Size: 300 x 730 mm
Colour: Black
Pharma Codes: Front: 2182 & Back: 2183
Spec: Printed on 30 GSM Bible paper, front & back side printing.
Note: Pharma code position and Orientation will be change based on folding size.

Valganciclovir Tablets, USP

2182 2183

2024R04

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VALGANCICLOVIR TABLETS safely and effectively. See full prescribing information for VALGANCICLOVIR TABLETS.
VALGANCICLOVIR Tablets USP, for oral use
Initial U.S. Approval: 2001

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS
See full prescribing information for complete boxed warning.

- **Hematologic Toxicity: Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow aplasia and aplastic anemia have been reported in patients treated with valganciclovir tablets (5.1).**
- **Impairment of Fertility: Based on animal data, valganciclovir tablets may cause temporary or permanent inhibition of spermatogenesis (5.2)**
- **Fetal Toxicity: Based on animal data, valganciclovir tablets have the potential to cause birth defects in pregnant women (5.3).**
- **Mutagenesis and Carcinogenesis: Based on animal data, valganciclovir tablets have the potential to cause cancers in humans (5.4).**

—RECENT MAJOR CHANGES—

Indications and Usage, Pediatric Patients (1.2)	04/2015
Dosage and Administration, Pediatric Patients (2.3)	04/2015

—INDICATIONS AND USAGE—

Valganciclovir tablets, USP are a cytomegalovirus (CMV) nucleoside analogue DNA polymerase inhibitor indicated for:

Adult Patients (1.1)

- Treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).
- Prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk.

Pediatric Patients (1.2)

- Prevention of CMV disease in heart transplant patients at high risk.

—DOSAGE AND ADMINISTRATION—

Adult Dosage (2.2)	
Treatment of CMV retinitis	Induction: 900 mg (two 450 mg tablets) twice a day for 21 days Maintenance: 900 mg (two 450 mg tablets) once a day
Prevention of CMV disease in heart or kidney-pancreas transplant patients	900 mg (two 450 mg tablets) once a day within 10 days of transplantation until 100 days post-transplantation
Prevention of CMV disease in kidney transplant patients	900 mg (two 450 mg tablets) once a day within 10 days of transplantation until 200 days post-transplantation
Pediatric Dosage (2.3)	
Prevention of CMV disease in heart transplant patients 4 month to 16 years of age	Dose once a day within 10 days of transplantation until 100 days post-transplantation according to dosage recommended based on body surface area (preferably using a modified Schwartz formula in children)

- Valganciclovir tablets should be taken with food (2.1, 12.3).
- Valganciclovir tablets should not be broken or crushed (2.6).
- Adult patients should use valganciclovir tablets, not valganciclovir for oral solution (2.1).
- Adults with renal impairment: Adjust dose based on creatinine clearance. For adult patients receiving hemodialysis a dose recommendation cannot be given (2.5, 8.6, 12.3).

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS
1 INDICATIONS AND USAGE
1.1 Adult Patients
1.2 Pediatric Patients
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Recommended Dosage in Adult Patients with Normal Renal Function
2.3 Recommended Dosage in Pediatric Patients
2.5 Dosage Recommendation for Adult Patients with Renal Impairment
2.6 Handling and Disposal
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hematologic Toxicity
5.2 Impairment of Fertility
5.3 Fetal Toxicity
5.4 Mutagenesis and Carcinogenesis
5.5 Acute Renal Failure
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Adult Patients
14.2 Pediatric Patients
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

—DOSAGE FORMS AND STRENGTHS—

- Tablets: 450 mg (3)

—CONTRAINDICATIONS—

Hypersensitivity to valganciclovir or ganciclovir (4)

—WARNINGS AND PRECAUTIONS—

- Hematologic toxicity: Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression, and aplastic anemia have occurred with the use of valganciclovir tablets or ganciclovir. Avoid valganciclovir tablets use if absolute neutrophil count is less than 500 cells/µL, platelet count is less than 25,000/µL, or hemoglobin is less than 8 g/dL. Use with caution in pre-existing cytopenias and when receiving myelosuppressive drugs or irradiation. Monitor with frequent testing of platelet and complete blood counts (5.1).
- Impairment of fertility: Based on animal studies, valganciclovir tablets may cause temporary or permanent inhibition of spermatogenesis (5.2).
- Fetal toxicity: Based on animal studies, valganciclovir tablets may cause fetal harm. Females of reproductive potential should use effective contraception during and following treatment and males should practice barrier contraception during and following treatment (5.3).
- Mutagenicity and carcinogenicity: Based on animal studies, valganciclovir tablets are potentially mutagenic and carcinogenic (5.4).
- Acute renal failure: Acute renal failure may occur in elderly patients (with or without reduced renal function), patients who receive concomitant nephrotoxic drugs, or inadequately hydrated patients. Use with caution in elderly patients or those taking nephrotoxic drugs, reduce dosage in patients with renal impairment, and monitor renal function (2.5, 5.5, 5.6, 6.2, 12.3).

—ADVERSE REACTIONS—

- Adult patients: Most common adverse events and laboratory abnormalities (reported in at least one indication by greater than or equal to 20% of patients) are diarrhea, pyrexia, nausea, tremor, neutropenia, anemia, graft rejection, thrombocytopenia, and vomiting (6.1).
- Pediatric patients: Most common adverse events and laboratory abnormalities (reported in greater than or equal to 20% of pediatric solid organ transplant recipients) are diarrhea, pyrexia, hypertension, upper respiratory tract infection, urinary tract infection, vomiting, neutropenia, leukopenia, and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

—DRUG INTERACTIONS—

- Zidovudine: Potential to cause neutropenia and anemia. Monitor with frequent tests of white blood cell counts with differential and hemoglobin levels (7).
- Probenecid: May increase ganciclovir levels. Monitor for evidence of ganciclovir toxicity (7).
- Mycophenolate mofetil (MMF): May increase ganciclovir concentrations and levels of MMF metabolites in patients with renal impairment. Monitor for ganciclovir and MMF toxicity (7).
- Didanosine: May increase didanosine concentrations. Monitor for didanosine toxicity (7).

—USE IN SPECIFIC POPULATIONS—

- Lactation: Breastfeeding is not recommended with use of valganciclovir tablets (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Palo Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due to Roche Palo Alto LLC's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Revised: 03/2016

FULL PRESCRIBING INFORMATION

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS

- Hematologic Toxicity: Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow aplasia and aplastic anemia have been reported in patients treated with valganciclovir tablets *[see Warnings and Precautions (5.1)]*.
- Impairment of Fertility: Based on animal data, valganciclovir tablets may cause temporary or permanent inhibition of spermatogenesis *[see Warnings and Precautions (5.2)]*.
- Fetal Toxicity: Based on animal data, valganciclovir tablets have the potential to cause birth defects in pregnant women *[see Warnings and Precautions (5.3)]*.
- Mutagenesis and Carcinogenesis: Based on animal data, valganciclovir tablets have the potential to cause cancers in humans *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

1.1 Adult Patients

Treatment of Cytomegalovirus (CMV) Retinitis: Valganciclovir tablets, USP are indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) *[see Clinical Studies (14.1)]*.

