VALCYTE®
(valganciclovir hydrochloride tablets)

R_X only

WARNING

THE CLINICAL TOXICITY OF VALCYTE, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

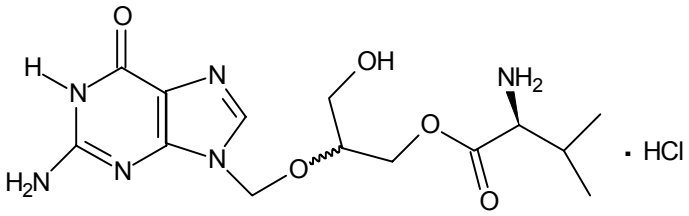
DESCRIPTION

Valcyte (valganciclovir HCl tablets) 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 cytomegalovirus (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®.

Valganciclovir HCl is a white to off-white crystalline powder with a molecular formula of $C_{14}H_{22}N_6O_5 \cdot HCl$ 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.

The chemical structure of valganciclovir HCl is:



All doses in this insert are specified in terms of valganciclovir.

VIROLOGY

Mechanism of Action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two diastereomers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human cytomegalovirus in vitro and in vivo.

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 metabolized intracellularly (half-life 18 hours). 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 ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the in vitro susceptibility of human herpesviruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (IC_{50}), vary greatly depending upon a number of factors. Thus the IC_{50} of ganciclovir that inhibits human CMV replication in vitro (laboratory and clinical isolates) has ranged from 0.02 to 5.75 μg/mL (0.08 to 22.94 μM). Ganciclovir inhibits mammalian cell proliferation (IC_{50}) in vitro at higher concentrations ranging from 10.21 to >250 μg/mL (40 to >1000 μM). Bone marrow-derived colony-forming cells are more sensitive (IC_{50} = 0.69 to 3.06 μg/mL: 2.7 to 12 μM).

Viral Resistance

Viruses resistant to ganciclovir can arise after prolonged treatment with valganciclovir by selection of mutations in either the viral protein kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or in the viral DNA polymerase gene (UL54). Virus with mutations in the UL97 gene is resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals that target the same sites on viral DNA polymerase.

The current working definition of CMV resistance to ganciclovir in in vitro assays is $IC_{50} \geq 1.5$ μg/mL (≥ 6.0 μM). CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR VALCYTE TABLETS. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

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 ganciclovir pharmacokinetic measures following administration of 900 mg Valcyte and 5 mg/kg intravenous ganciclovir and 1000 mg three times daily oral ganciclovir in HIV-positive/CMV-positive patients are summarized in **Table 1**.

Table 1 Mean Ganciclovir Pharmacokinetic* Measures in Healthy Volunteers and HIV-positive/CMV-positive Adults at Maintenance Dosage

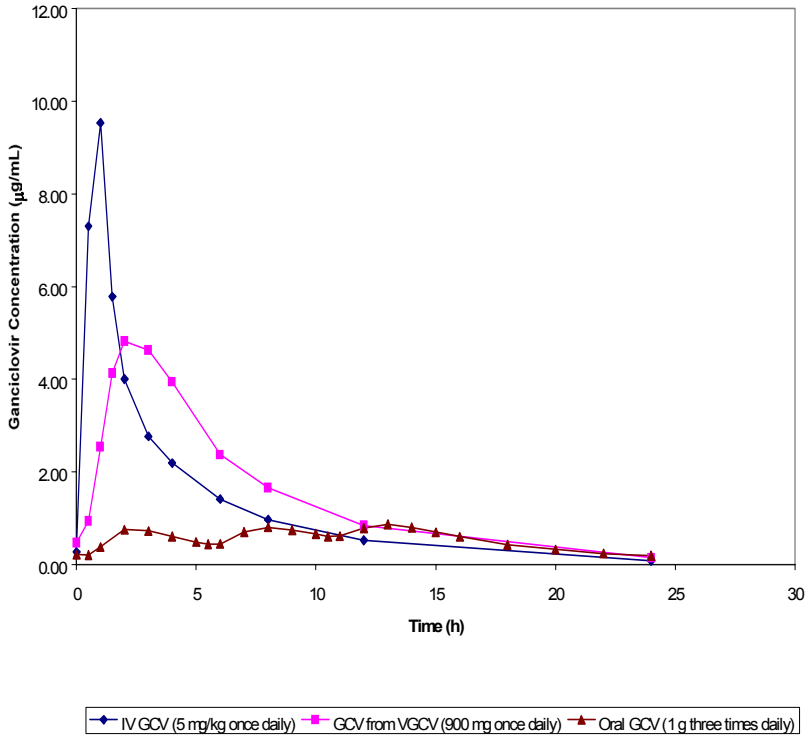
Formulation	Valcyte Tablets	Cytovene®-IV	Ganciclovir Capsules
Dosage	900 mg once daily with food	5 mg/kg once daily	1000 mg three times daily with food
$AUC_{0\text{-}24\ hr}$ (μg·h/mL)	29.1 ± 9.7 (3 studies, n=57)	26.5 ± 5.9 (4 studies, n=68)	Range of means 12.3 to 19.2 (6 studies, n=94)
C_{max} (μg/mL)	5.61 ± 1.52 (3 studies, n=58)	9.46 ± 2.02 (4 studies, n=68)	Range of means 0.955 to 1.40 (6 studies, n=94)
Absolute oral bioavailability (%)	59.4 ± 6.1 (2 studies, n=32)	Not Applicable	Range of means 6.22 ± 1.29 to 8.53 ± 1.53 (2 studies, n=32)
Elimination half-life (hr)	4.08 ± 0.76 (4 studies, n=73)	3.81 ± 0.71 (4 studies, n=69)	Range of means 3.86 to 5.03 (4 studies, n=61)
Renal clearance (mL/min/kg)	3.21 ± 0.75 (1 study, n=20)	2.99 ± 0.67 (1 study, n=16)	Range of means 2.67 to 3.98 (3 studies, n=30)

*Data were obtained from single and multiple dose studies in healthy volunteers, HIV-positive patients, and HIV-positive/CMV-positive patients with and without retinitis. Patients with CMV retinitis tended to have higher ganciclovir plasma concentrations than patients without CMV retinitis.

The area under the plasma concentration-time curve (AUC) for ganciclovir administered as Valcyte tablets is comparable to the ganciclovir AUC for intravenous ganciclovir. Ganciclovir C_{max} following Valcyte administration is 40% lower than following

intravenous ganciclovir administration. During maintenance dosing, ganciclovir $AUC_{0\text{-}24\ hr}$ and C_{max} following oral ganciclovir administration (1000 mg three times daily) are lower relative to Valcyte and intravenous ganciclovir. The ganciclovir C_{min} following intravenous ganciclovir and Valcyte administration are less than the ganciclovir C_{min} following oral ganciclovir administration. The clinical significance of the differences in ganciclovir pharmacokinetics for these three ganciclovir delivery systems is unknown.

