PRODUCT MONOGRAPH

PR MYLAN-VALGANCICLOVIR

Valganciclovir Tablets, USP
450 mg (as valganciclovir hydrochloride)

USP Standard

Antiviral Agent

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Valganciclovir Tablets, USP
450 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Film-Coated Tablet / 450 mg valganciclovir (as valganciclovir hydrochloride)	None. *For a complete listing of non-medicinal ingredients see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride) is indicated for adult patients:

- For the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

- For the prevention of cytomegalovirus (CMV) disease in solid organ transplant patients who are at risk. This indication is based on a double-blind, double-dummy, active comparator study in heart, liver, kidney and kidney-pancreas transplant patients at high risk for CMV disease (donor CMV seropositive/recipient seronegative [D+/R-] (see WARNINGS and PRECAUTIONS and CLINICAL TRIALS for information on specific solid organ transplant subgroups)).

CONTRAINDICATIONS

- MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride) is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any component of the product (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- Due to the similarity of the chemical structure of valganciclovir and that of acyclovir and valacyclovir, a cross-hypersensitivity reaction between these drugs is possible.

WARNINGS AND PRECAUTIONS

General

The clinical toxicity of valganciclovir hydrochloride includes granulocytopenia, anemia and thrombocytopenia. In animal and *in-vitro* studies ganciclovir was mutagenic, carcinogenic, teratogenic and caused aspermatogenesis. Therefore it should be considered a potential teratogen and carcinogen in humans. MYLAN-VALGANCICLOVIR is indicated for use only in immunocompromised patients, where the potential benefit outweighs the risks. Safety and efficacy of valganciclovir hydrochloride have not been established for congenital or neonatal CMV disease; nor for the treatment of established CMV disease other than retinitis; nor for use in non-immunocompromised individuals.

Strict adherence to dosage recommendations is essential to avoid overdose.

Specific Solid Organ Transplant (SOT) Subgroups

Liver: In an unpowered subanalysis of the SOT study, PV16000, there was a higher incidence of tissue-invasive CMV disease in liver transplant patients treated with valganciclovir hydrochloride compared with the oral ganciclovir group (see CLINICAL TRIALS). The clinical significance of this is unknown.

Other: The safety and efficacy of valganciclovir hydrochloride for the prevention of CMV disease in other SOT patients not mentioned in the INDICATIONS & CLINICAL USE section, such as lung transplant patients, have not been established.

Carcinogenesis and Mutagenesis

No long-term carcinogenicity studies have been conducted with valganciclovir. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen (see TOXICOLOGY: Carcinogenesis, Mutagenesis for discussion on animal data).

Hematologic

MYLAN-VALGANCICLOVIR 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 80 g/L. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with valganciclovir hydrochloride tablets (and ganciclovir) (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION: Dosing Considerations).

MYLAN-VALGANCICLOVIR should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or 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. Colony-stimulating factors have been shown to increase neutrophil counts in patients receiving ganciclovir for treatment of CMV retinitis.

Renal

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. **If renal function is impaired, dosage adjustments are required for MYLAN-VALGANCICLOVIR**. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment).

Patients undergoing hemodialysis:

Dosage adjustment is necessary for patients on hemodialysis (CrCl < 10mL/min) (see DOSAGE AND ADMINISTRATION: Dosing Considerations and Dosage Adjustment and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Hemodialysis).

Sexual Function/Reproduction

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 TOXICOLOGY: Carcinogenesis). It is considered probable that in humans, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

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 MYLAN-VALGANCICLOVIR (see TOXICOLOGY: Carcinogenesis, Mutagenesis).

In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valganciclovir should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see SPECIAL HANDLING INSTRUCTIONS).

For further discussion on animal data see TOXICOLOGY: Reproduction.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. MYLAN-VALGANCICLOVIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see TOXICOLOGY: Reproduction).

Nursing Women: It is not known whether ganciclovir or valganciclovir is excreted in human milk. However, many drugs are excreted in human milk and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely. Mothers should be instructed to discontinue the drug or discontinue nursing if they are receiving MYLAN-VALGANCICLOVIR.

Pediatrics: Safety and efficacy of valganciclovir hydrochloride in pediatric patients have not been established. The use of MYLAN-VALGANCICLOVIR in children warrants extreme caution due to the probability of long-term carcinogenicity and reproductive toxicity. Administration to children should be undertaken only after careful evaluation and only if the potential benefits of treatment outweigh these considerable risks.

Geriatrics (> *65* years of age): The pharmacokinetic profiles of valganciclovir hydrochloride 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 MYLAN-VALGANCICLOVIR (see DOSAGE AND ADMINISTRATION).

Clinical studies of valganciclovir hydrochloride 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. Valganciclovir hydrochloride 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 WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Insufficiency and DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment).

Monitoring and Laboratory Tests

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving MYLAN-VALGANCICLOVIR (see ADVERSE REACTIONS), 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. In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, it is recommended that treatment with hematopoietic growth factors and/or dose interruption be considered. Increased serum creatinine levels have been observed in trials evaluating valganciclovir hydrochloride

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: Dosage Adjustment, Renal Impairment).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

Valganciclovir is a prodrug of ganciclovir, and is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir usage can therefore be expected to occur with MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride). All of the adverse events observed in clinical studies of valganciclovir hydrochloride have been previously observed with ganciclovir.

Treatment of CMV Retinitis in AIDS Patients

The safety profiles of valganciclovir and intravenous ganciclovir during 28 days of randomized study phase (21 days induction dose and 7 days maintenance) in 79 patients each were comparable. The most frequently reported events were diarrhea, neutropenia and pyrexia. More patients reported diarrhea, oral candidiasis, headache and fatigue in the oral valganciclovir arm, and nausea and injection site related events in the intravenous ganciclovir arm (see Table 1).

Table 1: Percentage of Patients with Selected Adverse Events Occurring During the Randomized Study Phase

Adverse event	Valganciclovir arm N=79	Intravenous ganciclovir arm N=79
Diarrhea	19%	10%
Oral candidiasis	14%	6%
Headache	9%	5%
Fatigue	8%	5%
Nausea	9%	14%
Venous phlebitis and thrombophlebitis	-	6%
Pyrexia	14%	13%
Neutropenia	14%	13%

Table 2 shows the adverse events regardless of seriousness and drug relationship with an

incidence of ≥ 5% obtained either from trials looking at the use of valganciclovir in patients with CMV retinitis or the use of valganciclovir in solid organ transplant patients.

The information in Table 2 pertaining to the patients with CMV retinitis is based on two clinical trials (n=370) where patients with CMV retinitis received valganciclovir hydrochloride at a dosage of 900 mg twice daily or once daily, corresponding to the induction or maintenance regimen, respectively.

A total of 370 patients received maintenance therapy with valganciclovir hydrochloride tablets 900 mg once daily, with approximately 252 (68%) of these patients receiving valganciclovir hydrochloride tablets for more than nine months (maximum duration was 36 months).

The most frequently reported adverse events (% of patients), regardless of seriousness and drug relationship in patients taking valganciclovir hydrochloride reported from these two clinical trials (n=370) were diarrhea (41%), pyrexia (31%), nausea (30%), neutropenia (27%) and anemia (26%). The majority of the adverse events were of mild or moderate intensity. The most frequently reported adverse reactions (% of patients), regardless of seriousness that were considered related (remotely, possibly or probably) to valganciclovir hydrochloride by the investigator were neutropenia (23%), anemia (17%), diarrhea (13%) and nausea (10%).

Prevention of CMV Disease in Solid Organ Transplantation

Table 2 shows the adverse events regardless of seriousness 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 valganciclovir (N=244) or oral ganciclovir (N=126) starting within 10 days of transplantation until Day 100 post-transplant. The most frequently reported adverse events (% of patients), regardless of seriousness and drug relationship in patients taking valganciclovir hydrochloride reported in this clinical trial (n=244) were diarrhea (30%), tremors (28%), graft rejection (24%), nausea (23%), headache (22%), edema lower limb (21%), constipation (20%), back pain (20%), insomnia (20%), hypertension (18%) and vomiting (16%). These events were also seen with oral ganciclovir at a comparable incidence. The majority of adverse events were of mild or moderate intensity.

The most frequently reported adverse reactions (% of patients), regardless of seriousness, that were considered related (remotely, possibly or probably) to valganciclovir hydrochloride by the investigator in solid organ transplant patients treated until Day 100 post-transplant were leukopenia (9%), diarrhea (7%), nausea (6%), neutropenia (5%). Leukopenia and neutropenia were more common in patients taking valganciclovir hydrochloride compared to the oral ganciclovir arm (4% and 1%, respectively).