Prevention of CMV Disease: Valganciclovir tablets, USP are indicated for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk *[Donor CMV seropositive/Recipient CMV seronegative (D+/R-) *[see Clinical Studies (14.1)]*]*.

1.2 Pediatric Patients

Prevention of CMV Disease: Valganciclovir tablets, USP are indicated for the prevention of CMV disease in heart transplant patients 4 month to 16 years of age) at high risk *[see Clinical Studies (14.2)]*.

Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Palo Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due to Roche Palo Alto LLC's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

- Adult patients should use valganciclovir tablets, not valganciclovir for oral solution.
- Valganciclovir tablets should be taken with food *[see Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage in Adult Patients with Normal Renal Function

For dosage recommendations in adult patients with renal impairment see *[see Dosage and Administration (2.5)]*.

Treatment of CMV Retinitis:

- Induction: The recommended dosage is 900 mg (two 450 mg tablets) taken orally twice a day for 21 days.
- Maintenance: Following induction treatment, or in adult patients with inactive CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) taken orally once a day.

Prevention of CMV Disease:

- For adult patients who have received a heart or kidney-pancreas transplant, the recommended dosage is 900 mg (two 450 mg tablets) taken orally once a day starting within 10 days of transplantation until 100 days post-transplantation.
- For adult patients who have received a kidney transplant, the recommended dosage is 900 mg (two 450 mg tablets) taken orally once a day starting within 10 days of transplantation until 200 days post-transplantation.

2.3 Recommended Dosage in Pediatric Patients

Prevention of CMV Disease in Pediatric Heart Transplant Patients: For pediatric heart transplant patients 4 month to 16 years of age, the recommended once daily mg dose (7x BSA x CrCL) should not exceed the adult dose. Limit transplantation until 100 days post-transplantation.

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

Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using a modified Schwartz formula). If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m², then a maximum value of 150 mL/min/1.73m² should be used in the dose calculation. The k values used in the modified Schwartz formula are based on gender in pediatric age, as shown in **Table 1**.

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

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

Table 1. k Values According to Pediatric Patient Age *

k value	Pediatric Patient Age
0.33	Infants less than 1 year of age with low birth weight for gestational age
0.45	Infants less than 1 year of age with birth weight appropriate for gestational age
0.45	Children aged 1 to less than 2 years
0.55	Boys aged 2 to less than 13 years Girls aged 2 to less than 13 years
0.7	Boys aged 13 to 16 years

* The k values provided are based on the Jaffe method of measuring serum creatinine, and may require correction when enzymatic methods are used*

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

All calculated dose should be rounded to the nearest 10 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. Valganciclovir for oral solution is available for pediatric patients who cannot swallow valganciclovir tablets. Dosing based on the formula above, however, valganciclovir tablets may be used if the calculated dose are within 10% of available tablet strength (450 mg). For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken. Before prescribing valganciclovir tablets, pediatric patients should be assessed for the ability to swallow tablets.

Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Palo Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due to Roche Palo Alto LLC's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2.5 Dosage Recommendation for Adult Patients with Renal Impairment

Serum creatinine levels or creatinine clearance should be monitored regularly during treatment. Dosage recommendations for adult patients with reduced renal function are provided in **Table 2**. For adult patients on hemodialysis (CrCl less than 10 mL/min), a dose recommendation for valganciclovir tablets cannot be given *[see Use in Specific Populations (8.6, 8.6), Clinical Pharmacology (12.3)]*.

Table 2 Dosage Recommendations for Adult Patients with Impaired Renal Function

	Valganciclovir Tablets 450 mg		
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	
< 10 (on hemodialysis)	not recommended	not recommended	

*An estimated creatinine clearance in adults is calculated from serum creatinine by the following formula:

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

For females = 0.85 x male value

Dosing in pediatric patients with renal impairment can be done using the recommended equations because CrCl is a component in the calculation *[see Dosage and Administration (2.3)]*.

2.6 Handling and Disposal

Caution should be exercised in the handling of valganciclovir tablets. Tablets should not be broken or crushed. Because valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be exercised in handling crushed tablets. Pregnant women should not handle crushed valganciclovir tablets 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.

Handle and dispose valganciclovir tablets according to guidelines for antineoplastic drugs because ganciclovir shares some of the properties of antitumor agents (i.e., carcinogenicity and mutagenicity)1.

3 DOSAGE FORMS AND STRENGTHS

450 mg, pink, oval, biconvex, film-coated tablets, debossed with 'J' on one side and '15E' on the other side.

4 CONTRAINDICATIONS

Valganciclovir tablets are contraindicated in patients who have had a demonstrated clinically significant hypersensitivity reaction (e.g., anaphylaxis) to valganciclovir, ganciclovir, or any component of the formulation *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow aplasia, and aplastic anemia have been reported in patients treated with valganciclovir tablets or ganciclovir. Valganciclovir tablets should be avoided if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25,000/µL, or hemoglobin is less than 8 g/dL. Use with caution in pre-existing cytopenias and when receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may worsen with continued dosing. Cell counts usually begin to recover within 3 to 7 days after discontinuing drug.

Due to the frequency of neutropenia, anemia, and thrombocytopenia in patients receiving valganciclovir tablets *[see Adverse Reactions (6.1)]*, complete blood counts with differential and platelet counts should 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 valganciclovir tablets, or if intravenous ganciclovir is given concomitantly *[see Clinical Pharmacology (12.3), Clinical Pharmacology (12.2)]*.

5.2 Impairment of Fertility

Based on animal data with ganciclovir, valganciclovir tablets at the recommended human dosas may cause temporary or permanent inhibition of spermatogenesis in males, and may cause suppression of fertility in females. Advise patients that fertility may be impaired with use of valganciclovir tablets *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

5.3 Fetal Toxicity

Ganciclovir may cause fetal toxicity when administered to pregnant women based on findings in animal studies. When given to pregnant rabbits at dosages resulting in 2-times the human exposure (based on AUC), ganciclovir caused malformations in multiple organs of the fetuses. Maternal and fetal toxicity were also observed in pregnant mice and rabbits. Therefore, valganciclovir has the potential to cause birth defects. Pregnancy should be avoided if the potential benefit does not justify the potential risk to the fetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with valganciclovir tablets. Similarly, males should be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir tablets *[see Dosage and Administration (2.6), Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

5.4 Mutagenesis and Carcinogenesis

Animal data indicate that ganciclovir is mutagenic and carcinogenic. Valganciclovir tablets should therefore be considered a potential carcinogen in humans *[see Dosage and Administration (2.6), Nonclinical Toxicology (13.1)]*.

5.5 Acute Renal Failure

Acute renal failure may occur in:

- Elderly patients with or without reduced renal function. Caution should be exercised when administering valganciclovir tablets to elderly patients, and dosage reduction is recommended for those with impaired renal function *[see Dosage and Administration (2.5), Use in Specific Populations (8.5, 8.6)]*.
- Patients receiving potential nephrotoxic drugs. Caution should be exercised when administering valganciclovir tablets to patients receiving potential nephrotoxic drugs.
- Patients without adequate hydration. Adequate hydration should be maintained for all patients.