Figure 1 Ganciclovir Plasma Concentration Time Profiles in HIV-positive/CMV-positive Patients*



*Plasma concentration-time profiles for ganciclovir (GCV) from Valcyte (VGCV) and intravenous ganciclovir were obtained from a multiple dose study (WV15376 n=21 and n=18, respectively) in HIV-positive/CMV-positive patients with CMV retinitis. The plasma concentration-time profile for oral ganciclovir was obtained from a multiple dose study (GAN2230 n=24) in HIV-positive/CMV-positive patients without CMV retinitis.

In solid organ transplant recipients, the mean systemic exposure to ganciclovir was 1.7 x higher following administration of 900 mg Valcyte tablets once daily versus 1000 mg ganciclovir capsules three times daily, when both drugs were administered according to their renal function dosing algorithms. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation (see **Table 2**).

Table 2 Mean Ganciclovir Pharmacokinetic Measures by Organ Type (Study PV16000)

Parameter	Ganciclovir Capsules	Valcyte Tablets
Dosage	1000 mg three times daily with food	900 mg once daily with food
Heart Transplant Recipients	N=13	N=17
$AUC_{0\text{-}24\ hr}$ (μg·h/mL)	26.6 ± 11.6	40.2 ± 11.8
C_{max} (μg/ml)	1.4 ± 0.5	4.9 ± 1.1
Elimination half-life (hr)	8.47 ± 2.84	6.58 ± 1.50
Liver Transplant Recipients	N=33	N=75
$AUC_{0\text{-}24\ hr}$ (μg·h/mL)	24.9 ± 10.2	46.0 ± 16.1
C_{max} (μg/ml)	1.3 ± 0.4	5.4 ± 1.5
Elimination half-life (hr)	7.68 ± 2.74	6.18 ± 1.42
Kidney Transplant Recipients*	N=36	N=68
$AUC_{0\text{-}24\ hr}$ (μg·h/mL)	31.3 ± 10.3	48.2 ± 14.6
C_{max} (μg/ml)	1.5 ± 0.5	5.3 ± 1.5
Elimination half-life (hr)	9.44 ± 4.37	6.77 ± 1.25

* Includes kidney-pancreas

In a pharmacokinetic study in liver transplant patients, the ganciclovir $AUC_{0\text{-}24\ hr}$ achieved with 900 mg valganciclovir was 41.7 ± 9.9 μg·h/mL (n=28) and the $AUC_{0\text{-}24\ hr}$ achieved with the approved dosage of 5 mg/kg intravenous ganciclovir was 48.2 ± 17.3 μg·h/mL (n=27).

Absorption

Valganciclovir, a prodrug of ganciclovir, is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from Valcyte tablets following administration with food was approximately 60% (3 studies, n=18; n=16; n=28). Ganciclovir median T_{max} following administration of 450 mg to 2625 mg Valcyte tablets ranged from 1 to 3 hours. Dose proportionality with respect to ganciclovir AUC following administration of Valcyte tablets was demonstrated only under fed conditions. Systemic exposure to the

prodrug, valganciclovir, is transient and low, and the AUC_{24} and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Food Effects

When Valcyte tablets were administered with a high fat meal containing approximately 600 total calories (31.1 g fat, 51.6 g carbohydrates and 22.2 g protein) at a dose of 875 mg once daily to 16 HIV-positive subjects, the steady-state ganciclovir AUC increased by 30% (95% CI 12% to 51%), and the C_{max} increased by 14% (95% CI -5% to 36%), without any prolongation in time to peak plasma concentrations (T_{max}). Valcyte tablets should be administered with food (see **DOSAGE AND ADMINISTRATION**).

Distribution

Due to the rapid conversion of valganciclovir to ganciclovir, plasma protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir is 1% to 2% over concentrations of 0.5 and 51 µg/mL. When ganciclovir was administered intravenously, the steady-state volume of distribution of ganciclovir was 0.703 ± 0.134 L/kg (n=69).

After administration of Valcyte tablets, no correlation was observed between ganciclovir AUC and reciprocal weight; oral dosing of Valcyte tablets according to weight is not required.

Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabeled ganciclovir (1000 mg single dose) accounted for more than 1% to 2% of the radioactivity recovered in the feces or urine.

Elimination

The major route of elimination of valganciclovir is by renal excretion as ganciclovir through glomerular filtration and active tubular secretion. Systemic clearance of intravenously administered ganciclovir was 3.07 ± 0.64 mL/min/kg (n=68) while renal clearance was 2.99 ± 0.67 mL/min/kg (n=16).

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of Valcyte tablets to either healthy or HIV-positive/CMV-positive subjects was 4.08 ± 0.76 hours (n=73), and that following administration of intravenous ganciclovir was 3.81 ± 0.71 hours (n=69). In heart, kidney, kidney-pancreas, and liver transplant patients, the terminal elimination half-life of ganciclovir following oral administration of Valcyte was 6.48 ± 1.38 hours, and following oral administration of ganciclovir capsules was 8.56 ± 3.62.

Special Populations

Renal Impairment

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

Table 3 Pharmacokinetics of Ganciclovir From a Single Oral Dose of 900 mg Valcyte Tablets

Estimated Creatinine Clearance (mL/min)	N	Apparent Clearance (mL/min) Mean ± SD	AUC_{last} (μg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51-70	6	249 ± 99	49.5 ± 22.4	4.85 ± 1.4
21-50	6	136 ± 64	91.9 ± 43.9	10.2 ± 4.4
11-20	6	45 ± 11	223 ± 46	21.8 ± 5.2
≤10	6	12.8 ± 8	366 ± 66	67.5 ± 34

Decreased renal function results in decreased clearance of ganciclovir from valganciclovir, and a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for patients with impaired renal function (see **PRECAUTIONS: General**).

Hemodialysis

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% following Valcyte administration. Patients receiving hemodialysis (CrCl <10 mL/min) cannot use Valcyte tablets because the daily dose of Valcyte tablets required for these patients is less than 450 mg (see **PRECAUTIONS**: **General** and **DOSAGE AND ADMINISTRATION: Hemodialysis Patients**).

Patients with Hepatic Impairment

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

Race/Ethnicity and Gender

Insufficient data are available to demonstrate any effect of race or gender on the pharmacokinetics of valganciclovir.