Table 2: Percentage of Patients with Adverse Events Occurring in ≥ 5% of Patients in either CMV Retinitis or Solid Organ Transplantation Clinical Trials with Valganciclovir or Ganciclovir

	Patients with CMV Retinitis (Studies WV15376 and WV15705)	Solid Organ Transplant Patients (Study PV16000) (Dosing until Day 100 Post-Transplant)	
System Organ Class	**Valganciclovir N = 370 (%)**	**Valganciclovir N = 244 (%)**	**Oral Ganciclovir N = 126 (%)**
Blood and lymphatic system disorders			
Neutropenia	27	8	3
Anemia	26	12	15
Thrombocytopenia	6	5	5
Leukopenia	5	14	7
Lymphadenopathy	5	--	--
Eye disorders			
Retinal detachment	15	--	--
Vision blurred	7	1	4
Vitreous floaters	5	--	--
Macular edema	5	--	--
Gastrointestinal disorders			
Diarrhea Nausea	41	30	29
Vomiting	30	23	23
Abdominal pain	21	16	14
Constipation	15	14	14
Abdominal pain upper	8	20	20
Dyspepsia	6	9	6
Abdominal distention	4	12	10
Ascites	3	6	6
	--	9	6
General disorders and administration site disorders			
Pyrexia	31	13	14
Fatigue	21	13	15
Edema lower limb	6	21	16
Influenza-like illness	6	3	1
Weakness	5	6	6
Pain	3	5	7
Edema	1	11	9
Edema peripheral	1	6	7
Hepatobiliary disorders			
Hepatic function abnormal	5	9	11
Immune system disorders			
Graft rejection	--	24	30

	Patients with CMV Retinitis (Studies WV15376 and WV15705)	Solid Organ Transplant Patients (Study PV16000) (Dosing until Day 100 Post-Transplant)	
System Organ Class	**Valganciclovir N = 370 (%)**	**Valganciclovir N = 244 (%)**	**Oral Ganciclovir N = 126 (%)**
Infections and infestations			
Oral candidiasis	24	3	3
Influenza	15	--	--
Upper respiratory tract infection	12	7	7
Pharyngitis/nasopharyngitis	12	4	8
Sinusitis	12	3	--
Bronchitis	11	--	1
Pneumonia	9	4	2
Pneumocystis carnii pneumonia	6	--	--
Urinary tract infection	6	11	9
Candida	5	1	1
Esophageal candidiasis	5	--	--
Injury, poisoning and procedural complications			
Wound drainage increased	--	5	9
Wound dehiscence	< 1	5	6
Investigations			
Weight decrease	11	3	3
Blood creatinine increased	1	10	14
Metabolism and nutrition disorders			
Appetite decreased	9	4	5
Dehydration	7	5	6
Cachexia	6	--	--
Anorexia	5	3	--
Hypokalemia	3	8	8
Hyperkalemia	1	14	14
Hypomagnesemia	1	8	8
Hyperglycemia	1	6	7
Hypocalcemia	1	4	6
Hypophosphatemia	< 1	9	6
Musculoskeletal and connective tissue disorders			
Back pain	8	20	15
Arthralgia	8	7	7
Pain in limb	4	5	7
Muscle cramps	3	6	11
Neoplasms, benign, malignant and unspecified			
Kaposi's sarcoma	5	--	--

	Patients with CMV Retinitis (Studies WV15376 and WV15705)	Solid Organ Transplant Patients (Study PV16000) (Dosing until Day 100 Post-Transplant)	
System Organ Class	**Valganciclovir N = 370 (%)**	**Valganciclovir N = 244 (%)**	**Oral Ganciclovir N = 126 (%)**
Nervous system disorders			
Headache	22	22	27
Insomnia	16	20	16
Dizziness (excluding vertigo)	11	10	6
Peripheral neuropathy	9	1	1
Paresthesia	8	5	5
Anxiety	5	6	5
Tremors	2	28	25
Psychiatric disorders			
Depression	11	7	6
Renal and urinary disorders			
Dysuria	2	7	6
Renal impairment	1	7	12
Respiratory, thoracic and mediastinal disorders			
Cough Dyspnea	19	6	8
Productive cough	9	11	10
Nasal congestion	6	2	2
Sore throat	5	4	1
Rhinorrhea	5	3	5
Pleural effusion	3	4	6
	< 1	7	8
Skin and subcutaneous tissue disorders			
Dermatitis	22	4	5
Pruritus	8	7	4
Night sweats	8	3	4
Acne	< 1	4	6
Surgical and medical procedures			
Postoperative pain	2	13	7
Postoperative wound infection	2	11	6
Postoperative complications	1	12	8
Vascular disorders			
Hypertension	3	18	15
Hypotension	1	3	8

Serious adverse events considered related by the company to the use of valganciclovir

hydrochloride reported from these three clinical trials (n= 614) with a frequency of less than 5% and which are not mentioned in the two tables above, are listed below:

Bleeding complications: Potentially life-threatening bleeding associated with thrombocytopenia

Body as a whole: Valganciclovir hypersensitivity

Central and peripheral nervous system: Convulsion, psychotic disorder, hallucinations, confusion, agitation

Hemic and lymphatic system: Pancytopenia, bone marrow depression, aplastic anemia

Urogenital system: Decreased creatinine clearance

Experience with ganciclovir

Valganciclovir hydrochloride is rapidly converted to ganciclovir. Key adverse events reported with ganciclovir, and not mentioned above, are listed below. However, for a full listing of ganciclovir adverse reactions please refer to the current CYTOVENE product monograph.

Body as a whole - general disorders: asthenia, bacterial, fungal and viral infections, hemorrhage, malaise, mucous membrane disorder, photosensitivity reaction, rigors, sepsis.

Hepatic system disorders: hepatitis, jaundice.

Cardiovascular system disorders: arrhythmia (including ventricular arrhythmia), migraine, phlebitis, tachycardia, thrombophlebitis deep, vasodilatation.

Central and peripheral nervous system disorders: abnormal dreams, amnesia, ataxia, coma, dry mouth, emotional disturbance, hyperkinetic syndrome, hypertonia, libido decreased, myoclonic jerks, nervousness, somnolence, thinking abnormal.

Gastrointestinal system disorders: cholangitis, dysphagia, eructation, esophagitis, fecal incontinence, flatulence, gastritis, gastrointestinal disorder, gastrointestinal hemorrhage, mouth ulceration, pancreatitis, tongue disorder.

Hemic and lymphatic: eosinophilia, leukocytosis, splenomegaly.

Hepatic system disorders: hepatitis, jaundice.

Metabolic and nutritional disorders: blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood glucose decreased, blood lactic dehydrogenase increased, diabetes mellitus, hypoproteinemia.

Musculoskeletal system disorders: musculoskeletal pain, myasthenic syndrome.

Respiratory system disorders: sinus congestion.

Skin and appendages disorders: alopecia, dry skin, sweating increased, urticaria.

Special senses: amblyopia, blindness, earache, eye hemorrhage, eye pain, deafness, glaucoma, taste disturbance, tinnitus, vision abnormal, vitreous disorder.

Urogenital system disorders: hematuria present, impotence, renal failure, urinary frequency.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities reported with valganciclovir hydrochloride tablets in CMV retinitis studies and transplantation are listed below.

Table 3: Laboratory Abnormalities Reported in Two Clinical Studies in the Treatment of CMV Retinitis and One Clinical Study in Transplantation

Laboratory Abnormalities	CMV Retinitis Patients (WV15376 and WV15705)	Solid Organ Transplant Patients (PV16000)	
	Valganciclovir N = 370 (%)	Valganciclovir N = 244 (%)	Oral Ganciclovir N = 126 (%)
Anemia: Hemoglobin g/L			
<65	7	1	2
65 - <80	13	5	7
80 - <95	16	31	25
Neutropenia: ANC/µL			
<500	19	5	3
500 - <750	17	3	2
750 - <1000	17	5	2
Serum Creatinine: mg/dL			
>2.5	3	14	21
>1.5 - 2.5	12	45	47
Thrombocytopenia: Platelets/µL			
<25000	4	0	2
25000 - <50000	6	1	3
50000 - <100000	22	18	21

Severe neutropenia (ANC <500/µL) is seen more frequently in CMV retinitis patients (19%) undergoing treatment with valganciclovir than in solid organ transplant patients

receiving valganciclovir (5%) or oral ganciclovir (3%) until Day 100 post-transplant. There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 post- transplant with both valganciclovir and oral ganciclovir when compared to CMV retinitis patients. Impaired renal function is a feature common to solid organ transplantation patients.

Post-Market Adverse Drug Reactions

As valganciclovir hydrochloride is rapidly and extensively converted to ganciclovir, any adverse events associated with ganciclovir might also occur with MYLAN-VALGANCICLOVIR. Adverse reactions from post-marketing spontaneous reports with intravenous and oral ganciclovir not mentioned in any section above, and for which a causal relationship cannot be excluded are listed below:

- Anaphylaxis
- Decreased fertility in males

Adverse events that have been reported during the post-marketing period are consistent with those seen in clinical trials with valganciclovir hydrochloride and ganciclovir. For a full listing of ganciclovir post-marketing adverse events please refer to the current CYTOVENE product monograph.