6 ADVERSE REACTIONS

The following serious adverse events are discussed in greater detail in other sections of the labeling:

- Hematologic toxicity *[see Warnings and Precautions (5.1)]*.
- Acute renal failure *[see Warnings and Precautions (5.5)]*.

The most common adverse events and laboratory abnormalities reported in at least one indication by greater than or equal to 20% of adult solid organ transplant patients are diarrhea, pyrexia, nausea, tremor, neutropenia, anemia, graft rejection, thrombocytopenia, and vomiting (6.1). The most common reported adverse events and laboratory abnormalities reported in greater than or equal to 20% of pediatric solid organ transplant recipients are diarrhea with valganciclovir tablets are diarrhea, pyrexia, hypertension, upper respiratory tract infection, urinary tract infection, vomiting, neutropenia, leukopenia, and head ache.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

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 valganciclovir tablets.

Adverse Events in Adults:

Treatment of CMV Retinitis in AIDS Patients: In a clinical study for the treatment of CMV retinitis in HIV-infected patients with AIDS, 160 patients were randomized to receive induction dosage of 900 mg (two 450 mg tablets) valganciclovir (n=75) for 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose), respectively, included diarrhea (30%, 10%), nausea (8%, 14%), headache (9%, 5%), and catheter-related infections (3%, 11%). The incidence of these events were similar between the patients who received valganciclovir tablets and the group who received intravenous ganciclovir, with the exception of catheter-related infections, which occurred with greater frequency in patients randomized to receive intravenous ganciclovir. The frequencies of neutropenia (ANC less than 500/µL) were 11% for patients receiving valganciclovir tablets compared with 13% for those receiving intravenous ganciclovir, and anemia (Hb less than 6.5 g/dL) were 1% of patients in each group. Other laboratory abnormalities occurred with similar frequency in the two groups.

Adverse events and abnormal laboratory values data are available for 370 patients who received maintenance therapy with valganciclovir tablets (900 mg once daily or two open-label clinical trials, (Ganciclovir, 262 (60%) of these patients received valganciclovir tablets for more than one months (maximum duration was 24 months). **Table 3** and **Table 4** show the pooled adverse event data and abnormal laboratory values from these patients.

Table 3 Pooled Selected Adverse Events Reported in greater than or equal to 5% of Patients who Received Valganciclovir Tablets Maintenance Therapy for CMV Retinitis

	Patients with CMV Retinitis	
Adverse Events According to Body System	Valganciclovir Tablets (N=370) %	
Gastrointestinal system		
Diarrhea	41	
Nausea	30	
Vomiting	21	
Abdominal pain	15	
Body as a Whole		
Pyrexia	31	
Headache	22	
Central and peripheral nervous system		
Insomnia	16	
Peripheral neuropathy	9	
Paresthesia	8	
Special senses		
Retinal detachment	15	

Table 4 Pooled Laboratory Abnormalities Reported in Patients Who Received Valganciclovir Tablets Maintenance Therapy for the Treatment of CMV Retinitis

	Patients with CMV Retinitis	
Laboratory Abnormalities	Valganciclovir Tablets (N=370) %	
Neutropenia: ANC/µL		
< 500	19	
500 – < 750	17	
750 – <1000	17	
Anemia: Hemoglobin g/dL		
< 6.5	7	
6.5 – < 8	13	
8 – < 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 5** shows selected adverse events regardless of severity and drug relationship with an incidence of greater than or equal to 5% from a clinical trial (up to 28 days after transplantation) enrolling kidney-pancreas and liver transplant patients received valganciclovir tablets (N=246) or oral ganciclovir (N=128) until Day 100 post-transplant. The majority of the adverse events were of mild or moderate intensity.

Table 5 Percentage of Selected Grades 1 to 4 Adverse Events Reported in greater than or equal to 5% of Adult Patients from a Study of Solid Organ Transplant Patients

Adverse Event	Valganciclovir Tablets (N=246) %	Oral Ganciclovir (N=128) %
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
Pyrexia	15	14

Table 6 shows selected adverse events regardless of severity and drug relationship with an incidence of greater than or equal to 5% from another clinical trial where kidney transplant patients received either valganciclovir once daily starting within 10 days post-transplant until Day 100 post-transplant followed by 100 days of placebo or valganciclovir once daily starting within 10 days post-transplant until Day 200 post-transplant. The overall safety profile of valganciclovir did not change with the extension of prophylaxis until Day 200 post-transplant in high risk kidney transplant patients.

Table 6 Percentage of Selected Grades 1 to 4 Adverse Events Reported in greater than or equal to 5% of Adult Patients from a Study of Kidney Transplant Patients

Adverse Event	Valganciclovir Tablets Day 100 Post-transplant (N=164) %	Valganciclovir Tablets Day 200 Post-transplant (N=156) %
Diarrhea	26	31
Tremors	12	17
Hypertension	13	12
Nausea	11	11
Pyrexia	12	9
Transplant rejection	9	6
Headache	10	6
Insomnia	7	6
Vomiting	6	3

Adverse events not included in **Table 5** and **Table 6**, which either occurred at a frequency of greater than or equal to 5% in clinical studies with solid organ transplant patients, or were selected serious adverse events regardless of frequency, include those with CMV retinitis or in studies with solid organ transplant patients with a frequency of less than 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 disorders: neutropenia, thrombocytopenia, pancytopenia, bone marrow depression, aplastic anemia, febrile neutropenia

Hepatobiliary disorders: abnormal hepatic function

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

Injury, poisoning, and procedural complications: postoperative complications, postoperative pain, increased wound healing, incisional hernia

Metabolism and nutrition disorders: hyperkalemia, hypokalemia, hypomagnesemia, hyperglycemia, anorexia, 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: hypertension

Laboratory abnormalities reported with valganciclovir tablets in two studies in adult solid organ transplant patients are listed in **Table 7** and **Table 8**.

Table 7 Selected Laboratory Abnormalities Reported in a Study of Adult Solid Organ Transplant Patients*

Laboratory Abnormalities	Valganciclovir Tablets (N=246) %	Ganciclovir Capsules (N=128) %
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	5	7
8 – < 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

*Laboratory abnormalities are those reported by investigators.

Table 8 Selected Laboratory Abnormalities Reported in a Study of Adult Kidney Transplant Patients*

Laboratory Abnormalities	Valganciclovir Tablets Day 100 Post-transplant (N=164) %	Valganciclovir Tablets Day 200 Post-transplant (N=156) %
Neutropenia: ANC/µL		
< 500	9	10
500 – < 750	6	6
750 – <1000	7	5
Anemia: Hemoglobin g/dL		
< 6.5	0	1
6.5 – < 8	5	1
8 – < 9.5	17	15
Thrombocytopenia: Platelets/µL		
< 25000	0	0
25000 – < 50000	1	0
50000 – < 100000	7	3
Serum Creatinine: mg/dL		
> 2.5	17	14
> 1.5 – 2.5	50	48

*Laboratory abnormalities are those reported by investigators.