Pediatrics

Valcyte tablets have not been studied in pediatric patients; the pharmacokinetic characteristics of Valcyte tablets in these patients have not been established (see **PRECAUTIONS: Pediatric Use**).

Geriatrics

No studies of Valcyte tablets have been conducted in adults older than 65 years of age (see **PRECAUTIONS: Geriatric Use**).

INDICATIONS AND USAGE

Valcyte tablets are indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) (see **CLINICAL TRIALS**).

Valcyte is indicated for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [(D+/R-)]).

Valcyte is not indicated for use in liver transplant patients (see **CLINICAL TRIALS** and **WARNINGS**).

The safety and efficacy of Valcyte for the prevention of CMV disease in other solid organ transplant patients such as lung transplant patients have not been established.

CLINICAL TRIALS

Induction Therapy of CMV Retinitis

Study WV15376

In a randomized, open-label controlled study, 160 patients with AIDS and newly diagnosed CMV retinitis were randomized to receive treatment with either Valcyte tablets (900 mg twice daily for 21 days, then 900 mg once daily for 7 days) or with intravenous ganciclovir solution (5 mg/kg twice daily for 21 days, then 5 mg/kg once daily for 7 days). Study participants were: male (91%), White (53%), Hispanic (31%), and Black (11%). The median age was 39 years, the median baseline HIV-1 RNA was 4.9 $\log_{10}$, and the median CD_4 cell count was 23 cells/mm^3. A determination of CMV retinitis progression by the masked review of retinal photographs taken at baseline and week 4 was the primary outcome measurement of the 3-week induction therapy. **Table 4** provides the outcomes at 4 weeks.

Table 4 Week 4 Masked Review of Retinal Photographs in Study WV15376

	Cytovene-IV	Valcyte
Determination of CMV retinitis progression at Week 4	N=80	N=80
Progressor	7	7
Non-progressor	63	64
Death	2	1
Discontinuations due to Adverse Events	1	2
Failed to return	1	1
CMV not confirmed at baseline or no interpretable baseline photos	6	5

Maintenance Therapy of CMV Retinitis

No comparative clinical data are available on the efficacy of Valcyte for the maintenance therapy of CMV retinitis because all patients in study WV15376 received open-label Valcyte after week 4. However, the AUC for ganciclovir is similar following administration of 900 mg Valcyte tablets once daily and 5 mg/kg intravenous ganciclovir once daily. Although the ganciclovir C_{max} is lower following Valcyte administration compared to intravenous ganciclovir, it is higher than the C_{max} obtained following oral ganciclovir administration (see **Figure 1** in **CLINICAL PHARMACOLOGY**). Therefore, use of Valcyte as maintenance therapy is supported by a plasma concentration-time profile similar to that of two approved products for maintenance therapy of CMV retinitis.

Prevention of CMV Disease in Heart, Kidney, Kidney-Pancreas, and Liver Transplantation

A double-blind, double-dummy active comparator study was conducted in 372 heart, liver, kidney, and kidney-pancreas transplant patients at high-risk for CMV disease (D+/R-). Patients were randomized (2 Valcyte: 1 oral ganciclovir) to receive either Valcyte (900 mg once daily) or oral ganciclovir (1000 mg three times a day) starting within 10 days of transplantation until Day 100 posttransplant. The proportion of patients who developed CMV disease, including CMV syndrome and/or tissue-invasive disease during the first 6 months posttransplant was similar between the Valcyte arm (12.1%, N=239) and the oral ganciclovir arm (15.2%, N=125). However, in liver transplant patients, the incidence of tissue-invasive CMV disease was significantly higher in the Valcyte group compared with the ganciclovir group. These results are summarized in **Table 5**.

Mortality at six months was 3.7% (9/244) in the Valcyte group and 1.6% (2/126) in the oral ganciclovir group.

Table 5 Percentage of Patients with CMV Disease and Tissue-Invasive CMV Disease by Organ Type: Endpoint Committee, 6 Month ITT Population

	CMV Disease[1]		Tissue-Invasive CMV Disease		CMV Syndrome	
Organ	VGCV (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)
Liver (n=177)	19% (22 / 118)	12% (7 / 59)	14% (16 / 118)	3% (2 / 59)	5% (6 / 118)	9% (5 / 59)
Kidney (n=120)	6% (5 / 81)	23% (9 / 39)	1% (1 / 81)	5% (2 / 39)	5% (4 / 81)	18% (7 / 39)
Heart (n=56)	6% (2 / 35)	10% (2 / 21)	0% (0 / 35)	5% (1 / 21)	6% (2 / 35)	5% (1 / 21)
Kidney / Pancreas (n=11)	0% (0 / 5)	17% (1 / 6)	0% (0 / 5)	17% (1 / 6)	0% (0 / 5)	0% (0 / 6)

GCV = oral ganciclovir; VGCV = Valcyte

[1] Number of Patients with CMV Disease = Number of Patients with Tissue-Invasive CMV Disease + Number of Patients with CMV Syndrome.

CONTRAINDICATIONS

Valcyte tablets are contraindicated in patients with hypersensitivity to valganciclovir or ganciclovir.

WARNINGS

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Hematologic

Valcyte tablets should not be administered if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25,000/µL, or the hemoglobin is less than 8 g/dL. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Valcyte tablets (and ganciclovir) (see **PRECAUTIONS: Laboratory Testing** and **ADVERSE EVENTS**).

Valcyte tablets should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or who are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may increase with

continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug.

Impairment of Fertility

Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see **PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility‡).** It is considered probable that in humans, Valcyte at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

Teratogenesis, Carcinogenesis and Mutagenesis

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with Valcyte tablets (see **PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility‡,** and **Pregnancy: Category C**‡).

In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valcyte should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see **DOSAGE AND ADMINISTRATION: Handling and Disposal**).

Tissue Invasive CMV Disease in Liver Transplant Patients

In liver transplant patients, there was a significantly higher incidence of tissue-invasive CMV disease in the Valcyte-treated group compared with the oral ganciclovir group (see **CLINICAL TRIALS**).

PRECAUTIONS

General

Strict adherence to dosage recommendations is essential to avoid overdose.

The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets. Valcyte tablets cannot be substituted for ganciclovir capsules on a one-to-one basis (see **DOSAGE AND ADMINISTRATION**).

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR VALCYTE TABLETS. Such adjustments should be based on measured or estimated creatinine clearance values (see **DOSAGE AND ADMINISTRATION: Renal Impairment**).