DRUG INTERACTIONS

Overview

Drug Interaction Studies Conducted with Valganciclovir: Valganciclovir is rapidly and extensively converted to ganciclovir; therefore interactions associated with ganciclovir will be expected for MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride). In a rat *in situ* model of intestinal permeability, there was no interaction of valacyclovir, didanosine, nelfinavir, cyclosporine, omeprazole and mycophenolate mofetil with valganciclovir.

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 valganciclovir hydrochloride and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Drug-Drug Interactions

Table 4: 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 valganciclovir hydrochloride 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 administered with ganciclovir	1000 mg every 8 hours	12	No effect on ganciclovir PK parameters observed	No effect expected.
	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 valganciclovir hydrochloride 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.

Table 5: 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 valganciclovir hydrochloride 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.

Cyclosporine: There was no evidence that introduction of ganciclovir affects the pharmacokinetics of cyclosporine based on the comparison of cyclosporine trough concentrations. However, there was some evidence of increases in the maximum serum creatinine value observed following initiation of ganciclovir therapy.

Didanosine: Didanosine has been associated with pancreatitis. In three controlled trials, pancreatitis was reported in 2% of patients taking didanosine and CYTOVENE (ganciclovir sodium for injection) or ganciclovir capsules. The rates of pancreatitis were similar in the intravenous solution and capsule groups.

Other than laboratory abnormalities, concomitant treatment with zidovudine, didanosine, or zalcitabine did not appear to affect the type or frequency of reported adverse events, with the exception of moderately increased rates of diarrhea. Among patients taking CYTOVENE as ganciclovir sodium for injection or ganciclovir capsules, the diarrhea rates were 51% and 49% respectively with didanosine versus 39% and 35% respectively, without didanosine.

Imipenem-cilastatin: Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. MYLAN-VALGANCICLOVIR should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks.

Stavudine: No statistically significant pharmacokinetic interaction was observed when stavudine and oral ganciclovir were given in combination.

Other Medications: It is possible that drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia and germinal layers of skin and gastrointestinal mucosa may have additive toxicity when administered concomitantly with ganciclovir. In addition, toxicity may be enhanced when ganciclovir is coadministered with other drugs known to be associated with renal impairment. Therefore, drugs known to be myelosuppressive or associated with renal impairment, such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, doxorubicin, amphotericin B, trimethoprim/sulfamethoxazole combinations, other nucleoside analogues, or hydroxyurea, and pegylated interferons/ribavirin should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks.

Since ganciclovir is excreted through the kidney via glomerular filtration and active tubular secretion (seeACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Excretion), coadministration of valganciclovir with antiretroviral drugs that share the tubular secretion pathway, such as nucleos(t)ide reverse transcriptase inhibitors, may change the plasma concentrations of valganciclovir and/or the coadministered drug.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- **Caution - Strict adherence to dosage recommendations is essential to avoid overdose.**

- MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride) is administered orally, and should be taken with food (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Absorption). After oral administration, valganciclovir is rapidly and extensively converted into the active ingredient ganciclovir. The bioavailability of ganciclovir from valganciclovir hydrochloride is significantly higher than from oral ganciclovir. The dosage and administration of MYLAN-VALGANCICLOVIR tablets or oral solution as described below should be closely followed (see WARNINGS AND PRECAUTIONS: General and OVERDOSAGE).

- Dosage adjustment is necessary for patients on hemodialysis (CrCl < 10mL/min) (see WARNINGS AND PRECAUTIONS: General and Patients undergoing hemodialysis, DOSAGE AND ADMINISTRATION: Dosage Adjustment and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Hemodialysis).

- Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with valganciclovir hydrochloride tablets (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/μL, or the hemoglobin is less than 80 g/L, or the platelet count is less than 25,000/μL (see WARNINGS AND PRECAUTIONS: Hematologic, and Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

- Due to the frequency of leukopenia, granulocytopenia (neutropenia), anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia in patients taking valganciclovir hydrochloride, 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 cytopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment. Patients should have serum creatinine or creatinine clearance values followed carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION: Renal Impairment).

Recommended Dose For the Treatment of CMV Retinitis in Adult Patients with Normal Renal Function

Induction Treatment: For patients with active CMV retinitis, the recommended dosage is 900 mg twice a day (with food) for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see WARNINGS AND PRECAUTIONS: Hematologic).

Maintenance Treatment: Following induction treatment, or in patients with inactive CMV retinitis, the recommended dosage is 900 mg once daily (with food). Patients whose retinitis worsens may repeat induction treatment (see Induction Treatment).

Recommended Dose For the Prevention of CMV Disease in Adult Patients with Solid Organ Transplantation

For patients who have received a solid organ transplant, the recommended dose is 900 mg once daily (with food) starting within 10 days of transplantation and continuing until 100 days post-transplantation.

Evidence for safety and efficacy of valganciclovir hydrochloride for the prevention of CMV disease in solid organ transplant patients beyond the follow-up of 6 months post-transplant is not available.

Dosage Adjustment

Reduction of Dose: Dosage reductions in renally impaired patients are required for MYLAN-VALGANCICLOVIR (see Renal Impairment). Dosage reductions should also be considered for those with neutropenia, anemia and/or thrombocytopenia (see ADVERSE REACTIONS). MYLAN-VALGANCICLOVIR should not be administered in patients with severe neutropenia (ANC less than 500/μL), severe thrombocytopenia (platelets less than 25,000/μL), or severe anemia (hemoglobin less than 80 g/L).

Renal Impairment: Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance as shown in Table 6 below (see WARNINGS AND PRECAUTIONS: Renal and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Insufficiency).

The dose-reduction algorithm was based on predicted ganciclovir exposures. The range of exposures in renally impaired patients may be greater than in renally sufficient patients. Thus, increased monitoring for cytopenias may be warranted in patients with renal impairment (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Patients undergoing hemodialysis:
Dosage adjustment is necessary for patients on hemodialysis (CrCl < 10 mL/min) and a dosing recommendation is given in Table 7 below (see WARNINGS AND PRECAUTIONS: Patients

undergoing hemodialysis, DOSAGE AND ADMINISTRATION: Dosing Considerations and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Hemodialysis).

Table 6: Valganciclovir hydrochloride Tablet Dose for Patients with Impaired Renal Function

CrCl* (mL/min)	Treatment of CMV Retinitis		Prophylaxis of CMV Disease in Solid Organ Transplantation valganciclovir hydrochloride Tablets
	Induction Dose valganciclovir hydrochloride Tablets	Maintenance Dose valganciclovir hydrochloride Tablets	
≥ 60	900 mg twice daily	900 mg once daily	900 mg once daily
40 - 59	450 mg twice daily	450 mg once daily	450 mg once daily
25 - 39	450 mg once daily	450 mg every 2 days	450 mg every 2 days
10 - 24	450 mg every 2 days	450 mg twice weekly	450 mg twice weekly
< 10	not recommended	not recommended	not recommended

*Creatinine clearance is calculated from serum creatinine by the following formulas:

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

For females = 0.85 x male value

Missed Dose

The missed dose should be taken as soon as remembered, then the regular dosing schedule should be continued. Two doses of MYLAN-VALGANCICLOVIR should not be taken at the same time.

Administration

MYLAN-VALGANCICLOVIR should be administered orally, and should be taken with food (see ACTION AND CLINICAL PHARMACOLOGY: Absorption).

Several guidelines for the handling and disposal of hazardous pharmaceuticals (including cytotoxic drugs) are available (e.g. CSHP, 1997) (see SPECIAL HANDLING INSTRUCTIONS).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Overdose Experience with valganciclovir hydrochloride 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 (decreased creatinine clearance).

It is expected that an overdose of valganciclovir hydrochloride could result in increased renal toxicity (see WARNINGS AND PRECAUTIONS: General and DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment).

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

Overdose Experience With Intravenous Ganciclovir
Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during post-marketing experience. In some of these cases no adverse reactions were reported. The majority of patients experienced one or more of the following adverse reactions:

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting.

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

Hepatotoxicity: hepatitis, liver function disorder.

Neurotoxicity: generalized tremor, convulsion.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Valganciclovir is an L-valyl ester salt (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 herpes viruses *in vitro* and *in vivo*.

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

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, further viral DNA elongation.

The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) *in vitro* (laboratory strains or clinical isolates) has ranged from 0.02 to 3.58 μg/mL (0.08 to 14.32 μM). Ganciclovir inhibits mammalian cell proliferation (CIC_{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 (CIC_{50} 0.69 to 3.06 μg/mL; 2.7 to 12 μM). The relationship of *in vitro* sensitivity of CMV to ganciclovir and clinical response has not been established.

