PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Auro-Valganciclovir

Valganciclovir Powder for Oral Solution

Powder for solution, 50 mg/mL when reconstituted valganciclovir (as valganciclovir hydrochloride), Oral

Antiviral Agent

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RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Auro-Valganciclovir (valganciclovir hydrochloride) is indicated for adult patients for:

- The treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).
- 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 7 WARNINGS AND PRECAUTIONS and 14 CLINICAL TRIALS for information on specific solid organ transplant subgroups)).

1.1 Pediatrics

Pediatrics (< 18 years of age): Safety and efficacy of valganciclovir hydrochloride in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): The pharmacokinetic profiles of valganciclovir hydrochloride in elderly patients have not been established. (See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Auro-Valganciclovir (valganciclovir hydrochloride) is contraindicated in patients who are hypersensitive to valganciclovir, ganciclovir or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- The clinical toxicity of Auro-Valganciclovir (valganciclovir hydrochloride) includes: Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure, and aplastic anemia (see 8 ADVERSE REACTIONS).
- In animal and in vitro studies, ganciclovir was mutagenic, teratogenic, carcinogenic and caused aspermia; therefore it should be considered a potential teratogen and carcinogen in humans (see 16 NON-CLINICAL TOXICOLOGY).

- Auro-Valganciclovir is indicated for use only in immunocompromised patients, where the potential benefit outweighs the risks stated herein.
- The safety and efficacy of Auro-Valganciclovir have not been evaluated for congenital or neonatal CMV disease, nor for treatment of CMV infection in non-immunocompromised individuals (see 1 INDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Note: This Product Monograph is for Auro-Valganciclovir as a powder for oral solution only. When Auro-Valganciclovir oral tablets are used, the Product Monograph for Auro-Valganciclovir (Valganciclovir hydrochloride tablet) should be consulted.

- **Caution - Strict adherence to dosage recommendations is essential to avoid overdose.**
- Auro-Valganciclovir (valganciclovir hydrochloride) is administered orally, and should be taken with food (see 10 CLINICAL PHARMACOLOGY, 10.3 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 valganciclovir hydrochloride tablets or Auro-Valganciclovir powder for oral solution as described below should be closely followed (see 7 WARNINGS AND PRECAUTIONS, General and 5 OVERDOSAGE).

- Dosage adjustment is necessary for patients on hemodialysis (CrCl < 10 mL/min) (see 7 WARNINGS AND PRECAUTIONS, General and Renal, Patients undergoing hemodialysis, 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hemodialysis).

- The ganciclovir systemic exposure following administration of 900 mg valganciclovir oral solution is equivalent to a 900 mg valganciclovir dose administered as two 450 mg tablets (see 14 CLINICAL TRIALS, 14.3 Comparative Bioavailability Studies).

- 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/mcL, or the hemoglobin is less than 80 g/L, or the platelet count is less than 25,000/mcL (see 7 WARNINGS AND PRECAUTIONS, Hematologic and Monitoring and Laboratory Tests and 8 ADVERSE REACTIONS).

- Due to the frequency of leukopenia, granulocytopenia (neutropenia), anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia in patients taking Auro-Valganciclovir, 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/mcL 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 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

- The oral dispenser is graduated in mL. A 50 mg dose is equivalent to 1 mL.

Valganciclovir dose	Auro-Valganciclovir for Oral Solution to be administered
50 mg	1 mL
75 mg	1.5 mL
100 mg	2 mL
500 mg	10 mL

4.2 Recommended Dose and Dosage Adjustment

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

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 Auro-Valganciclovir (see Renal Impairment). Dosage reductions should also be considered for those with neutropenia, anemia and/or thrombocytopenia (see 8 ADVERSE REACTIONS). Auro-

Valganciclovir should not be administered in patients with severe neutropenia (ANC less than 500/mcL), severe thrombocytopenia (platelets less than 25,000/mcL), or severe anemia (hemoglobin less than 80 g/L).

Renal Impairment: Serum creatinine or estimated creatinine clearance levels should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance as shown in Tables 1 and 2 below (see 7 WARNINGS AND PRECAUTIONS, Renal and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, 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 7 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 2 below (see 7 WARNINGS AND PRECAUTIONS, Renal, Patients undergoing hemodialysis, 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations Dosing and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hemodialysis).

Table 1: 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

Table 2: Auro-Valganciclovir Powder for Oral Solution Dose for Patients with Impaired Renal Function

CrCl* (mL/min)	Treatment of CMV Retinitis		Prophylaxis of CMV Disease in Solid Organ Transplantation Auro-Valganciclovir Oral Solution
	Induction Dose Auro-Valganciclovir Oral Solution	Maintenance Dose Auro-Valganciclovir Oral Solution	
≥ 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	225 mg once daily	225 mg once daily
10 - 24	225 mg once daily	125 mg once daily	125 mg once daily

< 10	200 mg (three times a week after dialysis)	100 mg (three times a week after dialysis)	100 mg (three times a week after dialysis)

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

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

Pediatrics

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, 1.1 Pediatrics, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

4.3 Reconstitution Oral Solutions:

Auro-Valganciclovir powder for oral solution requires reconstitution prior to oral administration.