Adverse Events in Pediatrics Patients:

Valganciclovir tablets have been studied in 109 pediatric solid organ transplant patients who were at risk for developing CMV disease (aged 4 months to 16 years) and in 34 neonates with symptomatic congenital CMV infection (aged 1 to 29 days). Most pediatric ganciclovir exposure ranging from 2 to 100 days *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

Prevention of CMV Disease in Pediatric Solid Organ Transplant Patients: The most frequently reported adverse events (greater than 10% of patients), regardless of seriousness and drug relationship in pediatric solid organ transplant patients taking valganciclovir tablets until Day 100 post-transplant were diarrhea, pyrexia, upper respiratory tract infection, hypertension, vomiting, anemia, neutropenia, constipation, nausea and transplant rejection.

In general, the safety profile was similar in pediatric patients compared to that observed in adult patients. However, the ratio of certain adverse events and laboratory abnormalities, such as upper respiratory tract infection, pyrexia, nasopharyngitis, anemia, and abdominal pain were reported more frequently in pediatric patients than in adults *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*. Neutropenia was reported with similar incidence in the two pediatric studies as compared to adults, but there was no correlation between neutropenia and dose or exposure to ganciclovir in pediatrics.

Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Palo Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due Roche Palo Alto LLC's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

6.2 Postmarketing Experience

The following adverse events have been identified during post-approval use of valganciclovir tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. As valganciclovir tablets are rapidly and extensively converted to ganciclovir, any adverse events associated with ganciclovir might also occur with valganciclovir.

- Anaphylaxis
- Decreased fertility in males

In general, the adverse events reported during the postmarketing use of valganciclovir tablets were similar to those identified during the clinical trials.

7 DRUG INTERACTIONS

Pharmacokinetic drug interaction studies were not conducted with valganciclovir. However, because valganciclovir is rapidly and extensively converted to ganciclovir, drug-drug interactions associated with ganciclovir will be expected for valganciclovir tablets. Established and other potentially significant drug interactions conducted with ganciclovir are listed in **Table 9**.

Table 9 Established and Other Potentially Significant Drug Interactions With Ganciclovir

Name of the Concomitant Drug	Change in the Concentration of Ganciclovir or Concomitant Drug	Clinical Comment
Zidovudine	↑ Ganciclovir ↑ Zidovudine	Zidovudine and valganciclovir tablets each have the potential to cause neutropenia or anemia
Probenecid	↑ Ganciclovir	Patients taking probenecid and valganciclovir tablets should be monitored for evidence of ganciclovir toxicity
Mycophenolate Mofetil (MMF)	↔ Ganciclovir (in patients with normal renal function) ↔ MMF (in patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of MMF metabolites and ganciclovir may increase
Didanosine	↑ Ganciclovir ↑ Didanosine	Patients should be closely monitored for didanosine toxicity

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Teratogenic Effects

Risk Summary

After oral administration, valganciclovir (prodrug) is converted to ganciclovir (active drug) and, therefore, valganciclovir tablets are expected to have reproductive toxicity effects similar to ganciclovir. In animal studies, ganciclovir caused maternal and fetal toxicity and embryo-fetal mortality in pregnant mice and rabbits (and fetal toxicity in teratogenicity in rabbits at exposures two-times the human exposure. There are no available human data on use of valganciclovir tablets in pregnant women. Ganciclovir administration during pregnancy in rabbits and mice caused fetal malformations. The background risk of major birth defects and miscarriage for the indicated populations is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and the risk of miscarriage is 15 to 20% of clinically recognized pregnancies. Advice pregnant women of the potential risk to the fetus *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3)]*.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Congenital or neonatal CMV infections are asymptomatic or they may be associated with a self-limited mononucleosis-like syndrome. However, in immunocompromised patients (i.e., transplant patients or patients with AIDS) CMV infections may be symptomatic and may result in significant maternal morbidity and mortality. The transmission of CMV to the fetus is a result of maternal viremia and transplacental infection. Perinatal infection can also occur from exposure of the neonate to CMV shedding in the genital tract. Approximately 10% of children with congenital CMV infection are symptomatic at birth. Of the asymptomatic children born to seronegative mothers, 10% of symptomatic surviving newborns experience significant morbidity, including mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems. The risk of congenital CMV infection resulting from primary maternal CMV infection may be higher and of greater severity than that resulting from maternal reactivation of CMV infection.

Data

Animal Data

Oral ganciclovir, administered to pregnant mice and rabbits during their period of organogenesis, caused embryo-fetal toxicity (fetal resorptions and fetal malformations) at maternal systemic exposure levels (based on AUC) approximately 0.1-times the human exposure (based on AUC) administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the male offspring, as well as pathologic changes in the nonglandular region of the stomach.

Data from an ex-vivo human placental model showed that ganciclovir crosses the human placenta. The transfer occurred by passive diffusion and was not saturable over a concentration range of 1 to 10 mg/mL.

8.2 Lactation

Risk Summary

No data are available regarding the presence of valganciclovir (prodrug) or ganciclovir (active drug) in human milk, the effects on the breastfed infant, or the effects on milk production. The Centers for Disease Control and Prevention recommend that women infected with HIV not breastfeed their infants to avoid risking postnatal transmission of HIV. Advise nursing mothers that breastfeeding is not recommended during treatment with valganciclovir tablets because of the potential for serious adverse events in nursing infants and because of the potential for transmission of HIV *[see Breast Warning, Warnings and Precautions (5.1, 5.2, 5.3, 5.4), Nonclinical Toxicology (13.1)]*.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of valganciclovir tablets *[see Use in Specific Populations (8.1)]*.

Patient Information Valganciclovir (val gan ci SYE klo ver)

What is the most important information I should know about valganciclovir tablets?

- **Valganciclovir tablets can affect your blood cells and bone marrow causing serious and life-threatening problems.** Valganciclovir tablets can lower the amount of your white blood cells,

Contraception

Females

Because of the mutagenic and teratogenic potential of valganciclovir tablets, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with valganciclovir tablets *[see Dosage and Administration (2.6), Warnings and Precautions (5.3), Nonclinical Toxicology (13.1)]*.

Males

Because of its mutagenic potential, males should be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir tablets *[see Dosage and Administration (2.6), Warnings and Precautions (5.3), Nonclinical Toxicology (13.1)]*.

Infertility

Valganciclovir tablets at the recommended doses may cause temporary or permanent female and male infertility *[see Warnings and Precautions (5.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Valganciclovir tablets are indicated for the prevention of CMV disease in pediatric heart transplant patients 4 months to 16 years of age at risk for developing CMV disease *[see Indications and Usage (1.2), Dosage and Administration (2.2)]*.

Study 1 was a safety and pharmacokinetic study in pediatric solid organ transplant patients (kidney, liver, heart, and kidney/pancreas). Valganciclovir tablets was administered once daily within 10 days of transplantation, for a maximum of 100 days post-transplantation.