For patients on hemodialysis (CrCl <10 mL/min) it is recommended that ganciclovir be used (in accordance with the dose-reduction algorithm cited in the Cytovene®-IV and ganciclovir capsules complete product information section on DOSAGE AND ADMINISTRATION: Renal Impairment) rather than Valcyte tablets (see **DOSAGE AND ADMINISTRATION: Hemodialysis Patients** and **CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis**).

Information for Patients (see Patient Information)

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 **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION**).

Valcyte is changed to ganciclovir once it is absorbed into the body. All patients should be informed that the major toxicities of ganciclovir include granulocytopenia (neutropenia), anemia and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take Valcyte tablets with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause decreased fertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Because of the potential for serious adverse events in nursing infants, mothers should be instructed not to breast-feed if they are receiving Valcyte tablets. Women of childbearing potential should be advised to use effective contraception during treatment with Valcyte tablets. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with Valcyte tablets.

Although there is no information from human studies, patients should be advised that ganciclovir should be considered a potential carcinogen.

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

Patients should be told that ganciclovir is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with Valcyte tablets. Some patients will require more frequent follow-up.

Laboratory Testing

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving Valcyte tablets (see **ADVERSE EVENTS**), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom

ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Increased monitoring for cytopenias may be warranted if therapy with oral ganciclovir is changed to Valcyte, because of increased plasma concentrations of ganciclovir after Valcyte administration (see **CLINICAL PHARMACOLOGY**).

Increased serum creatinine levels have been observed in trials evaluating Valcyte tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see **DOSAGE AND ADMINISTRATION: Renal Impairment**). The mechanism of impairment of renal function is not known.

Drug Interactions

Drug Interaction Studies Conducted With Valcyte

No in vivo drug-drug interaction studies were conducted with valganciclovir. However, because valganciclovir is rapidly and extensively converted to ganciclovir, interactions associated with ganciclovir will be expected for Valcyte tablets.

Drug Interaction Studies Conducted With Ganciclovir

Binding of ganciclovir to plasma proteins is only about 1% to 2%, and drug interactions involving binding site displacement are not anticipated.

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of Valcyte tablets and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Table 6 Results of Drug Interaction Studies With Ganciclovir: Effects of Coadministered Drug on Ganciclovir Plasma AUC and C_{max} Values

Coadministered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC ↓ 17 ± 25% (range: -52% to 23%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	12	AUC ↓ 21 ± 17% (range: -44% to 5%)	Effect not likely to be clinically significant.
Didanosine 200 mg every 12 hours simultaneously	1000 mg every 8 hours	12	No effect on ganciclovir PK parameters observed	No effect expected.

Coadministered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
administered with ganciclovir	IV ganciclovir 5 mg/kg twice daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg once daily	11	No effect on ganciclovir PK parameters observed	No effect expected.
Probenecid 500 mg every 6 hours	1000 mg every 8 hours	10	AUC ↑ 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 20% (range: -54% to -4%)	Patients taking probenecid and Valcyte should be monitored for evidence of ganciclovir toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	AUC ↑13%	Effect not likely to be clinically significant.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Ganciclovir renal clearance ↓ 16.3% Half-life ↑15%	Effect not likely to be clinically significant.
Mycophenolate Mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

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Table 7 Results of Drug Interaction Studies With Ganciclovir: Effects of Ganciclovir on Plasma AUC and C_{max} Values of Coadministered Drug

Coadministered Drug	Ganciclovir Dosage	N	Coadministered Drug Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC_{0-4} ↑ 19 ± 27% (range: -11% to 74%)	Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours when administered 2 hours prior to or concurrent with ganciclovir	1000 mg every 8 hours	12	AUC_{0-12} ↑111 ± 114% (range: 10% to 493%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg twice daily	11	AUC_{0-12} ↑70 ± 40% (range: 3% to 121%) C_{max} ↑49 ± 48% (range: -28% to 125%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg once daily	11	AUC_{0-12} ↑50 ± 26% (range: 22% to 110%) C_{max} ↑36 ± 36% (range: -27% to 94%)	Patients should be closely monitored for didanosine toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	No clinically relevant PK parameter changes	No effect expected.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Increase (12%) in C_{min}	Effect not likely to be clinically significant.
Mycophenolate Mofetil (MMF) 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No PK interaction observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

Carcinogenesis, Mutagenesis and Impairment of Fertility‡

No long-term carcinogenicity studies have been conducted with Valcyte. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen.

Ganciclovir was carcinogenic in the mouse at oral doses that produced exposures approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma

concentration curve (AUC) comparisons. At the higher dose there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the lower dose, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. Ganciclovir should be considered a potential carcinogen in humans.

Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic. Valganciclovir was not mutagenic in the Ames Salmonella assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro. In the mouse micronucleus assay, ganciclovir was clastogenic. Ganciclovir was not mutagenic in the Ames Salmonella assay.

Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir (see **WARNINGS: Impairment of Fertility**). Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses that produced an exposure approximately 1.7x the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons. Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of the recommended human intravenous dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

Pregnancy

Category C‡

Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered doses that produced 2x the human exposure based on AUC comparisons. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily intravenous doses administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see **WARNINGS: Teratogenesis, Carcinogenesis and Mutagenesis**). The drug exposure in mice as estimated by the AUC was approximately 1.7x the human AUC.

Data obtained using an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer

was not saturable over a concentration range of 1 to 10 mg/mL and occurred by passive diffusion.

Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Valcyte tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

‡**Footnote:** All dose comparisons presented in the Carcinogenesis, Mutagenesis and Impairment of Fertility, and Pregnancy subsections are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir.

Nursing Mothers

It is not known whether ganciclovir or valganciclovir is excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, the possibility of serious adverse events from ganciclovir in nursing infants is possible (see **WARNINGS**). Because of potential for serious adverse events in nursing infants, **mothers should be instructed not to breast-feed if they are receiving Valcyte tablets.** In addition, the Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

Safety and effectiveness of Valcyte tablets in pediatric patients have not been established.

Geriatric Use

The pharmacokinetic characteristics of Valcyte in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of Valcyte (see **DOSAGE AND ADMINISTRATION**).

Clinical studies of Valcyte did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Valcyte is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see **PRECAUTIONS: General**, **CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment**, and **DOSAGE AND ADMINISTRATION: Renal Impairment**).

ADVERSE EVENTS

Experience With Valcyte Tablets

Valganciclovir, a prodrug of ganciclovir, is rapidly converted to ganciclovir after oral administration. Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte tablets.

Treatment of CMV Retinitis in AIDS Patients

As shown in **Table 8**, the safety profiles of Valcyte tablets and intravenous ganciclovir during 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose) in 158 patients were comparable, with the exception of catheter-related infection, which occurred with greater frequency in patients randomized to receive IV ganciclovir.