Since Auro-Valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling the powder and the reconstituted solution. Avoid inhalation or direct contact of the powder and solution with skin and mucous membranes. If such contact occurs, wash thoroughly with soap and water. If the powder or solution gets into the eyes, rinse eyes thoroughly with sterile water or plain water if sterile water is not available (see 12 SPECIAL HANDLING INSTRUCTIONS).

It is recommended that Auro-Valganciclovir powder for oral solution be reconstituted by the pharmacist prior to dispensing to the patient.

Preparation of solution

- Measure 91 mL of purified water in a graduated cylinder.
- Remove the child resistant cap, add the water to the bottle, and close the bottle with the child resistant cap. Shake the closed bottle until the powder is dissolved.
- Remove the child resistant cap and push the bottle adapter into the neck of the bottle.
- Close bottle with child resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.
- Write the date of expiration of the reconstituted solution on the bottle label. The shelf-life of the reconstituted solution is 49 days when stored at 2-8°C (see 11 STORAGE, STABILITY AND DISPOSAL).

Several guidelines for the handling and disposal of hazardous pharmaceuticals (including cytotoxic drugs) are available (e.g. CSHP, 1997) (see 11 STORAGE, STABILITY AND DISPOSAL).

4.4 Administration

Auro-Valganciclovir should be administered orally, and should be taken with food (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Absorption).

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

4.5 Missed Dose

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

5 OVERDOSAGE

Overdose Experience with Valganciclovir hydrochloride Tablets and with Intravenous Ganciclovir

Ganciclovir is readily removable by hemodialysis. Data obtained during intermittent haemodialysis in patients dosed with valganciclovir showed estimated dialysis clearance as 138 mL/min ± 9.1% (N = 3) and intra-dialysis half-life estimated to 3.47 h (N = 6). During a 3 hour dialysis session, 55% of ganciclovir was removed (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hemodialysis).

One adult developed fatal bone marrow failure (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 Auro-Valganciclovir could result in increased renal toxicity (see 7 WARNINGS AND PRECAUTIONS, General and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

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

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting.

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

Hepatotoxicity: hepatitis, liver function disorder.

Neurotoxicity: generalized tremor, seizure.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Note: This Product Monograph is for Auro-Valganciclovir as a powder for oral solution only. When Auro-Valganciclovir oral tablets are used, the Product Monograph for Auro-Valganciclovir (Valganciclovir hydrochloride tablet) should be consulted.

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Powder for oral solution / 50 mg/mL valganciclovir (as valganciclovir hydrochloride) when reconstituted	Mannitol, Povidone, Saccharin sodium, Sodium Benzoate, Tartaric Acid and Tutti Frutti Flavour 51880 AP0551

Powder for Oral Solution
Each bottle contains 5.515 g valganciclovir hydrochloride (corresponding to 5 g valganciclovir), in 12 g powder for oral solution. Following reconstitution, 1 mL solution contains 55.15 mg valganciclovir hydrochloride corresponding to 50 mg valganciclovir (free base).

Auro-Valganciclovir powder for oral solution is available as a white to off white powder (granulate). Available in a carton containing an amber glass bottle with child-resistant plastic screw cap, a bottle adapter and a sealed bag containing 2 oral dispensers.

Each bottle contains 12 g of powder for oral solution. When reconstituted, the volume of the solution is 100 mL, providing a minimal usable volume of 88 mL.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 aspermia. Therefore it should be considered a potential teratogen and carcinogen in humans. Auro-Valganciclovir is indicated for use only in immunocompromised patients, where the potential benefit outweighs the risks. Safety and efficacy of valganciclovir hydrochloride has 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 14 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 1 INDICATIONS 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 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Genotoxicity for discussion on animal data).

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery. Adverse reactions such as seizures, dizziness, ataxia and/or confusion have also been reported with the use of valganciclovir hydrochloride and/or ganciclovir (see 8 ADVERSE REACTIONS). If they occur, such effects may affect tasks requiring alertness, including a patient's ability to drive and operate machinery.

Hematologic

Auro-Valganciclovir should not be administered if the absolute neutrophil count is less than 500 cells/mcL, the platelet count is less than 25,000/mcL, or the hemoglobin is less than 80 g/L. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia have been observed in patients treated with valganciclovir hydrochloride tablets (and ganciclovir) (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations).

Auro-Valganciclovir should, therefore, be used with caution in patients with pre-existing hematological cytopenias, a history of drug-related hematological cytopenia, 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.

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving valganciclovir hydrochloride (see 8 ADVERSE REACTIONS), complete blood counts with differential and platelet counts should be performed frequently, especially in patients with renal

impairment and 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/mcL at the beginning of treatment.

Thrombocytopenia

Patients with low baseline platelet counts (<100,000 /mcl) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with HIV. Severe thrombocytopenia may be associated with potentially life-threatening bleeding. (See 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

The safety and efficacy of valganciclovir hydrochloride have not been established in patients with hepatic impairment.

HIV and CMV Retinitis

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

Patients with HIV may be receiving zidovudine (ZDV); patients should be counselled that as zidovudine and Auro-Valganciclovir each have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy (see 9 DRUG INTERACTIONS).