Pharmacokinetics

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 hydrochloride tablets following food was approximately 60% (3 studies, n=18; n=16; n=28). Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir hydrochloride tablets in the dose range 450 to 2625 mg was demonstrated only under fed conditions. Systemic exposure to the prodrug, valganciclovir, was transient and low, and the AUC_{24} and C_{max} values were approximately 1% and 3% of those of ganciclovir, respectively.

When valganciclovir hydrochloride tablets were administered with food at a dose of 900 mg, the area under the plasma concentration time curve (AUC) over 24 hours was 28.0 ± 8.9 μg•h/mL (n=75), and the maximum plasma concentration (C_{max}) was 5.37 ± 1.53 μg/mL (n=76).

Following the administration of valganciclovir as an oral solution, equivalent systemic ganciclovir exposures were obtained compared to the tablet formulation (see CLINICAL TRIALS: Comparative Bioavailability Studies).

Food Effects:
When valganciclovir hydrochloride tablets were administered with a meal containing 569 calories (31.1 g fat, 51.6 g carbohydrates, and 22.2 g protein) at a dosage 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}). Therefore it is recommended that valganciclovir hydrochloride 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 was 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 0.680 ± 0.161 L/kg (n=114).

After administration of valganciclovir hydrochloride tablets, no correlation was observed between ganciclovir AUC and weight; oral dosing of valganciclovir hydrochloride 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.

Excretion: 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 3.05 ± 0.81 mL/min/kg (n=86) while renal clearance was 2.40 ± 0.93 mL/min/kg (n=46).

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of valganciclovir hydrochloride tablets to either healthy or HIV-positive/CMV-positive subjects was 4.18 ± 0.80 hours (n=244), and that following administration of intravenous ganciclovir was 3.85 ± 0.74 hours (n=87). In liver transplant recipients, the $t_{½}$ of ganciclovir after oral administration of valganciclovir hydrochloride tablets (900 mg dose) was 5.10 ± 1.10 hours (n=28), compared to 5.17 ± 1.39 hours (n=27) after intravenous administration of ganciclovir.

Special Populations and Conditions

Pediatrics: The pharmacokinetic characteristics of valganciclovir hydrochloride in pediatric patients have not been well established (see WARNINGS AND PRECAUTIONS: Special Populations, Pediatrics and CLINICAL TRIALS).

Geriatrics: No studies of valganciclovir hydrochloride have been conducted in adults older than 65 years of age (see WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics).

Gender: Insufficient data are available to demonstrate any effect of gender on the pharmacokinetics of valganciclovir.

Race: Insufficient data are available to demonstrate any effect of race on the pharmacokinetics of valganciclovir.

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

Table 7: Pharmacokinetics of Ganciclovir From a Single Oral Dose of 900 mg valganciclovir hydrochloride 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 resulted in decreased clearance of ganciclovir from valganciclovir, and a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see WARNINGS AND PRECAUTIONS: Renal and DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment).

STORAGE AND STABILITY

MYLAN-VALGANCICLOVIR tablets:

Preserve in tight container. Store at 25°C, excursion permitted between 15°C and 30°C.

SPECIAL HANDLING INSTRUCTIONS

Caution should be exercised in the handling of MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride) 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 AND PRECAUTIONS: Sexual Function/Reproduction). Avoid direct contact of broken or crushed tablets, powder or reconstituted solution with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with sterile water or plain water if sterile water is not available.

Disposal of unused/expired medicines: The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Used established "collection systems" if available at your location. Several guidelines for the handling and disposal of hazardous pharmaceuticals (including cytotoxic drugs) are available (e.g. CSHP, 1997). Disposal of MYLAN-VALGANCICLOVIR should follow provincial, municipal, and local hospital guidelines or requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Film-Coated Tablet

Composition: Each tablet contains 496.3 mg of valganciclovir hydrochloride (corresponding to 450 mg valganciclovir). The non-medicinal ingredients are: crospovidone, microcrystalline cellulose and stearic acid. The coating contains: hydroxypropyl methylcellulose, iron oxide red, polyethylene glycol 400/macrogol, polysorbate 80 and titanium dioxide.

Availability: MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride) 450 mg tablets are available in HDPE bottles of 60, as pink film-coated, oval, biconvex, beveled edge tablets debossed with "M" on one side of the tablet and "V45" on the other side.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name/Common name:	Valganciclovir Hydrochloride
Chemical name:	L-Valine, ester with 9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl] guanine, monohydrochloride L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride
Molecular formula and molecular mass:	$C_{14}H_{22}N_6O_5$**.**HCl 390.82 g/mol
Structural formula:	
Physicochemical properties:	Physical description: Valganciclovir hydrochloride is a white to off-white crystalline powder. Solubility: The solubility of valganciclovir in water is 740 mg/mL at 25°C. pKa and pH values**:** pKa = 7.6, pH = 4.01 (1% solution in water) Partition Co-efficient: Valganciclovir hydrochloride has an n-octanol/water partition coefficient of 0.0095 at pH 7.0.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single oral dose, randomized, double-blind, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Mylan-Valganciclovir (valganciclovir hydrochloride) 2 x 450 mg tablets (Mylan Pharmaceuticals ULC) and Valcyte® (valganciclovir hydrochloride) 2 x 450 mg tablets (Hoffmann-La Roche Limited, Canada) was performed in 21 healthy, adult male subjects under fed conditions.

A summary of the results is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Valganciclovir (2 × 450 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUCt (ng.hr/mL)	647.1 664.3 (21.5)	630.1 644.1 (20.4)	102.7	(100.5%; 105.0%)
AUCi (ng.h/mL)	661.8 679.3 (21.5)	641.1 655.5 (20.5)	103.2	(101.1%; 105.4%)
Cmax (ng/mL)	271.9 283.8 (26.7)	310.9 324.1 (29.4)	87.5	(77.5%; 98.6%)
T_{max}§ (h)	1.5 (0.8 - 4.5)	1.5 (0.8 - 4.0)		
$T_{½}$€ (h)	0.9 (24.0)	0.8 (24.7)		

* Mylan-Valganciclovir (valganciclovir hydrochloride) 450 mg tablets (Mylan Pharmaceuticals ULC).
† PrVALCYTE® (valganciclovir hydrochloride) 450 mg tablets (Hoffmann-La Roche Limited, Canada) were purchased in Canada.
§ Expressed as the median (range) only.
€ Expressed as the arithmetic mean (CV %) only.

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 valganciclovir hydrochloride tablets (900 mg twice daily for 21 days, then 900 mg once daily for 7 days) or with CYTOVENE-IV (ganciclovir sodium for injection) (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 CD4 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 three week induction therapy. Table 9 provides the outcomes at four weeks.

Table 8: Week 4 Masked Review of Retinal Photographs in Study WV15376

	CYTOVENE-IV	**Valganciclovir hydrochloride**
Determination of CMV retinitis progression at	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

In evaluable patients, photographic evidence of progression was observed in 7 of 70 patients (10%) in the intravenous ganciclovir treatment group and in 7 of 71 patients (9.7%) treated with valganciclovir hydrochloride. The difference in the proportion progressing was 0.1% (95% CI = -9.7 to 10.0%). Based on the *a priori* definition of comparable efficacy, valganciclovir hydrochloride tablets 900 mg twice daily demonstrated similar efficacy to that of intravenous ganciclovir 5 mg/kg twice daily.

Maintenance Therapy of CMV Retinitis

No comparative clinical data are available on the efficacy of valganciclovir hydrochloride for the maintenance therapy of CMV retinitis because all patients in study WV15376 received open-label valganciclovir hydrochloride after week 4. However, the AUC for ganciclovir is similar following administration of 900 mg valganciclovir once daily and 5 mg/kg intravenous ganciclovir once daily. Although the ganciclovir C_{max} is lower following valganciclovir administration compared to intravenous ganciclovir, it is higher than the C_{max} obtained following oral ganciclovir administration (see Figure 1 in DETAILED PHARMACOLOGY). Therefore, use of valganciclovir 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 Solid Organ Transplantation: Study PV16000

A double-blind, double-dummy clinical active comparator study has been conducted in 372 heart, liver and kidney transplant patients at high-risk for CMV disease (Donor seropositive/Recipient seronegative [(D+/R-)]). Patients were randomized (2 valganciclovir hydrochloride: 1 oral ganciclovir) to receive either valganciclovir hydrochloride tablets

(900 mg once daily) or oral ganciclovir (1000 mg three times a day) starting within 10 days of transplantation until Day 100 post-transplant. The proportion of patients who developed CMV disease, including CMV syndrome and/or tissue invasive disease during the first 6 months post-transplant was 12.1% in the patients treated with valganciclovir hydrochloride (N=239) compared with 15.2% in the oral ganciclovir arm (N=125). However, in liver transplant patients, the incidence of tissue-invasive CMV disease was significantly higher in the group treated with valganciclovir hydrochloride compared with the ganciclovir group. These results are summarized in Table 10.