The size of valganciclovir tablets for the prevention of CMV disease in pediatric heart transplant patients 4 month to 16 years of age is based on two studies (Study 2 described above and Study 3) that were supported by population pharmacokinetic modeling *[see Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

Study 3 was a pharmacokinetic and safety study of valganciclovir tablets administered to heart transplant patients less than 4 months of age who received a single dose of valganciclovir oral solution on each of two consecutive days. A physiologically based pharmacokinetic (PBPK) model was developed based on the available pharmacokinetic data from pediatric and adult patients to support dosing in heart transplant patients less than 1 month of age. Because of the uncertainty in model predictions for neonates, valganciclovir tablets is not indicated for prophylaxis in this age group.

The safety and efficacy of valganciclovir tablets have not been established in children for prevention of CMV disease in pediatric liver transplant patients, in kidney transplant patients less than 4 months of age, in heart transplant patients less than 1 month of age, in pediatric AIDS patients with CMV retinitis, and in infants with congenital CMV disease.

A pharmacokinetic and pharmacodynamic evaluation of valganciclovir for oral solution was performed in 24 neonates with congenital CMV infection involving the central nervous system. All patients were treated for 6 weeks with a combination of intravenous ganciclovir 6 mg per kg twice daily or valganciclovir oral solution at doses ranging from 14 mg per kg to 20 mg per kg twice daily. The pharmacokinetic results showed that in infants greater than 1 month of age, the exposure (AUC) to GCV from 16 mg per kg valganciclovir oral solution was comparable to ganciclovir systemic exposure (median AUC_{0-24} = 224 [range 18.8 to 38.5] mcg h/mL; n = 6) comparable to those obtained in infants up to 3 months of age from a 6 mg per kg dose of intravenous ganciclovir twice daily (AUC_{0-24} = 75.3 [range 2.4 to 89.7] mcg h/mL; n = 18) or the ganciclovir systemic exposures obtained in adults from a 900 mg dose of valganciclovir tablets twice daily. However, the efficacy and safety of intravenous ganciclovir administered twice daily for 6 weeks followed by 5 days per week for the next 18 weeks in infants with and no similar disease occurs in adults; therefore, efficacy cannot be extrapolated from intravenous ganciclovir use in adults.

Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Pale Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due to Roche Pale Alto LLC's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

8.5 Geriatric Use

Studies of valganciclovir tablets have not been conducted in adults older than 65 years of age. Clinical studies of valganciclovir tablets 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, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, and concomitant disease or other drug therapy. Valganciclovir is a prodrug of ganciclovir, which is substantially excreted by the kidneys, 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 Dosage and Administration (2.5), Warnings and Precautions (5.5), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Dose adjustments are recommended when administering valganciclovir tablets to patients with renal impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*.

For adult patients on hemodialysis (CrCl less than10 mL/min) valganciclovir tablets should not be used. Adult hemodialysis patients should use ganciclovir in accordance with the dose-modification table in the *Cytovene®-IV* complete product information section on DOSAGE AND ADMINISTRATION: Renal Impairment *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

Acute Oral Overdose With Valganciclovir Tablets: One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was 20 times the recommended dose and in the presence of impaired renal and hepatic function.

An overdose of valganciclovir tablets could also possibly result in increased renal toxicity *[see Dosage and Administration (2.5), Use in Specific Populations (8.6)]*.

Because ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of valganciclovir tablets *[see Clinical Pharmacology (12.3)]*. Adequate hydration should be maintained in a patient who has ingested a potentially toxic dose of valganciclovir tablets. Daily blood cell counts

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

Gastrointestinal toxicity: vomiting 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

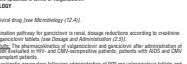
11 DESCRIPTION

Valganciclovir tablets, USP contains valganciclovir hydrochloride, USP 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.

Valganciclovir tablets, USP are available as a 450 mg tablet for oral administration. Each film-coated tablet contains 495 mg valganciclovir hydrochloride, USP equivalent to 450 mg valganciclovir, USP. Valganciclovir is a racemic mixture of two stereoisomers, microcrystalline cellulose, povidone and stearic acid. The tablets are coated with Opadry Pink which contains hypromellose, iron oxide red, polyethylene glycol, polysorbate 80 and titanium dioxide.

Valganciclovir hydrochloride, USP is a white to off-white powder, slightly hygroscopic with a molecular formula of $C_{14}H_{22}ClN_5O_5$ and a molecular weight of 397.82. It is freely soluble in water and dimethylsulfoxide (DMSO). USP is L-Valine, 2-[[2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl]methoxy]-3-hydroxypropyl ester, monohydrochloride. Valganciclovir hydrochloride, USP is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25°C at a pH of 7 and an n-octanol/water partition coefficient of 0.0005 at pH 7. The pKa for valganciclovir hydrochloride, USP is 7.5.

The chemical structure of valganciclovir hydrochloride, USP is:



HCl

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Valganciclovir is an antiviral drug [see Microbiology (12.4)].

12.3 Pharmacokinetics

Because the major elimination pathway for ganciclovir is renal, dosage reductions according to creatinine clearance are required for valganciclovir tablets *[see Dosage and Administration (2.5)]*.

Pharmacokinetic data for the pharmacokinetics of valganciclovir and ganciclovir after administration of valganciclovir tablets have been included in HIV- and CMV-seropositive patients, patients with renal impairment and CMV retinitis, and in solid organ transplant patients.

The ganciclovir pharmacokinetic parameters following administration of 900 mg valganciclovir tablets and 5 mg per kg intravenous ganciclovir and 1000 mg three times daily oral ganciclovir in HIV-positive/CMV-positive patients are summarized in **Table 10**.

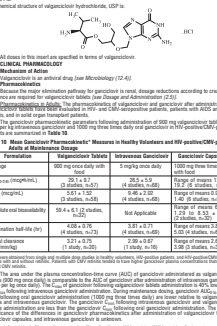
Table 10 Mean Ganciclovir Pharmacokinetic[a] Measures in Healthy Volunteers and HIV-positive/CMV-positive Adults at Maintenance Dosage

Formulation	Valganciclovir Tablets	Intravenous Ganciclovir	Ganciclovir Capsules
Dosage	900 mg once daily with food	5 mg/kg once daily	1000 mg three times daily with food
AUC_{0-24} (mcg/mL•hr)	29.3 ± 9.7 (3 studies, n=37)	35.5 ± 5.9 (4 studies, n=68)	Range of means: 12.3 to 30.4 (4 studies, n=80)
C_{max} (mcg/mL)	3.61 ± 1.52 (3 studies, n=58)	8.46 ± 2.02 (4 studies, n=68)	Range of means: 2.35 to 14.45 (8 studies, n=94)
Absolute oral bioavailability (%)	59.4 ± 6.1 (2 studies, n=20)	Not Applicable	Range of means: 6.92 ± 1.39 to 8.53 ± 1.53 (2 studies, n=20)
Elimination half-life (hr)	4.08 ± 0.76 (4 studies, n=73)	3.81 ± 0.71 (4 studies, n=68)	Range of means 3.86 to 5.05 (4 studies, n=81)
Renal clearance (mL/min/kg)	3.21 ± 0.75 (1 study, n=26)	2.99 ± 0.67 (1 study, n=18)	Range of means 2.67 to 3.60 (4 studies, n=26)

[a]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 systemic exposure than those without CMV retinitis.