Monitoring and Laboratory Tests

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving Auro-Valganciclovir (see 8 ADVERSE REACTIONS), complete blood counts with differential and platelet counts should be performed frequently, especially in patients with renal impairment and 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/mcL at the beginning of treatment.

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, treatment with hematopoietic growth factors and/or the dose interruption of therapy is recommended. 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 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

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 Auro-Valganciclovir.** Such adjustments should be based on measured or estimated creatinine clearance values (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

Auro-Valganciclovir should be used with caution in patients with impaired renal function. Both the plasma half-life of ganciclovir as well as peak plasma levels are increased in patients with elevated serum creatinine levels.

Patients undergoing hemodialysis

Dosage adjustment is necessary for patients on hemodialysis (CrCl < 10mL/min) (see 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations and 4.2 Recommended Dose and Dosage Adjustment and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hemodialysis).

Acute Kidney Injury

Acute kidney injury may occur in:
Elderly patients with or without reduced renal function. Caution should be exercised when administering Auro-Valganciclovir to geriatric patients, and dosage reduction is recommended for those with impaired renal function (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

Patients receiving potential nephrotoxic drugs. Caution should be exercised when administering Auro-Valganciclovir to patients receiving potential nephrotoxic drugs.

Patients without adequate hydration. Adequate hydration should be maintained for all patients.

Reproductive Health: Female and Male Potential

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 12 SPECIAL HANDLING INSTRUCTIONS).

- **Fertility**

  Based on non-clinical studies, valganciclovir hydrochloride may cause temporary or permanent inhibition of spermatogenesis. 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 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity). Animal data also indicate that suppression of fertility in females may occur.

Based on a clinical study in renal transplant patients receiving, valganciclovir hydrochloride for CMV prophylaxis for up to 200 days, spermatogenesis was inhibited during treatment with valganciclovir hydrochloride compared to an untreated control group.

- **Teratogenic Risk**

  Ganciclovir may cause fetal toxicity when administered to pregnant women based on findings in animal studies. When given to pregnant rabbits at dosages resulting in 2-times the human exposure (based on AUC), ganciclovir caused malformations in multiple organs of the fetuses. Maternal and fetal toxicity were also observed in pregnant mice and rabbits. Therefore, Auro-Valganciclovir has the potential to cause birth defects. Pregnancy should be avoided in female patients taking Auro-Valganciclovir and in females with male partners taking Auro-Valganciclovir.

  Prior to initiation of treatment with Auro-Valganciclovir, patients should be advised of the potential mutagenic and teratogenic risk of ganciclovir to the fetus. Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment. Similarly, men are recommended to use condoms with female partners during, and for at least 90 days following treatment with Auro-Valganciclovir. If pregnancy does occur during treatment or within 30 days from stopping treatment, the patient must be advised of the potential significant teratogenic risk of Auro-Valganciclovir to the fetus (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Genotoxicity).

  For further discussion on animal data see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

Transplant Recipients

Renal and hepatic dysfunction are reported more frequently in organ transplant patients.

7.1 Special Populations

7.1.1 Pregnant Women

Since there are no adequate and well-controlled studies in pregnant women, the safety of valganciclovir hydrochloride for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of valganciclovir hydrochloride should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

Ganciclovir may cause fetal toxicity when administered to pregnant women based on findings in animal studies (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

Human data are not available but animal data indicates that ganciclovir is excreted in the milk of

lactating rats. Since 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. Auro-Valganciclovir should not be given to breastfeeding mothers. Mothers should be instructed to discontinue the drug or discontinue nursing if they are receiving Auro-Valganciclovir.

7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of valganciclovir hydrochloride in pediatric patients (< 18 years of age) have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions). The use of Auro-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.

7.1.4 Geriatrics

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 Auro-Valganciclovir (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions).

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 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

8 ADVERSE REACTIONS

8.1 Adverse 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 valganciclovir hydrochloride. All of the adverse drug reactions and adverse events observed in clinical studies of valganciclovir hydrochloride have

been previously observed with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see Table 4).

In patients treated with valganciclovir/ganciclovir the most serious and frequent adverse drug reactions are haematological reactions and include neutropenia, anaemia and thrombocytopenia.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

HIV-1 INFECTED SUBJECTS

The frequencies presented in the table of adverse reactions are derived from a pooled population of HIV-infected patients (n=1704) receiving maintenance therapy with ganciclovir (GAN 1697, GAN 1653, 2304, GAN 1774, GAN 2226, AVI 034, GAN 041) or valganciclovir (WV1537, WV15705). Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia the frequencies of which are derived from post-marketing experience. Frequencies are presented as percentages and as CIOMS frequency categories defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in HIV patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC < 500/ mcL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

Table 4 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704)

ADR (MedDRA) System Organ Class	**Percentage**
Infections and infestations	
Candida infections including oral candidiasis.	22.42%
Upper respiratory tract infection	16.26
Sepsis	6.92
Influenza	3.23
Urinary tract infection	2.35