Table 9: Percentage of Patients with CMV Disease and Tissue-Invasive CMV Disease by Organ Type: Endpoint Committee, 6 Months ITT Population

	CMV Disease[1]		**Tissue-Invasive CMV**		**CMV Syndrome**	
Organ	V GC	G CV	V GC	G CV	V GC	G CV
Liver (n=177)	19	12	14	3%	5%	9%
Kidney (n=120)	6%	23	1%	5%	5%	18
Heart (n=56)	6%	10	0%	5%	6%	5%
Kidney / Pancreas (n=11)	0%	17	0%	17	0%	0%

GCV = oral ganciclovir; VGCV= valganciclovir hydrochloride

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

The majority of CMV disease events occurred after the end of the treatment phase, when patients were no longer receiving anti-CMV prophylaxis with either oral ganciclovir or valganciclovir. During this post-treatment period, time to CMV disease was generally shorter on the ganciclovir arm.

The incidence of acute graft rejection up to 6 months post-transplant was slightly higher on the ganciclovir arm of the study (36.0%, versus 29.7% on the valganciclovir arm).

Extending prophylaxis with valganciclovir hydrochloride up to 200 days post-transplant may provide some benefit in high-risk D+/R-kidney transplant recipients. However, a higher frequency of treatment-related adverse events, including leukopenia and neutropenia, was observed when the prophylaxis was extended to 200 days post-transplant compared with 100 days post-transplant. The decision to extend the prophylaxis should be undertaken only where the potential benefits outweigh the risks (See WARNINGS and PRECAUTIONS).

Pediatric Use

The pharmacokinetics and safety of valganciclovir was studied in 109 pediatric SOT recipients. Common adverse events (reported in more than 10% of patients) observed in these patients included diarrhea (32%), pyrexia (24%), hypertension (22%), upper respiratory tract infection (22%), vomiting (21%), anemia (14%), neutropenia (13%), constipation (11%), nausea (11%), and transplant rejection (10%).

Comparative Bioavailability Studies

A multi-centre, randomized, cross-over, open-label study was conducted to compare the bioavailability of ganciclovir from the valganciclovir tutti-frutti oral solution and the 450 mg tablet formulation at a dose of 900 mg administered in the fed state to male and female kidney transplant recipients (n=21). The statistical results below indicate that the bioavailability of ganciclovir from the tutti-frutti oral solution and the marketed tablet are comparable.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

ganciclovir from valganciclovir (2 x 450 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means#**	**Confidence Interval#**
AUC24 (µg.h/mL)	51.52 52.3 (19.7%)	51.57 52.2 (19.2%)	100	96-104 (90% CI)
AUC_{inf} (µg.h/mL)	54.97 55.85 (21.3%)	55.33 56.12 (20.8%)	99	96-103 (90% CI)
C_{max} (µg/mL))	6.38 6.60 (27.3%)	6.75 6.90 (21.6%)	95	89-101 (90% CI)
T_{max}§ (h)	2.11 2.33 (49.6%)	2.79 3.00 (34.5%)		
$T_{½}$§ (h)	5.51 5.67 (23.6%)	5.55 5.71 (24.5%)		

* Tutti-Frutti oral solution

† Film-coated tablet (identical to the Canadian commercial product)

§ Expressed only as arithmetic mean (CV%)

Calculated based on least-square mean estimates

DETAILED PHARMACOLOGY

Animal Pharmacology

A range of routine safety pharmacology studies was undertaken to assess the effect of valganciclovir on the major bodily systems. There were no clinically relevant effects detected with valganciclovir in safety pharmacology tests on renal, intestinal, autonomic nervous or cardio-respiratory systems and on gross behaviour.

Human Pharmacology

Because the major elimination pathway for ganciclovir is renal, dosage reductions according to creatinine clearance are required for MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride). 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 parameters which control the exposure of ganciclovir from valganciclovir are the oral absorption of valganciclovir and the renal excretion of ganciclovir.

The ganciclovir pharmacokinetic measures following administration of 900 mg valganciclovir and 5 mg/kg intravenous ganciclovir and 1000 mg three times daily oral ganciclovir are summarized in Table 10.

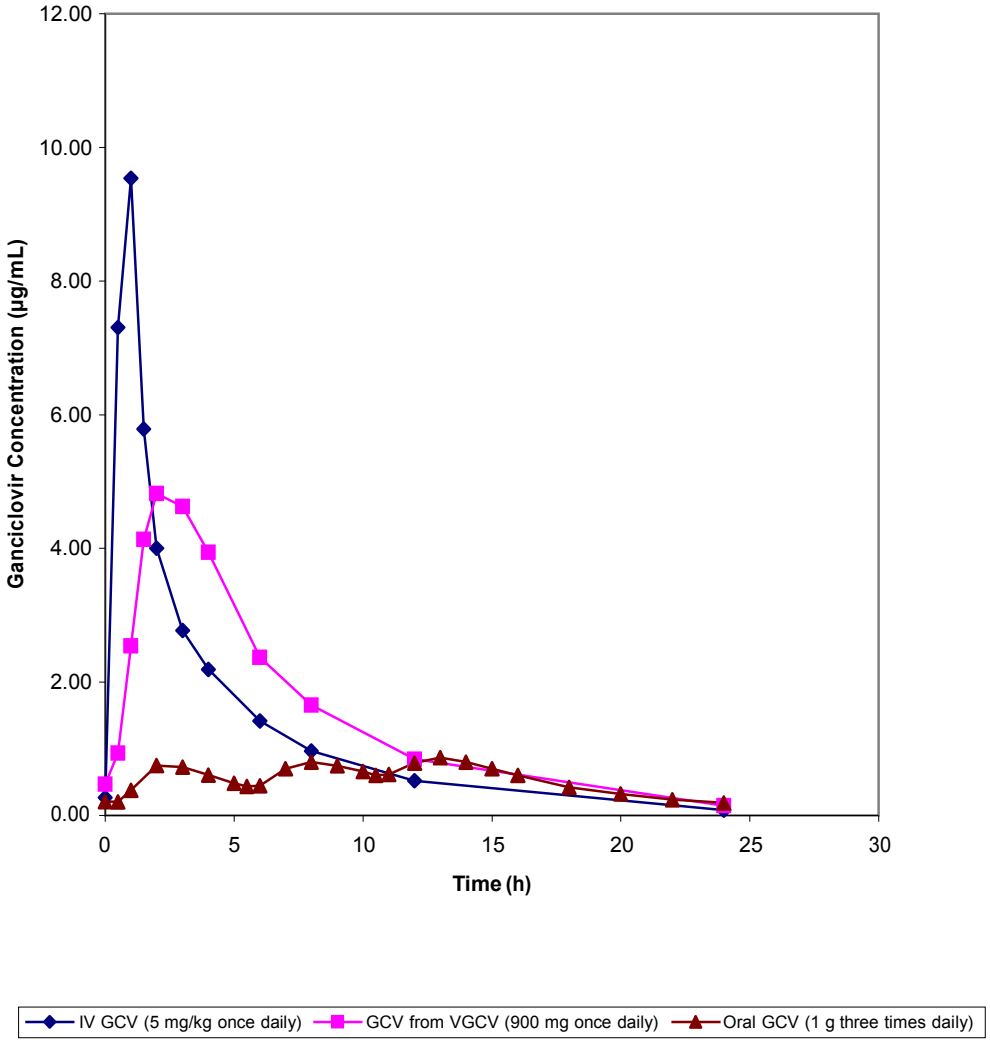
Table 10: Mean Ganciclovir Pharmacokinetic* Measures in Healthy Volunteers and HIV-positive/CMV-positive Adults at Maintenance Dosage

Formulation	valganciclovir hydrochloride 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 valganciclovir hydrochloride tablets is comparable to the ganciclovir AUC for intravenous ganciclovir. Ganciclovir $AUC_{0\text{-}24h}$, achieved by a single dose of 900 mg valganciclovir hydrochloride tablets under fed conditions was comparable to the $AUC_{0\text{-}24h}$ achieved following administration of 5 mg/kg intravenous ganciclovir (42.69 mg•h/mL vs 47.61 mg•h/mL, respectively). Ganciclovir C_{max} following valganciclovir administration is 40% lower than following intravenous ganciclovir administration. During maintenance dosing, ganciclovir $AUC_{0\text{-}24h}$ and C_{max} following oral ganciclovir administration (1000 mg three times daily) are lower relative to valganciclovir and intravenous ganciclovir. The ganciclovir C_{min} following intravenous ganciclovir and valganciclovir administration are less than the ganciclovir C_{min} following oral ganciclovir administration.

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



*Plasma concentration-time profiles for ganciclovir (GCV) from valganciclovir (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.

A study conducted with ganciclovir, GANS 2226, has demonstrated that ganciclovir AUC is the key pharmacokinetic parameter most predictive of clinical response.