Table 8 Percentage of Selected Adverse Events Occurring During the Randomized Phase of Study WV15376

Adverse Event	Valcyte Arm N=79	Intravenous Ganciclovir Arm N=79
Diarrhea	16%	10%
Neutropenia	11%	13%
Nausea	8%	14%
Headache	9%	5%
Anemia	8%	8%
Catheter-related infection	3%	11%

Tables 9 and 10 show the pooled adverse event data and abnormal laboratory values from two single arm, open-label clinical trials, WV15376 and WV15705. A total of 370 patients received maintenance therapy with Valcyte tablets 900 mg once daily. Approximately 252 (68%) of these patients received Valcyte tablets for more than nine months (maximum duration was 36 months).

Table 9 Pooled Selected Adverse Events Reported in ≥5% of Patients in Two Clinical Studies in CMV Retinitis

	Patients with CMV Retinitis (Studies WV15376 and WV15705)
Adverse Events According to Body System	**Valcyte (N=370) %**
Gastrointestinal system	
Diarrhea	41
Nausea	30
Vomiting	21
Abdominal pain	15
Body as a whole	
Pyrexia	31
Headache	22
Hemic and lymphatic system	
Neutropenia	27
Anemia	26
Thrombocytopenia	6
Central and peripheral nervous system	
Insomnia	16
Peripheral neuropathy	9
Paresthesia	8
Special senses	
Retinal detachment	15

Table 10 Pooled Laboratory Abnormalities Reported in Two Clinical Studies in the Treatment of CMV Retinitis

	CMV Retinitis Patients (Studies WV15376 and WV15705)
Laboratory Abnormalities	**Valcyte (N=370) %**
Neutropenia: ANC/μL	
<500	19
500 – <750	17
750 – <1000	17
Anemia: Hemoglobin g/dL	
<6.5	7
6.5 – <8.0	13
8.0 – <9.5	16
Thrombocytopenia: Platelets/μL	
<25000	4
25000 – <50000	6
50000 – <100000	22
Serum Creatinine: mg/dL	
>2.5	3
>1.5 – 2.5	12

Prevention of CMV Disease in Selected Solid Organ Transplantation

Table 11 shows selected adverse events regardless of severity and drug relationship with an incidence of ≥5% from a clinical trial, PV16000 (up to 28 days after study treatment) where heart, kidney, kidney-pancreas and liver transplant patients received Valcyte (N=244) or oral ganciclovir (N=126). The majority of the adverse events were of mild or moderate intensity.

Table 11 Percentage of Selected Grades 1-4 Adverse Events Reported in ≥5% of Selected Solid Organ Transplant Patients in Study PV16000

Adverse Event	Valcyte (N=244) %	Oral Ganciclovir (N=126) %
Diarrhea	30	29
Tremors	28	25
Graft rejection	24	30
Nausea	23	23
Headache	22	27
Insomnia	20	16
Hypertension	18	15
Vomiting	16	14
Leukopenia	14	7
Pyrexia	13	14

Laboratory adverse events are those reported by investigators.

Adverse events not included in **Table 11**, which either occurred at a frequency of ≥5% in clinical study PV16000, or were selected serious adverse events reported in studies WV15376, WV15705, or PV16000 with a frequency of <5% are listed below.

Allergic reactions: valganciclovir hypersensitivity

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia

Central and peripheral nervous system: paresthesia, dizziness (excluding vertigo), convulsion

Gastrointestinal disorders: abdominal pain, constipation, dyspepsia, abdominal distention, ascites

General disorders and administration site disorders: fatigue, pain, edema, peripheral edema, weakness

Hemic system: anemia, neutropenia, thrombocytopenia, pancytopenia, bone marrow depression, aplastic anemia

Hepatobiliary disorders: abnormal hepatic function

Infections and infestations: pharyngitis/nasopharyngitis, upper respiratory tract infection, urinary tract infection, local and systemic infections and sepsis, postoperative wound infection

Injury, poisoning and procedural complications: postoperative complications, postoperative pain, increased wound drainage, wound dehiscence

Metabolism and nutrition disorders: hyperkalemia, hypokalemia, hypomagnesemia, hyperglycemia, appetite decreased, dehydration, hypophosphatemia, hypocalcemia

Musculoskeletal and connective tissue disorders: back pain, arthralgia, muscle cramps, limb pain

Psychiatric disorders: depression, psychosis, hallucinations, confusion, agitation

Renal and urinary disorders: renal impairment, dysuria, decreased creatinine clearance

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, rhinorrhea, pleural effusion

Skin and subcutaneous tissue disorders: dermatitis, pruritus, acne

Vascular disorders: hypotension

Laboratory abnormalities reported with Valcyte tablets in one study in solid organ transplant patients are listed in **Table 12**.

Table 12 Laboratory Abnormalities Reported in Selected Solid Organ Transplant Patients in Study PV16000

Laboratory Abnormalities	Valcyte (N=244) %	Ganciclovir Capsules (N=126) %
Neutropenia: ANC/µL		
<500	5	3
500 – <750	3	2
750 – <1000	5	2
Anemia: Hemoglobin g/dL		
<6.5	1	2
6.5 – <8.0	5	7
8.0 – <9.5	31	25
Thrombocytopenia: Platelets/µL		
<25000	0	2
25000 – <50000	1	3
50000 – <100000	18	21
Serum Creatinine: mg/dL		
>2.5	14	21
>1.5 – 2.5	45	47

Experience With Ganciclovir

Valganciclovir is rapidly converted to ganciclovir upon oral administration. Adverse events reported with Valcyte in general were similar to those reported with ganciclovir. Please refer to the Cytovene-IV product information and ganciclovir capsule product information for more information on postmarketing adverse events associated with ganciclovir.

OVERDOSAGE

Overdose Experience With Valcyte Tablets

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's estimated degree of renal impairment.

It is expected that an overdose of Valcyte tablets could also possibly result in increased renal toxicity (see **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION: Renal Impairment**).

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of Valcyte tablets (see **CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis**). Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered (see **CLINICAL PHARMACOLOGY: Special Populations : Hemodialysis**).

Overdose Experience With Intravenous Ganciclovir

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during postmarketing experience. The majority of patients experienced one or more of the following adverse events:

Hematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leukopenia, neutropenia, granulocytopenia

Hepatotoxicity: hepatitis, liver function disorder

Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting

Neurotoxicity: generalized tremor, convulsion

DOSAGE AND ADMINISTRATION

Strict adherence to dosage recommendations is essential to avoid overdose. Valcyte tablets cannot be substituted for ganciclovir capsules on a one-to-one basis.