Cellulitis	1.47
Blood and lymphatic disorders:	
Neutropenia	26.12
Anemia	19.89
Thrombocytopenia	7.34
Leukopenia	3.93
Pancytopenia	1.06
Bone marrow failure	0.29
Aplastic anemia	0.06
Agranulocytosis*	0.02
Granulocytopenia*	0.02
Immune system disorders	
Hypersensitivity	1.12
Anaphylactic reaction*	0.02
Metabolic and nutritional disorders	
Decreased appetite	12.09
Weight decreased	6.46
Psychiatric disorders	
Depression	6.69
Confusional state	2.99
Anxiety	2.64
Agitation	0.59
Psychotic disorder	0.23
Thinking abnormal	0.18
Hallucinations	0.18
Nervous system disorders:	
Headache	17.37
Insomnia	7.22
Neuropathy peripheral	6.16
Dizziness	5.52
Paraesthesia	3.58
Hypoaesthesia	2.58
Seizures	2.29
Dysgeusia (taste disturbance)	1.35
Tremor	0.88
Eye Disorders	
Visual impairment	7.10
Retinal detachment**	5.93
Vitreous floaters	3.99
Eye pain	2.99
Conjunctivitis	1.58
Macular oedema	1.06
Ear and labyrinth disorders	
Ear pain	1.17
Deafness	0.65
Cardiac disorders	
Arrhythmias	0.47

Vascular disorders	
Hypotension	2.05
Respiratory, thoracic and mediastinal disorders	
Cough	18.31
Dyspnoea	11.80
Gastrointestinal disorders	
Diarrhea	34.27
Nausea	26.35
Vomiting	14.85
Abdominal pain	10.97
Dyspepsia	4.81
Flatulence	4.58
Abdominal pain upper	4.58
Constipation	3.70
Mouth ulceration	3.17
Dysphagia	2.93
Abdominal distention	2.41
Pancreatitis	1.64
Hepato-biliary disorders	
Blood alkaline phosphatase increased	3.58
Hepatic function abnormal	3.23
Aspartate aminotransferase increased	1.88
Alanine aminotransferase increased	1.23
Skin and subcutaneous tissue disorder	
Dermatitis	11.80
Night sweats	7.92
Pruritus	4.58
Rash	2.52
Alopecia	1.29
Dry skin	0.94
Urticaria	0.70
Musculo-skeletal and connective tissue disorders	
Back pain	4.46
Myalgia	3.52
Arthralgia	3.35
Muscle spasms	2.99
Renal and urinary disorders	
Renal impairment	2.52
Creatinine clearance renal decreased	2.35
Blood creatinine increased	1.88
Kidney injury	0.76
Hematuria	0.70
Reproductive system and breast disorders	
Infertility male	0.23
General disorders and administration site conditions	
Pyrexia	33.51
Fatigue	18.96

Pain	5.81
Chills	5.40
Malaise	2.11
Asthenia	2.00
Chest pain	0.88

** The frequencies of these adverse reactions are derived from post-marketing experience*
Description of selected adverse reactions
***Retinal detachment has only been reported in HIV patients treated for CMV retinitis*

Neutropenia

The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalizes within 2 to 5 days after discontinuation of the drug or dose reduction (see 7 WARNINGS AND PRECAUTIONS).

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 5).

Table 5: 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	-	6%
Pyrexia	14%	13%
Neutropenia	14%	13%

Table 6 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 6 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 6 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 6: 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

	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 (%)**
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	41	30	29
Nausea	30	23	23
Vomiting	21	16	14
Abdominal pain	15	14	14
Constipation	8	20	20
Abdominal pain upper	6	9	6
Dyspepsia	4	12	10
Abdominal distention	3	6	6
Ascites	--	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
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	--	--

	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 (%)**
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	--	--
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

	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 (%)**
Renal and urinary disorders			
Dysuria	2	7	6
Renal impairment	1	7	12
Respiratory, thoracic and mediastinal disorders			
Cough	19	6	8
Dyspnea	9	11	10
Productive cough	6	2	2
Nasal congestion	5	4	1
Sore throat	5	3	5
Rhinorrhea	3	4	6
Pleural effusion	< 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

8.3 Less Common Clinical Trial Adverse Reactions

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 failure, 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.

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, kidney injury, urinary frequency.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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

Table 7: Laboratory Abnormalities Reported in Two Clinical Studies in the Treatment of CMV Retinitis and One Clinical Study in Transplantation

	CMV Retinitis Patients (WV15376 and WV15705)	Solid Organ Transplant Patients (PV16000)

Laboratory Abnormalities	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/mcL			
<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/mcL			
<25000	4	0	2
25000 - <50000	6	1	3
50000 - <100000	22	18	21

Severe neutropenia (ANC <500/mcL) 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.

8.5 Post-Market Adverse Reactions

As valganciclovir hydrochloride is rapidly and extensively converted to ganciclovir, any adverse events associated with ganciclovir might also occur with valganciclovir hydrochloride. 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

Safety reports from the postmarketing setting are consistent with safety data from clinical trials with valganciclovir and ganciclovir (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions, CYTOVENE Post-Marketing Adverse Events) /valganciclovir.