Increases in ganciclovir average $AUC_{0\text{-}24h}$ were associated with statistically significant increases in time to progression of CMV retinitis when fitted by the Cox regression model (*P*=.0002). Multivariate regression analysis showed the association between $AUC_{0\text{-}24h}$ and time to progression of CMV retinitis was highly statistically significant (*P*=.0019), while the association of C_{max} and time to progression of CMV retinitis was not (*P*=.6022). These findings indicate that average $AUC_{0\text{-}24h}$ is a better predictor of time to progression, and that average C_{max} does not add predictive value over average $AUC_{0\text{-}24h}$.

In heart, kidney, kidney-pancreas, and liver transplant recipients, the mean systemic exposure to ganciclovir was 1.7 x higher following administration of 900 mg valganciclovir hydrochloride tablets once daily versus 1000 mg ganciclovir capsules three times daily, when both drugs were administered according to their renal function dosing algorithms. The steady state systemic exposure($AUC_{0\text{-}24h}$) of solid organ transplant patients to ganciclovir after daily oral administration of valganciclovir and ganciclovir was 46.3 ± 15.2 µg•h/mL and 28.0 ± 10.9 µg•h/mL, respectively. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation.

Table 11: Mean Ganciclovir Pharmacokinetic Measures by Organ Type (Study PV16000)

Parameter	Ganciclovir Capsules	valganciclovir hydrochloride 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

The pharmacokinetics of valganciclovir hydrochloride tablets in stable liver transplant recipients were investigated in one open label 4-part crossover study (n=28). The absolute bioavailability of ganciclovir from valganciclovir following a single dose of 900 mg valganciclovir hydrochloride tablets under fed conditions was approximately 60%, in agreement with the estimates obtained in other patient populations.

Ganciclovir $AUC_{0\text{-}24h}$, achieved following a single dose of 900 mg valganciclovir hydrochloride tablets under fed conditions, was 41.7 ± 9.9 μg•h/mL (n=28), compared to 48.2 ± 17.3 μg•h/mL (n=27) after 5 mg/kg of intravenous ganciclovir was administered.

MICROBIOLOGY

Antiviral Effect: *Treatment of CMV Retinitis in AIDS Patients*

In a study of valganciclovir hydrochloride (valganciclovir hydrochloride) tablets for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS), the antiviral effect of valganciclovir hydrochloride tablets was demonstrated by a decrease in CMV shedding (see Table 12).

Table 12: Antiviral Effect of valganciclovir hydrochloride Tablets

	Patients With Positive CMV Cultures		**Patients With Viremia by Qualitative CMV Polymerase Chain Reaction**	
Time	valganciclovir hydrochloride Tablets*	Intravenous Ganciclovir†	valganciclovir hydrochloride Tablets*	Intravenous Ganciclovir†
Pretreatment	46% (33/71)	65% (46/71)	40% (31/77)	51% (39/76)
Week 4	7% (4/58)	6% (4/64)	4% (3/71)	3% (2/70)

* 900 mg bid for 21 days followed by 900 mg daily for 7 days

† 5 mg/kg bid for 21 days followed by 5 mg/kg daily for 7 days

Viral Suppression: *Prevention of CMV Disease in Solid Organ Transplantation*

In a study of valganciclovir hydrochloride tablets in the prevention of CMV disease in heart, kidney, kidney- pancreas, and liver transplant recipients, the incidence of viremia (CMV viral load above a detection limit of 400 copies/mL) was lower on the valganciclovir arm while patients were receiving prophylaxis with study drug (2.9%, versus 10.4% on the ganciclovir arm). By the 6 month post transplant time point, a comparable proportion of patients had experienced viremia on the two treatment arms (39.7% valganciclovir, 43.2% ganciclovir).

Antiviral Activity against Human Herpes Viruses

Sensitive human viruses include human cytomegalovirus (HCMV), herpes-simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus type 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus. The demonstration of

antiviral activity against these viruses does not necessarily correlate to clinical response.

Viral Resistance
Viruses resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in either the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or in the viral 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 viral polymerase.

The current working definition of CMV resistance to ganciclovir in *in vitro* assays is IC_{50} >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.

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

Prevention of CMV Disease in Solid Organ Transplant Recipients
During a clinical study of valganciclovir (and ganciclovir) for the prevention of CMV disease in heart, kidney, kidney-pancreas and liver transplant recipients, resistance to ganciclovir was studied by genotypic analysis of CMV in white blood cell samples collected: 1) on Day 100 (end of study drug prophylaxis); and 2) in cases of suspected CMV disease with viremia up to 6 months post-transplant.

At the end of study drug prophylaxis (Day 100), the incidence of resistance was 0/198 samples (0%) for patients receiving valganciclovir and 2/103 samples (1.9%) for patients receiving ganciclovir.

For cases of CMV disease with viremia, the incidence of resistance was 0/50 samples (0%) for patients receiving valganciclovir and 2/29 samples (6.9%) for patients receiving ganciclovir.

TOXICOLOGY

Studies have shown that valganciclovir shares the same toxicity profile as ganciclovir.

Carcinogenesis: In a study conducted over 18 months, ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (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-time curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a significant increase in the incidence of tumours of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumours was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01x the human dose based on AUC comparison). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumours were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans.

Reproduction: Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. Valganciclovir is expected to have similar reprotoxicity effects as ganciclovir. Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (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 after daily intravenous doses of ≥ 2 mg/kg and daily oral doses of ≥ 10 mg/kg. These effects were reversible after daily intravenous doses of 2 mg/kg and daily oral doses of 10 mg/kg, but were irreversible or incompletely reversible after daily intravenous doses of 10 mg/kg and daily oral doses of 100 or 1000 mg/kg. Ganciclovir has also caused hypospermatogenesis in rats after daily oral doses of ≥ 100 mg/kg and in dogs after daily intravenous and oral doses of ≥ 0.4 mg/kg and 0.2 mg/kg, respectively.

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 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. 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 of 90 mg/kg 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. 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. MYLAN-VALGANCICLOVIR (valganciclovir hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Note: All dose comparisons presented in this subsection are based on the human AUC following administration of a single 5 mg/kg infusion of intravenous ganciclovir as used during the maintenance phase of treatment. Compared with the single 5 mg/kg intravenous infusion, human exposure is doubled during the intravenous induction phase (5 mg/kg bid). The cross-species dose comparisons should be multiplied by 2 for intravenous induction treatment with intravenous ganciclovir.

Acute Toxicity: The acute toxicity of valganciclovir was assessed in single-dose oral studies in mice and dogs. The studies performed, and their results, are presented in the following table.

Table 13: Acute (oral gavage) Toxicity Studies Conducted with Valganciclovir

Species Strain [Ref.#]	No/ group/ sex	Dose mg/kg	Dose volume mL/kg	Observation period (days)	Lethal dose	Observations
Mouse Swiss Webster [1012]	5 5 5	0 1000 2000	20 10 20	14	>2000*	Administration of valganciclovir did not induce any effects at the time of dosing and during the observation period. *One female mouse (2000 mg/kg) died 7-24 hours after dosing from an unknown cause.
Dog Beagle [1013]	1 1 1	0 500 1000	10 5 10	14	>1000	Administration of 1000 mg/kg/day to dogs by oral gavage induced vomiting within 3 hrs of dosing. WBC, neutrophil and platelet counts declined in males administered 500 and 1000 mg/kg and in females administered 500 mg/kg.

Multi-dose Toxicity: Studies in the mouse, rat and dog with valganciclovir demonstrated that the reproductive, hematopoietic, renal and gastrointestinal systems were the main organs for induced toxicity.

An i.v. study in mice, where the systemic exposure of valganciclovir was 10 times that expected in man demonstrated that valganciclovir induced the same range of findings as ganciclovir with no additional findings.

The male reproductive system was the most frequently affected target organ. Lesions seen were testicular epithelial cell atrophy, oligospermia, and changes in accessory sex organs at sub-therapeutic exposure levels. Female reproductive changes were confined to uterine, ovarian and clitoral atrophy.

Valganciclovir induced intestinal mucosal and/or crypt degeneration in mice and dogs. A range of hematopoietic changes were induced which included lymphoreticular gland atrophy, leukopenia - particularly neutropenia, anemia, thrombocytopenia and bone marrow hypocellularity.

Renal toxicity was recorded in mice as tubular basophilia, pelvic dilatation and necrosis with associated changes in clinical pathology.

No studies were undertaken on the reproductive toxicology or on carcinogenicity. Since valganciclovir behaves as ganciclovir in all studies, it is assumed that the teratogenicity, mutagenicity and carcinogenicity seen with ganciclovir will apply equally to valganciclovir.

The multi-dose toxicity studies performed with valganciclovir are summarized in the following table.