The area under the plasma concentration-time curve (AUC) of ganciclovir administered as valganciclovir tablets (900 mg once daily) is comparable to the AUC of ganciclovir after administration of intravenous ganciclovir (5 mg per kg once daily). The ganciclovir C_{max} following valganciclovir administration is approximately 40% of the C_{max} following intravenous ganciclovir administration. During maintenance dosing, ganciclovir $AUC_{0-24\ hrs}$ and C_{max} following oral ganciclovir administration (1000 mg three times daily) are lower relative to valganciclovir tablets and intravenous ganciclovir. The ganciclovir C_{max} following intravenous ganciclovir and valganciclovir tablets administration are less than the ganciclovir C_{max} following oral ganciclovir administration. The clinical relevance of the observed differences in ganciclovir pharmacokinetics after administration of valganciclovir tablets, ganciclovir capsules, and intravenous ganciclovir is unknown.

Figure 1 Ganciclovir Plasma Concentration Time Profiles in HIV-positive/CMV-positive Patients[a]



[a]Plasma concentration-time profiles for ganciclovir (GCV) from valganciclovir (VGCV) and intravenous ganciclovir were obtained from population pharmacokinetic simulations. Plasma concentrations for GCV from oral GCV were from a population pharmacokinetic model. Area under the curve profiles for oral ganciclovir are based on a multiple-dose study (n=24) in HIV-positive CMV-positive patients without CMV retinitis.

In solid organ transplant recipients, the mean systemic exposure to ganciclovir was 1.7x higher following administration of 900 mg valganciclovir tablets once daily versus 1000 mg ganciclovir capsules three times daily, based on the comparison of ganciclovir AUC values in the heart and liver transplant populations. The systemic ganciclovir exposures obtained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetic evaluation (see **Table 11**).

Table 11 Mean Ganciclovir Pharmacokinetic Measures by Organ Transplant Type

Parameter	Ganciclovir Capsules	Valganciclovir Tablets
Dosage	1000 mg three times daily with food	900 mg once daily with food
Heart Transplant Recipients	N=13	N=17
AUC_{0-24h} (mcg•hr/mL)	26.6 ± 11.6	46.2 ± 11.8
C_{max} (mcg/mL)	1.4 ± 0.5	4.9 ± 1.1
Elimination half-life (hr)	5.47 ± 2.84	6.58 ± 5.90
Liver Transplant Recipients	N=33	N=75
AUC_{0-24h} (mcg•hr/mL)	24.9 ± 10.2	48 ± 16.1
C_{max} (mcg/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=36
AUC_{0-24h} (mcg•hr/mL)	31.3 ± 10.3	48.2 ± 14.6
C_{max} (mcg/mL)	1.5 ± 0.5	5.3 ± 1.5
Elimination half-life (hr)	9.44 ± 4.37	6.77 ± 1.25

* Includes kidney-pancreas

The pharmacokinetic parameters of ganciclovir following 200 days of valganciclovir tablets administration in high-risk kidney transplant patients were similar to those previously reported in solid organ transplant patients who received valganciclovir tablets for 100 days.

In a pharmacokinetic study in liver transplant patients, the ganciclovir $AUC_{0-24\ hrs}$ achieved with 900 mg valganciclovir tablets once daily (AUC = 48 ± 16.1 mcg•hr/mL, n = 75) was comparable to the exposure achieved with 5 mg per kg intravenous ganciclovir (mean AUC = 27.5 mcg•hr/mL, n = 24).

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 valganciclovir tablets following administration with food was approximately 60% (3 studies, n=18; n=18; n=20). Valganciclovir is rapidly and extensively converted to ganciclovir in the intestinal wall and liver within 5 hours. Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir tablets was demonstrated only under fed conditions. Systemic exposure to the prodrug, valganciclovir, is transient and low, and the $AUC_{0-\infty}$ and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Food Effects: When valganciclovir tablets were administered with a high fat meal containing approximately 600 total calories (31.1 g fat, 51.6 g carbohydrate and 22.2 g protein) at a dose of 875 mg once daily (n=9) in 19 HIV-positive subjects, the steady-state ganciclovir AUC increased by 30% (90% CI 12% to 51%), and the C_{max} increased by 14% (90% CI -1% to 32%) compared to administration of valganciclovir tablets in the fasting state. Valganciclovir tablets should be administered with food *[see Dosage and Administration (2.1)]*.

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% and the steady-state volume of distribution of ganciclovir was 0.703 ± 0.134 L/kg (n=08).

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

Metabolism: Valganciclovir is partially 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 in plasma, urine, or feces.

Elimination: The major route of elimination of ganciclovir is by renal excretion as ganciclovir through glomerular filtration and tubular secretion. Following oral administration of valganciclovir tablets, ganciclovir is

The terminal half-life ($t_{1/2}$) of ganciclovir following oral administration of valganciclovir 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=68). In heart, kidney, kidney-pancreas, and liver transplant patients, the terminal elimination half-life of ganciclovir following oral administration of valganciclovir tablets were 6.48 ± 1.38 hours, and following oral administration of ganciclovir capsules was 6.56 ± 3.62 hours.

Renal Impairment

Renal Impairment: The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir tablets were evaluated in 24 HIV-positive adults with renal impairment.

Table 12 Pharmacokinetics of Ganciclovir from a Single Oral Dose of 900 mg Valganciclovir Tablets

Estimated Creatinine Clearance (mL/min)	N	$AUC_{0-\infty}$ (mcg•h/mL) Mean ± SD	AUC_{0-24} (mcg•h/mL) Mean ± SD	C_{max} (mcg/mL) Mean ± SD	$t_{1/2}$ (hours) Mean ± SD
51–70	6	249 ± 99	49.5 ± 22.4	4.85 ± 1.4	
21–50	6	138 ± 44	41.5 ± 9.3	10.2 ± 4.4	
11–20	6	45 ± 11	22.5 ±6	21.8 ± 5.2	
≤10	6	13.8 ± 8	398 ±66	57.3 ± 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.

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% following valganciclovir tablets administration. Adult patients receiving hemodialysis CrCl less than 10 mL/min cannot use valganciclovir tablets because there is no data available to support safe dosing. For these patients is less than 450 mg *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*.