CYTOVENE Post-Marketing Adverse Events

The following adverse events have been reported since the marketing introduction of CYTOVENE. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness frequency of reporting, the apparent causal connection, or a combination of these factors:

Acidosis, allergic reaction, anaphylactic reaction, arthritis, bronchospasm, cardiac arrest, cardiac conduction abnormality, cataracts, cholelithiasis, cholestasis, congenital anomaly, dry eyes, dysesthesia, dysphasia, elevated triglyceride levels, exfoliative dermatitis, extrapyramidal reaction, facial palsy, hallucinations, hemolytic anemia, hemolytic-uremic syndrome, hepatic failure, hepatitis, hypercalcemia, hyponatremia inappropriate serum ADH, infertility, intestinal ulceration, intracranial hypertension, irritability, ischemia, loss of memory, loss of sense of smell, myelopathy, peripheral oculomotor nerve paralysis, pulmonary fibrosis, renal tubular disorder, rhabdomyolysis, Stevens-Johnson syndrome, stroke, testicular hypotrophy, Torsades de Pointes, vasculitis, ventricular tachycardia.

Adverse events from post-marketing spontaneous reports with ganciclovir that were reported in HIV infected or other immunocompromised patients such as transplant recipients, which are not mentioned in any section above, and for which a causal relationship cannot be excluded, are: anaphylaxis, decreased fertility in males.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Drug Interaction Studies Conducted with Valganciclovir: Valganciclovir (pro-drug of ganciclovir) is rapidly and extensively converted to ganciclovir; therefore interactions associated with ganciclovir are expected.

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.

9.2 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.3 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 8: 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. A pharmacodynamic interaction may occur during concomitant administration of these drugs. 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	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 closely monitored for evidence of ganciclovir toxicity.
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 9: 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, A pharmacodynamic interaction may occur during concomitant administration of these drugs. 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 (e.g. pancreatitis).
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 (e.g. pancreatitis).
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 (e.g. pancreatitis).
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: Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamics interaction between these two drugs cannot be discounted. Valganciclovir hydrochloride 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.

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 / valganciclovir is coadministered with other drugs known to be myelosuppressive or associated with renal impairment. This includes nucleoside analogues (e.g. zidovudine, didanosine, stavudine), immunosuppressants (e.g. cyclosporine, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g.vincristine, vinblastine, doxorubicin, hydroxyurea), anti-infective agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine) and pegylated interferons/ribavirin. Therefore, these drugs should only be considered for concomitant use with valganciclovir if the potential benefits outweigh the potential risks.

Since ganciclovir is excreted through the kidney via glomerular filtration and active tubular secretion (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Elimination), 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.

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 (IC50) *in vitro* (laboratory strains or clinical isolates) has ranged from 0.02 to 3.58 mcg/mL (0.08 to 14.32 mcM). Ganciclovir inhibits mammalian cell proliferation (CIC50) *in vitro* at higher concentrations ranging from 10.21 to >250 mcg/mL (40 to >1000 mcM). Bone marrow-derived colony-forming cells are more sensitive (CIC50 0.69 to 3.06 mcg/mL; 2.7 to 12 mcM). The relationship of *in vitro* sensitivity of CMV to ganciclovir and clinical response has not been established.

10.2 Pharmacodynamics

Refer to Section 10.1 Mechanism of Action. Additional information in the Product Monograph not included at the time of authorization.

10.3 Pharmacokinetics

Because the major elimination pathway for ganciclovir is renal, dosage reductions according to creatinine clearance are required for valganciclovir hydrochloride. For dosing instructions in patients with renal impairment, refer to 4 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