Table 14: Multi-dose Studies Conducted with Valganciclovir

Species Strain [Ref.#]	Route	No/ Group/ Sex	Dose mg/kg/day Duration	Objectives/Observations
Mouse Crl:CD-1 (ICR) [1085]	Intravenous	10	0, 20, 100 14 days	*Objectives:* To record the valganciclovir toxicity profile under conditions of high i.v. exposure and thus avoid the effects of rapid first pass metabolism. *Observations*: − Daily i.v. administration of valganciclovir induced changes indicative of early nephritis and testicular atrophy in males, and atrophy and degeneration of secondary sex glands in both sexes. − There were no findings indicative of specific valganciclovir toxicity. − The kinetics of valganciclovir and ganciclovir as the main metabolite was linear with respect to dose, time and gender.
Mouse Crl:CFW (SW) [1015]	Oral gavage	10 (5 recovery)	0, 1.5, 15, 150, 500 4 weeks with 4 week recovery groups	*Objectives:* Standard 4-week study performed to support clinical administration and record the oral toxicity of valganciclovir. *Observations*: − Target organ toxicity was demonstrated in the reproductive, hematopoietic, and renal and gastrointestinal systems. − Toxicity findings were dose-related in severity but were extensive and severe in the high-dose group that exhibited high exposure to ganciclovir. − Reproductive changes consisted of marked and irreversible testicular epithelial cell atrophy with all doses in males. In females uterine, ovarian and clitoral atrophy developed in the high dose group. − In both sexes, a reversible anemia and bone marrow hypocellularity were induced. Necrosis of the glands of the stomach and large intestine, and urea-mia and kidney pelvic dilatation and necrosis were also recorded. − Intestinal necrosis was interpreted as an anti-proliferative effect on rapidly dividing intestinal cells induced by an exceptionally high systemic exposure to ganciclovir (AUC 527.5 µg•h/mL). No additional toxic symptoms related specifically to valganciclovir were recorded. − Kinetic values were linear with respect to dose and gender, except for high exposure to ganciclovir due to reduced high-dose clearance. − Kidney tubular dilatation, atrophy and necrosis were diagnosed in one male mouse in the 150 mg/kg/day group and in the majority of mice in the 500 mg/kg/day groups. This lesion was non-reversible.

Species Strain [Ref.#]	Route	No/ Group/ Sex	Dose mg/kg/day Duration	Objectives/Observations
Mouse Crl:CD-1 (ICR) [1016] 13-Week Interim Report [1017]	Oral gavage	20 (10 recovery)	0, 1, 10, 100 26 weeks with 4 week recovery groups	*Objectives:* To record the toxicity of valganciclovir administered for 13 and 26 weeks and to support extended clinical administration to patients. *Observations*: − Target organs were identified as the reproductive system in males and the hematopoietic system in both sexes. − In males, severe testicular atrophy and moderate to severe oligospermia and preputial gland inflammation and squamous metaplasia were recorded. − Mild, partially reversible anemia was present in both sexes at the high dose. A moderate, reversible uremia was detected at weeks 13 and 26 but there was no nephrotoxicity. − Toxicokinetic sampling indicated that valganciclovir was rapidly hydrolysed to ganciclovir resulting in a low systemic exposure of valganciclovir (<4% of ganciclovir) and that the kinetics of both compounds was linear with respect to dose. − Administering valganciclovir to mice over 26 weeks at toxic doses induced no new symptoms. − Severe and non-reversible testicular atrophy was present in the 10 and 100 mg/kg/day groups.
Rat HsdBrl:WH (Wistar) [1018]	Oral gavage	10	0, 2, 20, 200 13 weeks	*Objectives:* This gavage study was undertaken as a 13-week range-finding study. *Observations*: − The target organs were the male reproductive system and the hematopoietic system in both sexes. − Testicular atrophy was a marked toxicity finding which was accompanied by the formation of vacuolated cells (castration cells) in the anterior pituitary. − Leukopenia (males) and neutropenia (females) were induced. − Changes to clotting parameters (PT and aPPT) were recorded but not in proportion to dose and there were inconsistencies in results between bleed times and genders. In a subsequent 13-week investigatory study, ganciclovir administered i.v. induced mild but significant effects (P<0.01) upon PT and aPTT times. − Additional valganciclovir findings were not recorded.

Species Strain [Ref.#]	Route	No/ Group/ Sex	Dose mg/kg/day Duration	Objectives/Observations
Rat HsdBrl:WH (Wistar) [1019]	Oral valganciclovir i.v. valganciclovir	15 males	200, 400 50, 100 13 weeks	*Objectives:* − To establish if changes to PT and aPTT parameters, recorded in the 13-week rat study particularly in males, were induced by ganciclovir and, thus were not additional findings for valganciclovir. − Valganciclovir was administered orally at the same and twice the positive dose in the 13-week study. Ganciclovir was administered intravenously to overcome its low bioavailability and at dose levels estimated as producing systemic ganciclovir exposure levels equal to or higher than those arising from valganciclovir oral administration. A range-finding study was conducted for selecting the i.v. ganciclovir doses. *Observations*: − PT times were prolonged and aPTT times shortened (both $P<0.01$) with 100 mg/kg/day ganciclovir and blood clotting time reported as increased. No significant effects were recorded with valganciclovir. − Fibrinogen levels were increased by 50 and 100 mg/kg/day ganciclovir ($P<0.001$) but not by valganciclovir. *Conclusion:* − Both ganciclovir and valganciclovir at high doses in the rat appear to cause mild changes to blood clotting factors.
Dog Beagle [1020]	Oral gavage	3	0, 0.15, 1.5, 15, 50 4 weeks with 2 weeks recovery	*Objectives:* To determine the oral toxicity of valganciclovir in the non-rodent species, the dog. *Observations*: − Toxicity findings with valganciclovir included intestinal necrosis, nephritis, anemia and atrophy to hematopoietic glands and testes. − At therapeutic and sub-therapeutic dose levels, mild, reversible anemia, thrombocytopenia and depletion of bone marrow cells, testicular atrophy and leukopenia were seen.
Dog Beagle [1021]	Oral, liquid filled gelatin capsule	3 (2 recovery)	0, 0.2, 2, 20/10 13 weeks with 9 week recovery	*Objectives:* A 13-week oral capsule study was undertaken with valganciclovir for the purposes of supporting extended clinical dosing. *Observations*: − The target organs were the testes and hematopoietic system. − The testicular changes consisted of dose-related, irreversible atrophy. The hematopoietic changes were typified by mild to moderate neutropenia, thrombocytopenia and bone marrow hypoplasia that were dose-related in severity and reversible.

Mutagenesis: Ganciclovir caused point mutations and chromosomal damage in mammalian cells *in vitro* and *in vivo*, but did not cause point mutations in bacterial or yeast cells, dominant lethality in mice, or morphologically transformed cells *in vitro*.

Bacterial mutation, mammalian cell mutation, and *in vivo* chromosome analysis studies were undertaken to assess the mutagenic and clastogenic potential of valganciclovir. Valganciclovir was mutagenic in the Mouse Lymphoma Assay with and without metabolic activation and clastogenic in the Micronucleus Assay at a cytotoxic dose. The mutagencity studies performed are summarized in the table below.

Table 15: Mutagenicity Studies

Study Type [Ref.#]	Assay System	Concentration Assayed	Duration of Exposure	Data
Bacterial Cell Mutation (Ames Test) [1026]	1. Initial range-finder with pre-incubation with Salmonella Strains TA 1535, 1537, 1538, 98, 100 and *E. coli* WP2uvrA ± S9 activation 2. Main study with same strains ± S9 activation	1. 0-5000 µg/mL 2. 100-5000 µg/mL	48-72 hrs	No mutagenic activity with and without activation. No precipitation nor appreciable cytotoxicity
Mammalian Cell Gene Mutation (Mouse Lymphoma Assay) [1025]	Mouse lymphoma cells (L5178Y $TK^{\pm}$) ± S9 activation	Without activation 1000-5000 µg/mL With activation 10-500 µg/mL	24-48 hrs	Increased mutagenic activity with 2000 µg/mL and above without activation and 250 µg/mL and above with activation.
Chromosome Analysis *in vivo* [1024]	Mouse micronucleus study	0, 60, 300, 1500 mg/kg	24, 48, and 72 hrs	Increase in frequency of micro nucleated polychromatic erythrocytes with 1500 mg/kg which was also excessively cytotoxic.

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PART III: CONSUMER INFORMATION

PrMYLAN-VALGANCICLOVIR
Valganciclovir Tablets, USP
450 mg

This leaflet is part III of a three-part "Product Monograph" published when MYLAN-VALGANCICLOVIR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN-VALGANCICLOVIR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- MYLAN-VALGANCICLOVIR is a prescription medication that belongs to the family of drugs known as "antivirals".
- MYLAN-VALGANCICLOVIR is used to treat cytomegalovirus (CMV) retinitis in adults who have acquired immunodeficiency syndrome (AIDS).
- MYLAN-VALGANCICLOVIR is also used to prevent cytomegalovirus (CMV) disease in adults who have received a solid organ transplant and are at risk of developing CMV disease.