Valcyte tablets are administered orally, and should be taken with food (see **CLINICAL PHARMACOLOGY: Absorption**). After oral administration, valganciclovir is rapidly and extensively converted into ganciclovir. The bioavailability of ganciclovir from Valcyte tablets is significantly higher than from ganciclovir capsules. Therefore the dosage and administration of Valcyte tablets as described below should be closely followed (see **PRECAUTIONS: General** and **OVERDOSAGE**).

For the Treatment of CMV Retinitis in Patients With Normal Renal Function

Induction:

For patients with active CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) twice a day for 21 days with food.

Maintenance:

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) once daily with food.

For the Prevention of CMV Disease in Heart, Kidney, and Kidney-Pancreas Transplantation

For patients who have received a kidney, heart, or kidney-pancreas transplant, the recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days of transplantation until 100 days posttransplantation.

Renal Impairment

Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in **Table 13** (see **PRECAUTIONS: General** and **CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment**). Increased monitoring for cytopenias may be warranted in patients with renal impairment (see **PRECAUTIONS: Laboratory Testing**).

Table 13 Dose Modifications for Patients With Impaired Renal Function

CrCl* (mL/min)	Induction Dose	Maintenance Prevention Dose
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly

*An estimated creatinine clearance can be related to serum creatinine by the following formulas:

$$\text{For males} = \frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$$

For females = 0.85 x male value

Hemodialysis Patients

Valcyte should not be prescribed to patients receiving hemodialysis (see **CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis** and **PRECAUTIONS: General**).

For patients on hemodialysis (CrCl <10 mL/min) a dose recommendation cannot be given (see **CLINICAL PHARMACOLOGY: Special Populations: Hemodialysis**).

Handling and Disposal

Caution should be exercised in the handling of Valcyte tablets. Tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see **WARNINGS: Teratogenesis, Carcinogenesis and Mutagenesis**). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

Because ganciclovir shares some of the properties of antitumor agents (ie, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published (see **REFERENCES**).

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Valcyte (valganciclovir HCl tablets) is available as 450 mg pink convex oval tablets with "VGC" on one side and "450" on the other side. Each tablet contains valganciclovir HCl equivalent to 450 mg valganciclovir. Valcyte is supplied in bottles of 60 tablets (NDC 0004-0038-22).

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature].

REFERENCES

1. Recommendations for the Safe Handling of Cytotoxic Drugs. US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, September 1992. NIH Publication No. 92-2621
2. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm. 1990; 47:1033-1049
3. Controlling Occupational Exposures to Hazardous Drugs. US Department of Labor. Occupational Health and Safety Administration. OSHA Technical Manual. Section VI - Chapter 2, January 20, 1999

PATIENT INFORMATION

Read the Patient Information that comes with Valcyte before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider.

What is the most important information I should know about Valcyte?

- **Valcyte can affect your blood cells and bone marrow causing serious and life-threatening problems.** Valcyte can lower the amount of your white blood cells, red blood cells, and platelets. Your doctor may do regular blood tests to check your blood cells while you are taking Valcyte. Based on these tests, your doctor may change your dose or tell you to stop taking Valcyte.
- **Valcyte may cause cancer.** Valcyte causes cancer in animals. It is not known if Valcyte causes cancer in people.
- **Valcyte may cause birth defects.** Valcyte causes birth defects in animals. It is not known if Valcyte causes birth defects in people. Valcyte should not be used during pregnancy. **Tell your doctor right away if you get pregnant while taking Valcyte. If you can get pregnant, you should use effective birth control during treatment with Valcyte. Men should use a condom during treatment with Valcyte, and for 90 days after treatment, if their partner can get pregnant.** Talk to your doctor if you have questions about birth control. Valcyte may lower the amount of sperm in a man's body and cause fertility problems.
- **Valcyte changes into the medicine ganciclovir once it is in your body.** Ganciclovir is also the active ingredient in Cytovene®-IV and ganciclovir capsules. Do not take ganciclovir capsules or Cytovene-IV if you are taking Valcyte tablets. The dose of medicine in Valcyte tablets and ganciclovir capsules is different. **One tablet of Valcyte has more medicine than one capsule of ganciclovir. This means that one Valcyte tablet cannot be substituted for one ganciclovir capsule. You could overdose and become very sick if Valcyte is taken with ganciclovir capsules or Cytovene-IV.** Talk to your doctor or pharmacist if you have questions about your medicine.

What is Valcyte?

Valcyte is an "antiviral" medicine used:

- to treat cytomegalovirus (CMV) retinitis in people who have acquired immunodeficiency syndrome (AIDS). When CMV virus infects the eyes, it is called CMV retinitis.
- to prevent cytomegalovirus (CMV) disease in people who have received a **heart, kidney, or kidney-pancreas** transplant and who have a chance for getting CMV disease.

Valcyte may:

- slow the growth of CMV virus in your body. CMV is an infection caused by a herpesvirus called cytomegalovirus. If CMV retinitis isn't treated, it can cause blindness. Valcyte may protect your eyesight from damage due to CMV disease. CMV can also infect other parts of the body.

- prevent CMV disease for up to 6 months after **heart, kidney, or kidney-pancreas** transplant. Valcyte may prevent CMV virus from spreading into healthy cells.

Valcyte does not cure CMV retinitis. You may still get retinitis or worsening of retinitis during or after treatment with Valcyte. Therefore, it is important to stay under a doctor's care and have your eyes checked regularly.

Valcyte has not been studied in children or in adults older than age 65.

Who should not take Valcyte?

Do not take Valcyte if you:

- **are receiving hemodialysis.** The use of ganciclovir capsules rather than Valcyte tablets is recommended. Valcyte does not come in the right dose for people on hemodialysis.
- **are allergic to any of its ingredients or if you have ever had a serious reaction to ganciclovir capsules or Cytovene-IV.** See the end of this leaflet for a list of the ingredients in Valcyte.

In addition, Valcyte is not for use in prevention of CMV disease in patients who have received a liver transplant. More research is needed before Valcyte can be recommended for use in the prevention of CMV disease in other organ transplant patients such as liver or lung transplant patients.