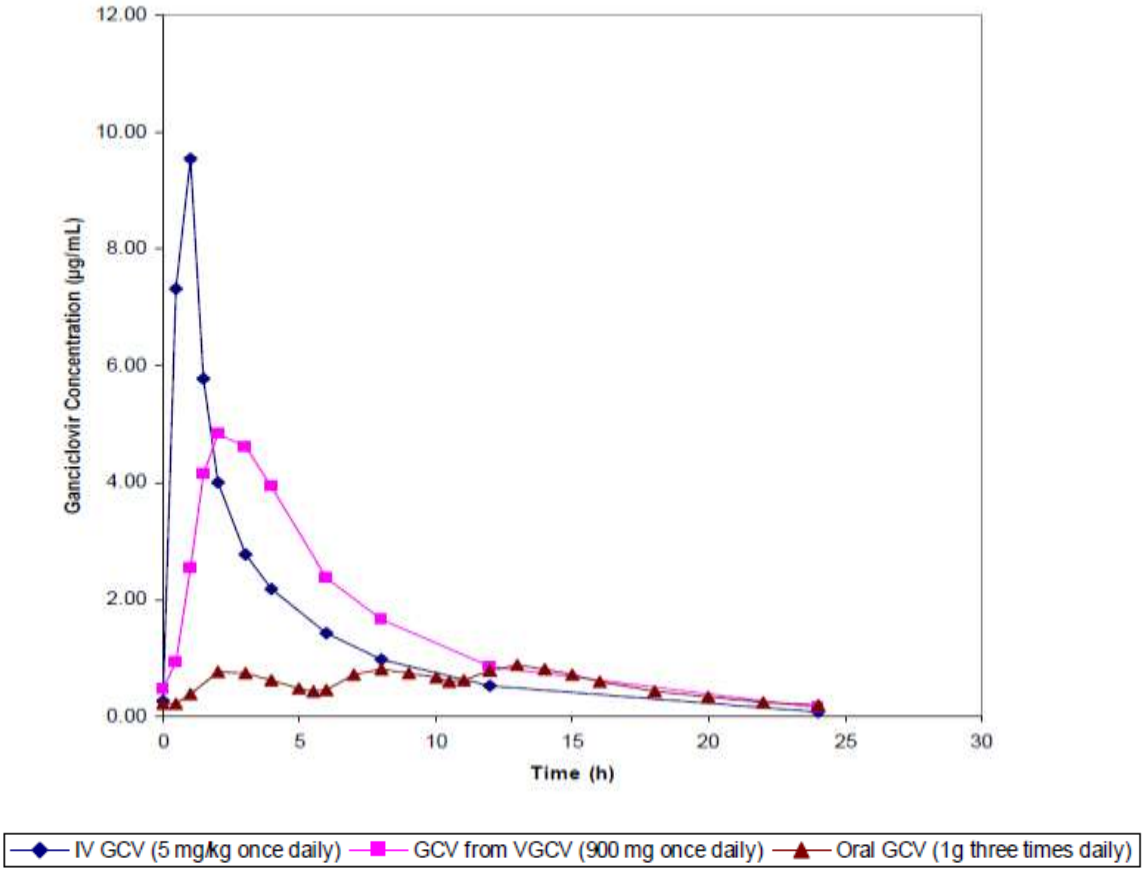
Formulation	Valganciclovir hydrochloride Tablets	CYTOVENE IV	Ganciclovir Capsules
Dosage	900 mg once daily with food	5 mg/kg once daily	1000 mg three times daily with food
$AUC_{0\text{-}24\ hr}$ (mcg•h/mL)	29.1 ±9.7 (3 studies, n=57)	26.5±5.9 (4 studies, n=68)	Range of means 12.3 to 19.2 (6 studies, n=94)
C_{max} (mcg/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 mcg•h/mL vs 47.61mcg•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_{0-24h}) of solid organ transplant patients to ganciclovir after daily oral administration of valganciclovir and ganciclovir was 46.3 ± 15.2 mcg•h/mL and 28.0 ± 10.9 mcg•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**
$AUC_{0-24\ hr}$ (mcg•h/mL)	26.6 ± 11.6	40.2 ± 11.8
C_{max} (mcg/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**
$AUC_{0-24\ hr}$ (mcg•h/mL)	24.9 ± 10.2	46.0 ± 16.1
C_{max} (mcg/mL)	1.3 ± 0.4	5.4 ± 1.5
Elimination half-life (hr)	7.68 ± 2.74	6.18 ±1.42
Kidney Transplant Recipients*	**N=36**	**N=68**
$AUC_{0-24\ hr}$ (mcg•h/mL)	31.3 ± 10.3	48.2 ± 14.6
C_{max} (mcg/mL)	1.5 ± 0.5	5.3 ± 1.5
Elimination half-life (hr)	9.44 ± 4.37	6.77 ± 1.25

* Includes kidney-pancreas

The pharmacokinetics of valganciclovir hydrochloride tablets in stable liver transplant patients were investigated in one open label 4-part crossover study (n=28). The bioavailability of ganciclovir from valganciclovir following a single dose of 900 mg valganciclovir hydrochloride tablets under fed conditions was approximately 60%.

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

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 mcg•h/mL (n=75), and the maximum plasma concentration (C_{max}) was 5.37 ± 1.53 mcg/mL (n=76).

Following the administration of valganciclovir as an oral solution, equivalent systemic ganciclovir exposures were obtained compared to the tablet formulation (see 14 CLINICAL TRIALS, 14.3 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 tablets be administered with food (see 4 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 mcg/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 tablets according to weight is not required.

Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. Ganciclovir itself is not metabolized to a significant extent (1%-2%).

Elimination

The major route of elimination of valganciclovir is by renal excretion as ganciclovir through glomerular filtration and active tubular secretion. Systemic clearance of intravenously administered ganciclovir was 3.05 ± 0.81 mL/min/kg (n=86) while renal clearance was 2.40 ± 0.93 mL/min/kg (n=46). In patients with normal renal function greater than 90% of IV administered, ganciclovir was recovered un-metabolized in the urine within 24 hours. In patients with normal renal function, the post-peak plasma concentrations of valganciclovir decline with a half-life ranging from 0.4 to 2.0 hours. In these patients, ganciclovir concentrations decline with a half-life ranging from 3.5 to 4.5 hours, similarly to that observed after direct IV administration of ganciclovir.

The terminal half-life (t½) 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 t½ 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** Based on the data submitted and reviewed by Health Canada, the pharmacokinetic characteristics of valganciclovir hydrochloride in pediatric patients have not been well established; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics and 14 CLINICAL TRIALS).

- **Geriatrics** No studies of valganciclovir hydrochloride have been conducted in adults older than 65 years of age (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics). However as valganciclovir is a pro-drug of ganciclovir and because ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in elderly.
- **Sex** Insufficient data are available to demonstrate any effect of gender on the pharmacokinetics of valganciclovir.
- **Ethnic Origin** Insufficient data are available to demonstrate any effect of race on the pharmacokinetics of valganciclovir.
- **Hemodialysis** Ganciclovir is readily removable by hemodialysis. Data obtained during intermittent haemodialysis in patients dosed with valganciclovir showed estimated dialysis clearance as 138 mL/min ± 9.1% (N = 3) and intra-dialysis half-life estimated to 3.47 h (N = 6). During a 3 hour dialysis session, 55% of ganciclovir was removed.