What it does:

- MYLAN-VALGANCICLOVIR works by slowing the growth of CMV virus, the virus that causes CMV retinitis as well as infection at other sites in the body. For most people with CMV retinitis, MYLAN-VALGANCICLOVIR prevents CMV from progressing (spreading) into healthy cells as quickly as it would without treatment, thereby protecting eyesight from damage due to CMV disease.
- MYLAN-VALGANCICLOVIR does not cure CMV retinitis, and some people may experience progression of retinitis during or following treatment with MYLAN-VALGANCICLOVIR. Therefore, you must follow your doctor's advice and have your eyes checked regularly.
- For most patients who have received a solid organ transplant, MYLAN-VALGANCICLOVIR prevents the occurrence of CMV disease up to 6 months after the transplant.
- MYLAN-VALGANCICLOVIR is a prodrug of ganciclovir. This means it is changed to ganciclovir once it is absorbed into the body. Ganciclovir is the active part of the drug that actually slows the growth of CMV virus.

When it should not be used:

Do not take MYLAN-VALGANCICLOVIR if you have ever had a serious reaction to valganciclovir, ganciclovir (as MYLAN-VALGANCICLOVIR or ganciclovir capsules or CYTOVENE®-IV). Do not take if you have had sensitivity reactions with acyclovir, ganciclovir and valacyclovir as a similar reaction can occur with MYLAN-VALGANCICLOVIR. Do not take MYLAN-VALGANCICLOVIR if you have any reaction to any of the non-medicinal ingredients (see "What the non-medicial ingredients are").

What the medicinal ingredient is:

The medicinal ingredient found in MYLAN-VALGANCICLOVIR is valganciclovir hydrochloride.

What the non-medicinal ingredients are:

MYLAN-VALGANCICLOVIR tablets contain the following non-medicinal ingredients: crospovidone, microcrystalline cellulose, purified water and stearic acid. The film-coat applied to the tablets is Opadry® Pink, which contains hydroxypropyl methylcellulose, iron oxide red, polyethylene glycol 400/macrogol, polysorbate 80 and titanium dioxide.

What dosage forms it comes in:

MYLAN-VALGANCICLOVIR is available as a pink 450 mg valganciclovir film-coated tablet (as valganciclovir hydrochloride).

BEFORE you use MYLAN-VALGANCICLOVIR talk to your doctor or pharmacist if:

- you have ever had a bad reaction to MYLAN-VALGANCICLOVIR (valganciclovir) or any of the inactive ingredients shown above.
- you have ever had a bad reaction to ganciclovir, acyclovir or valacyclovir.
- you are allergic to other medicines, food and dyes.
- you are taking ANY other medicines (prescription or nonprescription) including herbal or natural products.
- you have any other illnesses/diseases, including a history of liver or kidney disease.
- you are receiving hemodialysis as dosage adjustment is required.
- you have blood problems.
- you or your partner are pregnant, plan on becoming pregnant, or are breast-feeding a child, as MYLAN-VALGANCICLOVIR may cause birth defects in humans and should not be used during pregnancy. If there is any chance that you or your partner could become pregnant, it is very important for you to use effective contraception during and for at least 90 days following treatment with MYLAN-VALGANCICLOVIR. For women this means using barrier protection (condoms) and one additional form of contraception (birth control pills, intrauterine device). For men this means using barrier protection (condoms).

Women who are HIV positive should not breast feed because HIV infection can be passed to the baby via the breast milk.

This information will help your doctor and you decide whether you should use MYLAN-VALGANCICLOVIR and what extra care may need to be taken while you are on the medication. You should always consult your doctor or pharmacist before using other medications while on MYLAN-VALGANCICLOVIR.

Tell your doctor or pharmacist about all medications that you are taking, including those you buy over the counter and herbal or natural products. MYLAN-VALGANCICLOVIR may change the effect of other medications.

The following drugs may need to have their dose changed when taken with MYLAN-VALGANCICLOVIR:

- Videx® (didanosine, ddI)
- Retrovir® (zidovudine, ZDV, AZT)
- Benuryl™ (probenecid)

Talk to your doctor if you are taking imipenem-cilastin. Convulsions have occurred in patients taking imipenem-cilastin and ganciclovir. You may discuss different options with your doctor.

PROPER USE OF THIS MEDICATION

Dosing Considerations:

- Your doctor has prescribed MYLAN-VALGANCICLOVIR after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your MYLAN-VALGANCICLOVIR to anyone else.
- To make sure that your therapy is as effective as possible, take your MYLAN-VALGANCICLOVIR exactly as your doctor prescribes it. Do not skip any doses, or take more than the recommended dose.
- Take MYLAN-VALGANCICLOVIR with food.
- Do not break or crush MYLAN-VALGANCICLOVIR tablets. Avoid contact with broken MYLAN-VALGANCICLOVIR 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 sterile or plain water if sterile water is not available.

Usual Dose:

Treatment of CMV Retinitis in Patients with AIDS

- The usual dosage for adults to get active CMV retinitis under control (induction therapy) is two 450 mg tablets twice a day for 21 days.
- The usual dosage for adults to help keep CMV retinitis under control (maintenance therapy) is two 450 mg tablets once a day.

Prevention of CMV Disease Solid Organ Transplantation

- The usual dosage to prevent CMV in adults who received a solid organ transplant is two 450 mg tablets once a day starting within 10 days of transplant and continuing until 100 days after the transplant.

Overdose:

In case of drug overdose or suspected drug overdose, particularly accidental oral ingestion, contact a healthcare practitioner (e.g. doctor), hospital emergency department, or regional poison control centre, even if there are no symptoms.

Missed Dose:

- If you forget to take a dose of MYLAN-VALGANCICLOVIR take it as soon as possible, then just carry on with the regular times you take your medication. If you remember your missed dose close to the time for your next dose, do not take the missed dose. Two doses of MYLAN-VALGANCICLOVIR should not be taken at the same time.
- Do not let your MYLAN-VALGANCICLOVIR run out. The amount of virus in your blood may increase if your medicine is stopped, even for a short time.
- It may be a good idea to ask your doctor or pharmacist ahead of time what to do about missed doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking MYLAN-VALGANCICLOVIR.

Blood problems. MYLAN-VALGANCICLOVIR can cause serious blood cell problems. These include reduced numbers of certain white blood cells (granulocytopenia, neutropenia, or leukopenia), reduced numbers of red blood cells (anemia), and reduced numbers of platelets (thrombocytopenia). MYLAN-VALGANCICLOVIR may also cause blood creatinine elevation, increased potassium in the blood, and abnormal liver function. Your doctor should recommend that you have blood tests done on a regular basis.

Kidney problems. MYLAN-VALGANCICLOVIR can cause an increase in serum creatinine (an indicator of kidney function). An increase in serum creatinine may indicate abnormal kidney function. Your doctor may have blood tests done on a regular basis to monitor your serum creatinine.

Common side effects. MYLAN-VALGANCICLOVIR can cause other side effects. In studies, the most common side effects with the use of MYLAN-VALGANCICLOVIR (although not necessarily related to MYLAN-VALGANCICLOVIR) were diarrhea, nausea, vomiting, fever, headache, trembling, graft rejection, swelling of the legs, constipation, back pain, insomnia (sleeplessness), high blood pressure.

Other side effects. Convulsions, sedation, dizziness, ataxia (unsteadiness) and/or confusion have also been reported with the use of MYLAN-VALGANCICLOVIR. If they occur, these side effects may affect a person's ability to drive a car or operate machinery.

Although there is no supporting information from clinical trials in humans, animal studies indicate that MYLAN-VALGANCICLOVIR may cause cancer and infertility in humans.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Call your doctor or pharmacist
		Only if severe	In all cases	
Common	**Blood Problems** **-Reduced number of white blood cells** Symptoms of infection of the gums, throat, upper airways and skin include: chills, fever (over 100˚F or 38˚C), sore mouth, cough, redness, pain or swelling of any area of your body, or pain or burning when you pass your urine. **-Reduced number of red blood cells** Symptoms: tiredness and weakness. **-Reduced number of platelets** Symptoms: increased bruising and bleeding.	√		
Uncommon	**Kidney Problems** **-Increase in serum creatinine** Symptoms: decreased urine output, lower back pain or side pain, or swelling of feet or lower legs.	√		

This is not a complete list of side effects. For any unexpected effects while taking MYLAN-VALGANCICLOVIR, contact your doctor or pharmacist.

HOW TO STORE IT

Preserve in tight container. Store at 25°C, excursion permitted between 15°C and 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- **Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);**
- **By calling 1-866-234-2345 (toll-free);**
- **By completing a Consumer Side Effect Reporting Form and sending it by:**
  - **Fax to 1-866-678-6789 (toll-free), or**
  - **Mail to: Canada Vigilance Program**
    Health Canada,
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect. (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php)

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379.

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