|---|---|---|---|
| assumed CMV disease[2] | (43.6%) | (23.2%) | |
| Patients with confirmed CMV disease | 60/163 (36.8%) | 25/155 (16.1%) | <0.0001 |

[1] CMV Disease is defined as either CMV syndrome or tissue invasive CMV. [2] Confirmed CMV is a clinically confirmed case of CMV disease. Patients were assumed to have CMV disease if there was either no week 52 assessment or no confirmation of CMV disease before this time point.

The graft survival rate at 12 months post-transplant was 98.2% (160/163) for the 100 day dosing regimen and 98.1% (152/155) for the 200 day dosing regimen. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100 day dosing regimen and 11.0% (17/155) for the 200 day dosing regimen.

*Viral Resistance*

Viruses resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in either the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation or the viral polymerase gene (UL54). UL97 mutations arise earlier and more frequently than mutations in UL54. Virus containing mutations in the UL97 gene is 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 may show cross-resistance to other antivirals targeting the viral polymerase, and vice versa. 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).

*Treatment of CMV retinitis (Adult patients)*
Genotypic analysis of CMV in polymorphonuclear leukocytes (PMNL) isolates from 148 patients with CMV retinitis enrolled in one clinical study has shown that 2.2%, 6.5%, 12.8%, and 15.3% contain UL97 mutations after 3, 6, 12, and 18 months, respectively, of valganciclovir treatment.

*Prevention of CMV disease in transplant*

Resistance was studied by genotypic analysis of CMV in PMNL samples collected i) on Day 100 (end of study drug prophylaxis) and ii) in cases of suspected CMV disease up to 6 months after transplantation. From the 245 patients randomized to receive valganciclovir, 198 Day 100 samples were available for testing and no ganciclovir resistance mutations were observed. This compares with 2 ganciclovir resistance mutations detected in the 103 samples tested (1.9%) for patients in the oral ganciclovir comparator arm.

Of the 245 patients randomized to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 125 patients on the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which 2 resistance mutations were observed, giving an incidence of resistance of 6.9%.

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-) (see section 3.1.2 *Clinical/Efficacy Studies*). 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: 100 day 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.

### 3.1.3 Immunogenicity

Not applicable.

## 3.2 Pharmacokinetic Properties

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

The parameters which control the exposure of ganciclovir from valganciclovir are bioavailability and renal function. The bioavailability of ganciclovir from valganciclovir is comparable across all the patient populations studied (adults). 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 (see Section 2.2 *Dosage and Administration)*.

Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir in the dose range 450 to 2625 mg was demonstrated only under fed conditions.

### 3.2.1 Absorption

Valganciclovir is a prodrug of ganciclovir, which is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The bioavailability of ganciclovir from oral dosing of valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low, $AUC_{0\text{-}24h}$ and $C_{max}$ values are approximately 1% and 3% of those of ganciclovir, respectively.

When valganciclovir was given with food at the recommended dose of 900 mg, increases were seen in both mean ganciclovir $AUC_{24}$ (approximately 30%) and mean ganciclovir $C_{max}$ values (approximately 14%). Therefore, it is recommended that Valcyte be administered with food (see Section 2.2, *Dosage and Administration*).

### 3.2.2 Distribution

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. The steady state volume of distribution of ganciclovir after intravenous 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.

### 3.2.3 Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. Ganciclovir itself is not metabolized to a significant extent.

### 3.2.4 Elimination

Following dosing with oral valganciclovir, the drug is rapidly hydrolyzed 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-metabolized 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.

### 3.2.5 Pharmacokinetics in Special Populations

*Geriatric 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* 2.2.1 *Special Dosage Instructions).*

*Patients with renal impairment*

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir were evaluated in 24 otherwise healthy 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 2.2.1, *Special Dosage Instructions* and 2.4, *Warnings and Precautions*).

*Patients undergoing hemodialysis*

Ganciclovir is readily removable by hemodialysis. Data obtained during intermittent haemodialysis in 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 pharmacokinetics of ganciclovir from valganciclovir in stable liver transplant patients were investigated in one open label 4-part crossover study (N=28). The 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 patients.

*Hepatic impairment*

No pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment undergoing valganciclovir therapy.

*Patients with cystic fibrosis*

In a phase I pharmacokinetic study, steady state systemic exposure to ganciclovir was assessed in lung transplant recipients with or without cystic fibrosis (N=31) 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.

## 3.3 Nonclinical Safety

### 3.3.1 Carcinogenicity

Valganciclovir and ganciclovir were mutagenic in mouse lymphoma cells and clastogenic in mammalian cells. Such results are consistent with the positive mouse carcinogenicity study with ganciclovir. Ganciclovir is a potential carcinogen.

### 3.3.2 Genotoxicity

Valganciclovir and ganciclovir were mutagenic in mouse lymphoma cells and clastogenic in mammalian cells.

### 3.3.3 Impairment of Fertility

Ganciclovir causes impaired fertility and teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both drugs (see Section 2.4, *Warning and Precautions*).

Based upon animals studies where aspermia was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir (and valganciclovir) could cause temporary or permanent inhibition of human spermatogenesis (see Section 2.5.1 *Females and Males of Reproductive Potential, Fertility*).

### 3.3.4 Reproductive Toxicity

Ganciclovir causes teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both drugs (see Section 2.4, Warning and Precautions).

### 3.3.5 Other

No additional information is available.