Pharmacokinetics in Pediatric Patients: The pharmacokinetics of ganciclovir were evaluated following the administration of valganciclovir tablets to 9 pediatric solid organ transplant patients aged 4 months to 16 years. In this study, patients received oral doses of valganciclovir (either valganciclovir for oral solution or tablets) to produce exposure equivalent to an adult dose of 900 mg valganciclovir tablets *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

The pharmacokinetic parameters were similar across organ types and age ranges. Based on a population pharmacokinetic evaluation, clearance is influenced by both body weight and renal function, while the central and peripheral volumes of distribution are influenced by body weight. The ganciclovir clearance in a 2 kg child with a total clearance less 5.2 L/hr (38.5 mL/min) for a patient with creatinine clearance of 70.4 mL/min. The mean ganciclovir Cmax, AUC and half-life by age and organ type in studies using the pediatric valganciclovir dosing algorithm are listed in Table 13. Relative to adult transplant patients (Table 11), AUC values in pediatric patients were somewhat increased, but were within the range considered safe and effective in adults.

Table 13 Ganciclovir Pharmacokinetics by Age in Pediatric Solid Organ Transplant Patients

		Age Group			
Organ	PK Parameter mean (SD)	4 months to < 2 years	≥ 2 to < 12 years	≥ 12 years
	N	6	2	4
Heart (N=26)	AUC_{0-24} (mcg.h/mL)	55.4 (20.8)	58.6 (21)	60.6 (25)
	C_{max} (mcg/mL)	8.3 (2.5)	12.5 (1.2)	9.5 (3.5)
	$t_{1/2}$ (h)	3.8 (1.7)	2.8 (0.9)	4.9 (0.8)
	N	2	10[a]	19
Kidney (N=31)	AUC_{0-24} (mcg.h/mL)	67.6 (10)	55.9 (13.1)	47.8 (12.4)
	C_{max} (mcg/mL)	10.4 (5.4)	8.7 (2.1)	7.2 (2.1)
	$t_{1/2}$ (h)	4.5 (3.5)	4.8 (1)	6 (1.3)
	N	9	8	3
Liver (N=17)	AUC_{0-24} (mcg.h/mL)	69.9 (37)	59.4 (8.1)	35.4 (2.8)
	C_{max} (mcg/mL)	11.9 (7.1)	8.5 (2.3)	5.5 (1.1)
	$t_{1/2}$ (h)	2.8 (1.5)	3.8 (0.7)	4.4 (0.2)

N= number of patients

[a] Ganciclovir PK parameters were estimated by using population pharmacokinetic modeling.

* There was one subject in this age group who required both a kidney and liver transplant. The pharmacokinetic profile for this subject has not been included in this table as it is not possible to determine whether the effects observed are from the kidney or liver transplant.
* The pharmacokinetic profiles for two subjects in this age group who received kidney transplants have not been included in this table as the data were determined to be non-evaluable.

Pharmacokinetics in Geriatric Patients: The pharmacokinetic characteristics of valganciclovir tablets in elderly patients have not been established. Because elderly individuals frequently have a reduced glomerular filtration rate, renal function should be assessed before and during administration of valganciclovir tablets *[see Dosage and Administration (2.5), Use in Specific Populations (8.5)]*.

Drug Interactions: *In* vivo drug-drug interaction studies were not conducted with valganciclovir. However, because ganciclovir is eliminated by glomerular filtration and tubular secretion, interactions associated with ganciclovir will be expected for valganciclovir tablets *[see Drug Interactions (7)]*.

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and other renally eliminated drug following concomitant administration of valganciclovir 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 14 and **Table 15** provide a listing of established drug interaction studies with ganciclovir. **Table 14** provides the effects of coadministered drug on ganciclovir plasma pharmacokinetic parameters, whereas **Table 15** provides the effects of ganciclovir on plasma pharmacokinetic parameters of co-administered drug.

Table 14 Results of Drug Interaction Studies With Ganciclovir: Effects of Coadministered Drug on Ganciclovir Pharmacokinetic Parameters

Coadministered Drug	Ganciclovir Dosage	N	Ganciclovir Pharmacokinetic (PK) Parameter
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC_{0-8} ↓ 14% ± 27% (range: -12% to 25%) AUC^{ss} ↑ 9% ± 16% (range: -14% to 299%) Ganciclovir renal clearance ↓ 22 ± 20% (range: -54% to -4%)
Probenecid 500 mg every 6 hours	1000 mg every 8 hours	10	No effect on ganciclovir PK parameters observed
Mycophenolate Mofetil (MMF) 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)
Doravirine 200 mg every 12 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	12	AUC ↓ 21 ± 17% (range: -44% to 5%)
Doravirine 200 mg every 12 hours administered 4 hours after ganciclovir	1000 mg every 8 hours	12	No effect on ganciclovir PK parameters observed
	IV ganciclovir 5 mg/kg single dose	11	No effect on ganciclovir PK parameters observed
Doravirine 200 mg every 12 hours administered 4 hours after ganciclovir	IV ganciclovir 5 mg/kg single dose	11	No effect on ganciclovir PK parameters observed
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Ganciclovir renal clearance ↓ 16.3% Half-life ↑ 13%

Table 15 Results of Drug Interaction Studies With Ganciclovir: Effects of Ganciclovir on Pharmacokinetic Parameters of Coadministered Drug

Coadministered Drug	Ganciclovir Dosage	N	Coadministered Drug Pharmacokinetic (PK) Parameter
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC_{0-8} ↓ 13 ± 27% (range: -11% to 74%)
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)
Doravirine 200 mg every 12 hours when administered 2 hours after ganciclovir	1000 mg every 8 hours	12	$AUC_{0-\infty}$ ↑ 5.11 ± 3.14% (range: 10% to 480%)
Doravirine 200 mg every 12 hours	IV ganciclovir 5 mg/kg single dose	11	AUC_{0-12} ↑ 70 ± 40% (range: 3% to 131%) C_{max} ↑ 49 ± 48% (range: -20% to 125%)
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	AUC_{0-12} ↑ 50 ± 28% (range: 22% to 110%) C_{max} ↑ 36 ± 38% (range: -27% to 94%)

Increase (↑)/ decrease (↓) in C_{max}

Other potential drug interactions

Since ganciclovir is excreted through the kidney via glomerular filtration and active secretion *[see Pharmacokinetics (12.3)]*, coadministration of valganciclovir with administration drugs that share the tubular secretion pathway, such as nucleoside/nucleo-reverse transcriptase inhibitors, may change the plasma concentrations of valganciclovir and the coadministered drug.

Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Pale Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due to Roche Pale Alto LLC's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with valganciclovir tablets. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a carcinogenic hazard.

Ganciclovir was carcinogenic in the mouse at oral doses that produced exposures approximately 0.1 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, testes (interstitial cell), mammary gland, lymphoreticular system, and harderian gland in both sexes in female. At the lower dose, a slightly increased incidence of tumors of the testes, interstitial cell and adrenal cortical 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 and Precautions (5.2)]*. Ganciclovir caused decreased mating behavior, decreased fertility, and increased embryo/fetal mortality in male mice and hypospermatogenesis in mice at doses that produced an exposure approximately 3.7x the mean drug exposure in humans following the dose of 5 mg per 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. Ganciclovir caused testicular tubular degeneration in mice, rabbits, and dogs. In mice, this effect was observed at lower doses but irreversible at higher doses. It is considered likely that ganciclovir (and valganciclovir) could cause temporary or permanent inhibition of human spermatogenesis.