  For patients receiving hemodialysis (CrCl < 10 mL/min) valganciclovir hydrochloride powder for oral solution is recommended to provide an individualized dose (see 7 WARNINGS AND PRECAUTIONS, Renal, Patients undergoing hemodialysis and 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations and 4.2 Recommended Dose and Dosage Adjustment).
- **Hepatic Insufficiency** No pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment undergoing valganciclovir therapy.
- **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 12: 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} (mcg•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 7 WARNINGS AND PRECAUTIONS, Renal and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment, Renal Impairment).

11 STORAGE, STABILITY AND DISPOSAL

Auro-Valganciclovir powder for oral solution

Do not store dry powder above 30°C. Store reconstituted solution in a refrigerator at 2-8°C. After reconstitution with purified water, the solution should not be used for longer than 49 days. For preparation of the reconstituted medicinal product see 4 DOSAGE AND ADMINISTRATION, 4.3 Reconstitution.

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 Auro-Valganciclovir should follow provincial, municipal, and local hospital guidelines or requirements.

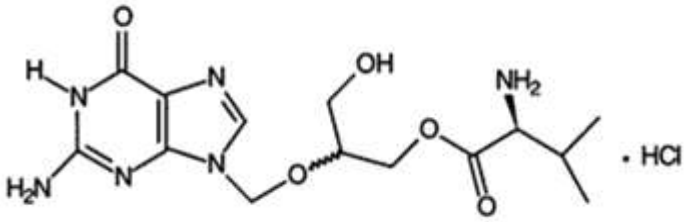
12 SPECIAL HANDLING INSTRUCTIONS

Caution should be exercised in the handling of Auro-Valganciclovir (valganciclovir hydrochloride) powder for oral solution. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential). 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. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Valganciclovir hydrochloride
Chemical name:	L-Valine, ester with 9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl] guanine, monohydrochloride
Molecular formula and Molecular Mass:	$C_{14}H_{22}N_6O_5HCl$ 390.83 g/mol
Structural formula:	
Physicochemical properties:	a. Physical Form: Valganciclovir hydrochloride is a white to off-white powder b. Solubility: Very slightly soluble in alcohol, practically insoluble in 2-propanol, in Hexane, in Acetone and in Ethyl Acetate. c. pKa and pH values: pKa = 7.6 pH (2% aqueous solution at 20°C) = 4.0 to 5.0 d. Melting Point: Valganciclovir hydrochloride melts with decomposition above 180°C

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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 log10, 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 13 provides the outcomes at four weeks.

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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). 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.

14.2 Study Results

Induction Therapy of CMV Retinitis: Study WV15376

Table 13: Week 4 Masked Review of Retinal Photographs in Study WV15376

	CYTOVENE-IV	Valganciclovir hydrochloride
Determination of CMV retinitis progression at Week 4	N=80	N=80
Progressor	7	7

Non-progressor	63	64
Death Discontinuations due to Adverse Events Failed to return	2 1 1	1 2 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.

Prevention of CMV Disease in Solid Organ Transplantation: Study PV16000

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 14.

Table 14: Percentage of Patients with CMV Disease and Tissue-Invasive CMV Disease by Organ Type: Endpoint Committee, 6 Months ITT Population

	CMV Disease1		**Tissue-Invasive CMV Disease**		**CMV Syndrome**	
Organ	VGCV (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)	VGCV (N=239)	GCV (N=125)
Liver (n=177)	19% (22/118)	12% (7/59)	14% (16/118)	3% (2/59)	5% (6/118)	9% (5/59)
Kidney (n=120)	6% (5/81)	23% (9/39)	1% (1/81)	5% (2/39)	5% (4/81)	18% (7/39)
Heart (n=56)	6% (2/35)	10% (2/21)	0% (0/35)	5% (1/21)	6% (2/35)	5% (1/21)
Kidney / Pancreas (n=11)	0% (0/5)	17% (1/6)	0% (0/5)	17% (1/6)	0% (0/5)	0% (0/6)

GCV = oral ganciclovir; VGCV= 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 7 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%).

14.3 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of Auro-Valganciclovir (Auro Pharma Inc.) with PrVALCYTE® (Hoffmann-La Roche Limited), administered as 18 mL x 50 mg/mL reconstituted oral solution, was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 37 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Valganciclovir (18 mL x 50 mg/mL) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	493.65 511.91 (34.1)	468.77 478.57 (20.5)	105.3	101.7 - 109.0
AUC_I (ng·hr/mL)	498.09 516.36 (33.9)	472.81 482.59 (20.4)	105.4	101.8 - 109.0
C_{max} (ng/mL)	275.69 309.22 (74.9)	258.45 270.10 (33.4)	106.7	98.4 - 115.7
T_{max}[3] (hr)	0.75 (0.20 - 2.00)	0.75 (0.33 - 2.00)		
$T_{1/2}$[4] (hr)	0.81 (16.2)	0.83 (15.4)		

[1] Auro-Valganciclovir (powder for solution, valganciclovir as valganciclovir hydrochloride), 50 mg/mL when reconstituted (Auro Pharma Inc.).