Before taking Valcyte, tell your doctor:

- **if you are pregnant or plan to become pregnant.** Valcyte may cause birth defects. (See "**What is the most important information I should know about Valcyte?**"
- **if you are breast-feeding.** It is not known if Valcyte passes into your milk and if it may harm your baby. You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk.
- **if you have kidney problems.** Your doctor may give you a lower dose of Valcyte, or check you more often if you are taking Valcyte.
- **if you have blood cell problems**
- **if you are having radiation treatment**
- **about all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. **Do not take ganciclovir capsules or Cytovene-IV if you are taking Valcyte tablets.** Valcyte and other medicines may affect each other. These interactions may cause serious problems. The following medicines may need dose changes if you are also taking Valcyte:
  - Videx® (didanosine, ddI)
  - Retrovir® (zidovudine, ZDV, AZT)
  - Probenecid

Tell your doctor if you take medicines such as chemotherapy medicines that can lower your bone marrow function.

How should I take Valcyte?

- Take Valcyte exactly as your doctor prescribes it. Your dose of Valcyte will depend on your medical condition. If you have kidney problems or are over age 65, your doctor may give you a lower dose of Valcyte.
  - the usual dose for adults to get active CMV retinitis under control (induction therapy) is two 450 mg tablets twice a day for 21 days.
  - the usual dose for adults to help keep CMV retinitis under control (maintenance therapy) is two 450 mg tablets once a day.
  - the usual dose to prevent CMV in adults who have had a **heart, kidney, or kidney-pancreas** transplant is two 450 mg tablets once a day starting within 10 days of transplant and continuing until 100 days after the transplant.
- Take Valcyte with food.
- Do not break or crush Valcyte tablets.
- If you miss a dose of Valcyte, take the missed dose as soon as you remember. Then, take the next dose at the usual scheduled time. However, if it is almost time for your next dose, **do not take the missed dose.**
- Do not let your Valcyte run out. The amount of virus in your blood may increase if your medicine is stopped, even for a short time.
- If you take too much Valcyte, call your local poison control center or emergency room right away. You may need treatment in a hospital.
- Do not substitute Valcyte tablets for ganciclovir capsules. Talk to your doctor, nurse or pharmacist if you have questions about your medicine.

What should I avoid while taking Valcyte?

- **Do not get pregnant.** Valcyte causes birth defects in animals. It is not known if Valcyte causes birth defects in people. Valcyte should not be used during pregnancy. **Tell your doctor right away if you get pregnant while taking Valcyte. If you can get pregnant, you should use effective birth control during treatment with Valcyte. Men should use a condom during treatment with Valcyte, and for 90 days after treatment, if their partner can get pregnant.** Talk to your doctor if you have questions about birth control. Valcyte may lower the amount of sperm in a man's body and cause fertility problems.
- **Do not breast-feed.** Valcyte may harm your baby. You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk.
- **Do not drive a car or operate other dangerous machinery until you know how Valcyte affects you.** Valcyte can cause seizures, sleepiness, dizziness, unsteady movements, and confusion.
- **Do not break or crush Valcyte tablets.** Avoid contact with broken Valcyte tablets on your skin, mucous membranes or eyes. If contact occurs, wash your skin well with soap and water or rinse your eyes well with plain water.

What are the possible side effects of Valcyte?

See **"What is the most important information I should know about Valcyte?"** for details on the most serious side effects. **Valcyte can also cause the following serious side effects:**

- **kidney problems.** Valcyte may affect your kidney function. Your doctor may do regular blood tests called serum creatinine levels to check your kidney function while you are taking Valcyte.
- **brain and nerve problems.** Valcyte may cause seizures, sleepiness, dizziness, unsteady movements, and confusion.

Common side effects of Valcyte include diarrhea, nausea, vomiting, stomach pain, fever, headache, shaky movements (tremors), graft rejection, swelling of the legs, constipation, back pain, trouble sleeping, and high blood pressure.

Common changes in blood tests for people taking Valcyte include low white blood cells (neutropenia or leukopenia), low red blood cells (anemia), increased blood creatinine levels, increased calcium in the blood, and abnormal liver function.

Talk to your doctor about side effects that bother you or that won't go away.

These are not all the side effects of Valcyte. For more information, ask your doctor or pharmacist.

How do I store Valcyte?

- Store Valcyte at room temperature, 59° to 86° F (15° to 30° C).
- **Keep Valcyte and all medicines out of the reach of children.**

General information about Valcyte

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Valcyte for a condition for which it was not prescribed. Do not give Valcyte to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Valcyte. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Valcyte that is written for health professionals. Information about Valcyte is also available at 1-800-526-6367 (toll-free).

What are the ingredients in Valcyte?

Active Ingredient: Valganciclovir HCl

Inactive Ingredients: microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film-coating applied to the tablets contains Opadry Pink®.

Cytovene-IV is a registered trademark of Hoffmann-La Roche Inc.

Videx is a registered trademark of Bristol-Myers Squibb Company.

Retrovir is a registered trademark of GlaxoSmithKline.

Valcyte tablets are manufactured by Patheon Inc., Mississauga, Ontario, Canada L5N 7K9

Distributed by:

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

xxxxxxxx

Revised: Month Year

Patient Information

VALCYTE® (VAL-site)

(valganciclovir HCl tablets) (Val-gan-Sl-klo-veer HCl)

R_X only

Read the Patient Information that comes with Valcyte before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider.

What is the most important information I should know about Valcyte?

- **Valcyte can affect your blood cells and bone marrow causing serious and life-threatening problems.** Valcyte can lower the amount of your white blood cells, red blood cells, and platelets. Your doctor may do regular blood tests to check your blood cells while you are taking Valcyte. Based on these tests, your doctor may change your dose or tell you to stop taking Valcyte.

- **Valcyte may cause cancer.** Valcyte causes cancer in animals. It is not known if Valcyte causes cancer in people.

- **Valcyte may cause birth defects.** Valcyte causes birth defects in animals. It is not known if Valcyte causes birth defects in people. Valcyte should not be used during pregnancy. **Tell your doctor right away if you get pregnant while taking Valcyte. If you can get pregnant, you should use effective birth control during treatment with Valcyte. Men should use a condom during treatment with Valcyte, and for 90 days after treatment, if their partner can get pregnant.** Talk to your doctor if you have questions about birth control. Valcyte may lower the amount of sperm in a man's body and cause fertility problems.

- **Valcyte changes into the medicine ganciclovir once it is in your body.** Ganciclovir is also the active ingredient in Cytovene®-IV and ganciclovir capsules. Do not take ganciclovir capsules or Cytovene-IV if you are taking Valcyte tablets. The dose of medicine in Valcyte tablets and ganciclovir capsules is different. **One tablet of Valcyte has more medicine than one capsule of ganciclovir**. **This means that one Valcyte tablet cannot be substituted for one ganciclovir capsule. You could overdose and become very sick if Valcyte is taken with ganciclovir**

capsules or Cytovene-IV. Talk to your doctor or pharmacist if you have questions about your medicine.