## 4. DESCRIPTION

Valcyte contains valganciclovir hydrochloride (valganciclovir HCl), a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diastereomers. Ganciclovir is a synthetic guanine derivative active against CMV.

Valcyte is available as a 450 mg tablet for oral administration. Each tablet contains 496.3 mg of valganciclovir HCl (corresponding to 450 mg of valganciclovir), and the inactive ingredients microcrystalline cellulose, povidone K-30, crospovidone and stearic acid. The film-coat applied to the tablets contains Opadry Pink® *(containing* hypromellose, titanium dioxide , polyethylene glycol, synthetic red iron oxide and polysorbate 80).

Valcyte is also available as a powder for oral solution, which when constituted with water as directed contains 50 mg/mL valganciclovir free base. The inactive ingredients of Valcyte for oral solution are sodium benzoate, fumaric acid, povidone K-30, saccharin sodium, mannitol and tutti-frutti flavor.

Valganciclovir HCl is a white to off-white crystalline powder with a molecular formula of C14H22N6O5·HCl and a molecular weight of 390.83. The chemical name for valganciclovir HCl is L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]-3-hydroxypropyl ester, monohydrochloride. Valganciclovir HCl is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25°C at a pH of 7.0 and an n-octanol/water partition coefficient of 0.0095 at pH 7.0. The pKa for valganciclovir HCl is 7.6.

# 5 PHARMACEUTICAL PARTICULARS

## 5.1 Storage

*Film-coated tablets:* Do not store above 30°C

*Powder for Oral Solution:* Do not store above 30°C

*Reconstituted Solution:* After reconstitution with purified water the solution should not be used for longer than 49 days.

The reconstituted solution should be stored in a refrigerator (2 to 8°C).

## 5.2 Special Instructions for Use, Handling and Disposal

**Stability**

Tablets should not be broken or crushed. Since Valcyte is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets or Valcyte Powder for Oral Solution (see Warnings and Precautions). Avoid direct contact of broken or crushed tablets, powder or reconstituted solution with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water or plain water if sterile water is not available.

It is recommended that Valcyte powder for oral solution be reconstituted by the pharmacist prior to dispensing to the patient. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

Preparation of solution

1 Measure 91 mL of purified water in a graduated cylinder.
2 Remove the child resistant cap and add the 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 with child resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.
5 Write the date of expiration of the reconstituted solution on the bottle label. [The shelf life of the reconstituted solution is 49 days. The reconstituted solution should be stored in a refrigerator (2 to 8°C)].

This medicine should not be used after the expiry date (Expiry date) shown on the pack.

*Disposal of unused/expired medicines*

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

### 5.3 Shelf life

*Film-coated tablets:* 36 Months if stored at recommended storage conditions

*Powder for Oral Solution:* 24 Months if stored at recommended storage conditions

Keep out of reach of children

### 5.4 Packs

*Presentations & Pack sizes*

| | |
|---|---|
| Tablets 450mg | 60 |

### 5.5 Incompatibilities

Not applicable

## 6. PATIENT COUNSELING INFORMATION

**Serious Adverse Reactions**
Inform patients that Valcyte may cause granulocytopenia (neutropenia), anemia, thrombocytopenia and elevated creatinine levels and that dose modification or discontinuation of dosing may be required. Complete blood counts, platelet counts, and creatinine levels should be monitored frequently during treatment *[see Warnings and Precautions]*.

**Pregnancy and Contraception**
Inform females of reproductive potential that Valcyte causes birth defects in animals. Advise them to use effective contraception during and for at least 30 days following treatment with Valcyte. Similarly, advise males to use condoms during and for at least 90 days following treatment with Valcyte *[see Use in Special Populations]*.

**Carcinogenicity**
Advise patients that Valcyte is considered a potential carcinogen *[see Nonclinical Toxicity]*.

**Lactation**
Advise mothers not to breast-feed if they are receiving Valcyte because of the potential for hematologic toxicity and cancer in nursing infants, and because HIV can be passed to the baby in breast milk *[see Use in Special Populations]*.

**Infertility**
Advise patients that Valcyte may cause temporary or permanent female and male infertility *[see Warnings and Precautions]*

**Impairment of Cognitive Ability**
Inform patients that tasks requiring alertness may be affected including the patient's ability to drive and operate machinery as seizures, dizziness, and/or confusion have been reported with the use of Valcyte *[see Warnings and Precautions]*.

**Use in Patients with CMV Retinitis**
Inform patients that Valcyte is not a cure for CMV retinitis, and they may continue to experience progression of retinitis during or following treatment. Advise patients to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with Valcyte. Some patients will require more frequent follow-up.

Inform patients to take Valcyte with food to maximize bioavailability.

## 7. DETAILS OF MANUFACTURER

**Manufactured by** F. Hoffmann- La Roche Ltd**,** Grenzacherstrasse 124, CH-4070 Basel, Switzerland at Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N7K9, Canada

**Imported by:**
Roche Products (India) Pvt. Ltd., C/O. Parekh Integrated Services Pvt. Ltd, Gala No. B1, Second Floor, Warehouse no. 6, BGR Logistics Park, NH-3, Zone 5, Bhiwandi, Maharashtra (India) – 421302

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Entero
Healthcare Solutions Pvt. Ltd.
Entero Healthcare Solutions Pvt. Ltd.,
605/606, 6th Floor, Trade Centre, BKC,
Bandra (East), Mumbai-400051 India

## 8. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Permission No.: Import-1018 dated 20 Nov 2003.

## 9. DATE OF REVISION

Current at October 2021; Version 9.0