14 CLINICAL STUDIES

14.1 Adult Patients

Indication Therapy of CMV Retinitis: In one randomized open-label controlled study, 160 patients with AIDS and newly diagnosed CMV retinitis were randomized to receive treatment with either valganciclovir tablets (900 mg twice daily for 21 days, then 900 mg once daily for 7 days) or with intravenous ganciclovir solution (5 mg per kg twice daily for 21 days, then 5 mg per kg once daily for 7 days). Study participants were: male (91%), Caucasian (71%), median age 38 years, median CD4 cell count 10 cells/mm3, median HIV-RNA 4.9 log10, and the median CD4 cell count was 22 cells/mm3. A determination of CMV retinitis progression was by the masked review of retinal photographs taken at baseline and Week 4 was the primary outcome measurement of the 2-week induction therapy. **Table 16** provides the outcomes at 4 weeks.

Table 16 Week 4 Masked Review of Retinal Photographs in CMV Retinitis Study

	Intravenous Ganciclovir	Valganciclovir Tablets
Determination of CMV retinitis progression at Week 4	N=80	N=80
Progression	7	7
Non-progressor	63	64
Death	2	1
Discontinuations due to Adverse Events	1	1
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 valganciclovir tablets for maintenance therapy. In one randomized controlled study, 103 patients with AIDS and CMV retinitis received open-label valganciclovir tablets after Week 4. However, the AUC for ganciclovir is similar following administration of 900 mg valganciclovir tablets once daily and 5 mg/kg intravenous ganciclovir once daily. Although the ganciclovir C_{max} is lower following valganciclovir tablets administration compared to intravenous ganciclovir, it is higher than the C_{max} obtained following oral ganciclovir administration *[see Figure 1 in Clinical Pharmacology (12.3)]*. Therefore, use of valganciclovir tablets 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, or Liver Transplantation: A double blind, double-dummy active comparator study was conducted in 372 heart, liver, kidney, or kidney-pancreas transplant patients at high risk for CMV disease (D+/R-). Patients were randomized (2 valganciclovir tablets 1 oral placebo) to receive either valganciclovir tablets (900 mg once daily) or oral ganciclovir (1000 mg three times a day) starting within 10 days post-transplant. Patients were followed for 100 days post-transplant for the occurrence of CMV disease, including CMV syndrome and/or tissue-invasive disease during the first 6 months post-transplant was similar between the valganciclovir tablets 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 valganciclovir tablets group compared with the ganciclovir group. These results are summarized in **Table 19**.

Mortality at six months was 3.7% (9/244) in the valganciclovir tablets group and 1.6% (2/125) in the oral ganciclovir group.

Table 19 Percentage of Patients With CMV Disease, Tissue-Invasive CMV Disease or CMV syndrome by Organ Type: Endpoint Committee, 6 Month ITT Population

Organ	CMV Disease[1]		Tissue-Invasive CMV Disease		CMV Syndrome[2]	
	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)	12 % (14 / 118)	14 % (8 / 59)	8 % (9 / 118)	3 % (2 / 59)
Kidney (n=120)	6 % (5 / 81)	5 % (3 / 39)	5 % (4 / 81)	3 % (1 / 39)	5 % (4 / 81)	3 % (1 / 39)
Heart (n=56)	6 % (2 / 35)	10 % (2 / 21)	0 % (0 / 35)	5 % (1 / 21)	1 % (1 / 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 = valganciclovir

[1] Number of patients with CMV disease = Number of patients with tissue-invasive CMV disease or CMV syndrome

[2] CMV syndrome was defined as evidence of CMV viremia accompanied with fever (less or equal to 38°C on two or more occasions separated by at least 24 hours within a 7-day period and one or more of the following: malaise, leukopenia, atypical lymphocytosis, thrombocytopenia, and elevation of hepatic transaminases

Prevention of CMV Disease in Kidney Transplantation: A double-blind, placebo-controlled study was conducted in 339 kidney transplant patients at high risk for CMV disease (D+/R-) to assess the efficacy and safety of extending valganciclovir tablets prophylaxis to 200 days post-transplant. Patients were randomized (2 valganciclovir tablets 1 oral placebo) to receive valganciclovir tablets (900 mg once daily) within 10 days of transplantation either until Day 100 post-transplant or until Day 200 post-transplant followed by 100 days of placebo. Extending CMV prophylaxis with valganciclovir tablets 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 (primary endpoint). These results are summarized in **Table 20**.

Table 20 Percentage of Kidney Transplant Patients With CMV Disease, Tissue-Invasive CMV Disease or CMV Syndrome, 12 Month ITT Population

	CMV Disease[1]		Tissue-Invasive CMV Disease		CMV Syndrome[2]	
	VGCV (N=163)	VGCV (N=155)	VGCV (N=163)	VGCV (N=155)	VGCV (N=163)	VGCV (N=155)
Cases	36.8% (60/163)	16.8% (26/155)	1.8% (3/163)	0.6% (1/155)	33% (53/163)	16.1% (25/155)

VGCV = valganciclovir.

[1] Number of patients with CMV disease = Number of patients with tissue-invasive CMV disease or CMV syndrome

[2] CMV syndrome was defined as evidence of CMV viremia accompanied with at least one of the followings: fever (greater than or equal to 38°C), severe malaise, leukopenia, atypical lymphocytosis, thrombocytopenia, and elevation of hepatic transaminases

* Two patients in the 100 day group had both tissue-invasive CMV disease and CMV syndrome; however these patients are counted as having only tissue-invasive CMV disease.

The percentage of kidney transplant patients with CMV disease at 24 months post-transplant was 38.7% (63/163) for the 100-day dosing regimen and 21.3% (33/155) for the 200-day dosing regimen.

14.2 Pediatric Patients

Prevention of CMV in Pediatric Heart, Kidney, or Liver Transplantation: Sixty-three children, 4 months to 16 years of age, who had a solid organ transplant (kidney 34, liver 11, heart 12, and kidney/liver 1) and were at risk for developing CMV disease, were enrolled in an open-label, safety, and pharmacokinetic study of oral valganciclovir tablets administered once daily within 10 days of transplantation and continued for a maximum of 100 days after transplant until a maximum of 100 days post-transplant. The daily doses of valganciclovir tablets were calculated at each study visit based on body surface area and a modified creatinine clearance *[see Dosage and Administration (2.2)]*.

The pharmacokinetics of ganciclovir were similar across organ transplant types and age ranges. The mean daily ganciclovir exposures in pediatric patients were somewhat increased relative to those in adult solid organ transplant patients receiving valganciclovir tablets 900 mg once daily, but were within the range considered safe and effective in adults. The incidence of CMV disease, CMV syndrome or tissue-invasive CMV disease was reported within the first six months post-transplantation.

**Pediatric use information for pediatric kidney transplant patients ages 4 months to 16 years and for pediatric heart transplant patients ages 1 to less than 4 months is approved for Roche Pale Alto LLC's VALCYTE (valganciclovir hydrochloride) tablets. However, due to Roche Pale Alto LLC's marketing