What is Valcyte?

Valcyte is an "antiviral" medicine used:

- to treat cytomegalovirus (CMV) retinitis in people who have acquired immunodeficiency syndrome (AIDS). When CMV virus infects the eyes, it is called CMV retinitis.
- to prevent cytomegalovirus (CMV) disease in people who have received a **heart, kidney, or kidney-pancreas** transplant and who have a chance for getting CMV disease.

Valcyte may:

- slow the growth of CMV virus in your body. CMV is an infection caused by a herpesvirus called cytomegalovirus. If CMV retinitis isn't treated, it can cause blindness. Valcyte may protect your eyesight from damage due to CMV disease. CMV can also infect other parts of the body.
- prevent CMV disease for up to 6 months after **heart, kidney, or kidney-pancreas** transplant. Valcyte may prevent CMV virus from spreading into healthy cells.

Valcyte does not cure CMV retinitis. You may still get retinitis or worsening of retinitis during or after treatment with Valcyte. Therefore, it is important to stay under a doctor's care and have your eyes checked regularly.

Valcyte has not been studied in children or in adults older than age 65.

Who should not take Valcyte?

Do not take Valcyte if you:

- **are receiving hemodialysis.** The use of ganciclovir capsules rather than Valcyte tablets is recommended. Valcyte does not come in the right dose for people on hemodialysis.
- **are allergic to any of its ingredients or if you have ever had a serious reaction to ganciclovir capsules or Cytovene-IV.** See the end of this leaflet for a list of the ingredients in Valcyte.

In addition, Valcyte is not for use in prevention of CMV disease in patients who have received a liver transplant. More research is needed before Valcyte can be recommended for use in the prevention of CMV disease in other organ transplant patients such as liver or lung transplant patients.

Before taking Valcyte, tell your doctor:

- **if you are pregnant or plan to become pregnant.** Valcyte may cause birth defects. (See "**What is the most important information I should know about Valcyte?**")

- **if you are breast-feeding.** It is not known if Valcyte passes into your milk and if it may harm your baby. You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk.

- **if you have kidney problems.** Your doctor may give you a lower dose of Valcyte, or check you more often if you are taking Valcyte.

- **if you have blood cell problems**

- **if you are having radiation treatment**

- **about all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. **Do not take ganciclovir capsules or Cytovene-IV if you are taking Valcyte tablets.** Valcyte and other medicines may affect each other. These interactions may cause serious problems. The following medicines may need dose changes if you are also taking Valcyte:

  - Videx® (didanosine, ddI)
  - Retrovir® (zidovudine, ZDV, AZT)
  - Probenecid

Tell your doctor if you take medicines such as chemotherapy medicines that can lower your bone marrow function.

How should I take Valcyte?

- Take Valcyte exactly as your doctor prescribes it. Your dose of Valcyte will depend on your medical condition. If you have kidney problems or are over age 65, your doctor may give you a lower dose of Valcyte.

  - the usual dose for adults to get active CMV retinitis under control (induction therapy) is two 450 mg tablets twice a day for 21 days.

  - the usual dose for adults to help keep CMV retinitis under control (maintenance therapy) is two 450 mg tablets once a day.

  - the usual dose to prevent CMV in adults who have had a **heart, kidney, or kidney-pancreas** transplant is two 450 mg tablets once a day starting within 10 days of transplant and continuing until 100 days after the transplant.

- Take Valcyte with food.

- Do not break or crush Valcyte tablets.

- If you miss a dose of Valcyte, take the missed dose as soon as you remember. Then, take the next dose at the usual scheduled time. However, if it is almost time for your next dose, **do not take the missed dose.**

- Do not let your Valcyte run out. The amount of virus in your blood may increase if your medicine is stopped, even for a short time.

- If you take too much Valcyte, call your local poison control center or emergency room right away. You may need treatment in a hospital.

- Do not substitute Valcyte tablets for ganciclovir capsules. Talk to your doctor, nurse or pharmacist if you have questions about your medicine.

What should I avoid while taking Valcyte?

- **Do not get pregnant.** Valcyte causes birth defects in animals. It is not known if Valcyte causes birth defects in people. Valcyte should not be used during pregnancy. **Tell your doctor right away if you get pregnant while taking Valcyte. If you can get pregnant, you should use effective birth control during treatment with Valcyte. Men should use a condom during treatment with Valcyte, and for 90 days after treatment, if their partner can get pregnant.** Talk to your doctor if you have questions about birth control. Valcyte may lower the amount of sperm in a man's body and cause fertility problems.

- **Do not breast-feed.** Valcyte may harm your baby. You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk.

- **Do not drive a car or operate other dangerous machinery until you know how Valcyte affects you.** Valcyte can cause seizures, sleepiness, dizziness, unsteady movements, and confusion.

- **Do not break or crush Valcyte tablets.** Avoid contact with broken Valcyte tablets on your skin, mucous membranes or eyes. If contact occurs, wash your skin well with soap and water or rinse your eyes well with plain water.

What are the possible side effects of Valcyte?

See "**What is the most important information I should know about Valcyte?**" for details on the most serious side effects. **Valcyte can also cause the following serious side effects:**

- **kidney problems.** Valcyte may affect your kidney function. Your doctor may do regular blood tests called serum creatinine levels to check your kidney function while you are taking Valcyte.

- **brain and nerve problems.** Valcyte may cause seizures, sleepiness, dizziness, unsteady movements, and confusion.

Common side effects of Valcyte include diarrhea, nausea, vomiting, stomach pain, fever, headache, shaky movements (tremors), graft rejection, swelling of the legs, constipation, back pain, trouble sleeping, and high blood pressure.

Common changes in blood tests for people taking Valcyte include low white blood cells (neutropenia or leukopenia), low red blood cells (anemia), increased blood creatinine levels, increased calcium in the blood, and abnormal liver function.

Talk to your doctor about side effects that bother you or that won't go away.

These are not all the side effects of Valcyte. For more information, ask your doctor or pharmacist.

How do I store Valcyte?

- Store Valcyte at room temperature, 59° to 86° F (15° to 30° C.)
- **Keep Valcyte and all medicines out of the reach of children.**

General information about Valcyte

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Valcyte for a condition for which it was not prescribed. Do not give Valcyte to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Valcyte. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Valcyte that is written for health professionals. Information about Valcyte is also available at 1-800-526-6367 (toll-free).

What are the ingredients in Valcyte?

Active Ingredient: Valganciclovir HCl

Inactive Ingredients: microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film-coating applied to the tablets contains Opadry Pink®.

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/s/

Jeffrey Murray

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