[2] PrVALCYTE® (powder for solution, valganciclovir as valganciclovir hydrochloride), 50 mg/mL when reconstituted (Hoffmann-La Roche Limited).

[3] Expressed as the median (range) only.

[4] Expressed as the arithmetic mean (CV%) only.

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.

Table 15: 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#**
AUC_{24} (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}§	2.11	2.79		
(h)	2.33 (49.6%)	3.00 (34.5%)		
T½ § (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

15 MICROBIOLOGY

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

In a study of 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 16).

Table 16: 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). UL97 mutations arise earlier and more frequently than mutations in UL54. Virus with mutations in the UL97 gene is resistant to ganciclovir alone with M460V/I, H520Q, C592G, A594V, L595S, C603W being the most frequently reported ganciclovir resistance-associated substitutions, whereas virus with mutations in the UL54 gene may show cross- resistance to other antivirals that target the viral polymerase and vice versa. Amino acid substitutions in UL54 conferring cross-resistance to ganciclovir and cidofovir are generally located within the exonuclease domains and region V, however amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805- 845).

The current working definition of CMV resistance to ganciclovir in *in vitro* assays is IC50 >1.5 mcg/mL (6.0 mcM). 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.

<u>Treatment of CMV Retinitis in AIDS Patients</u>

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.

<u>Prevention of CMV Disease in Solid Organ Transplant Recipients</u>

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.

16 NON-CLINICAL TOXICOLOGY

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

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.

General Toxicology:

Acute Toxicity: The acute toxicity of valganciclovir was assessed in single-dose oral studies in mice and dogs. Single oral doses of up to 2000 mg/kg valganciclovir to mice did not show adverse findings. In dogs, single doses of 500 and 1000 mg/kg led to reduced white blood cell, neutrophil and platelet counts. Vomiting was observed at 100 mg/kg within 3 hours of dosing.

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.

Carcinogenicity: 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.

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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. 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Valcyte, powder for oral solution, 50 mg / mL, submission control number 264707, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. (July 11, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Auro-Valganciclovir

Valganciclovir Powder for Oral Solution

Read this carefully before you start taking **Auro-Valganciclovir** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Auro-Valganciclovir**.

Serious Warnings and Precautions

- **Blood problems:** Auro-Valganciclovir can cause serious blood cell problems. These include reduced numbers of white blood cells, reduced numbers of red blood cells and reduced numbers of platelets. See "Serious side effects and what to do about them" table.
- **Cancer, Fertility and Birth Defects:** Auro-Valganciclovir causes cancer in animals and may cause cancer in people. Auro-Valganciclovir also has damaging effects on the reproductive system. In men, it may decrease the number of sperm in the semen and this may be complete and irreversible. In women, it may cause fertility problems. It may also cause birth defects. See "Other warnings you should know about".

What is Auro-Valganciclovir used for?

- Auro-Valganciclovir is used to treat a disease called cytomegalovirus (CMV) retinitis in adults who have acquired immunodeficiency syndrome (AIDS).
- Auro-Valganciclovir is also used to prevent CMV disease in adults who have received a solid organ transplant and are at risk of developing CMV disease.

How does Auro-Valganciclovir work?

- Auro-Valganciclovir is a prescription medicine that belongs to the family of drugs known as "antivirals". It is used to treat infections caused by viruses.
- Auro-Valganciclovir works by slowing the growth of the CMV virus.
- Auro-Valganciclovir contains valganciclovir, which is the starting form of the medicine ganciclovir. This means the valganciclovir 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.
- Your doctor will let you know how long to take Auro-Valganciclovir for and if it is working for you.

What are the ingredients in Auro-Valganciclovir?

Medicinal ingredient: valganciclovir hydrochloride

Non-medicinal ingredients: Mannitol, Povidone, Saccharin sodium, Sodium Benzoate, Tartaric Acid and Tutti Frutti Flavour 51880 AP0551

Auro-Valganciclovir comes in the following dosage form:

As a powder for oral solution. The fruit-flavoured solution containing 50 mg / mL valganciclovir (as valganciclovir hydrochloride) will be prepared by your pharmacist.

Do not use Auro-Valganciclovir if you:

- Are allergic to valganciclovir or to ganciclovir.
- Are allergic to any of the other ingredients in Auro-Valganciclovir or to a component of the container.
- Are allergic to the antiviral medicine acyclovir or to valacyclovir, as a similar reaction can occur with Auro-Valganciclovir.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Auro-Valganciclovir. Talk about any health conditions or problems you may have, including if you:

- Have kidney problems.
- Have liver problems.
- Are receiving hemodialysis since your dose of Auro-Valganciclovir will need to be modified.
- Are receiving or have received radiation therapy.

Other warnings you should know about:

Blood problems:
Auro-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). See "Serious Warnings and Precautions" box. If you have or had a history of blood problems or abnormal results on your blood tests, please talk to your healthcare professional before you take Auro-Valganciclovir. Auro-Valganciclovir may also cause blood creatinine elevation and abnormal liver function. Your doctor should recommend that you have blood tests done on a regular basis.

Kidney problems:
Auro-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.

Pregnancy and Birth Defects:
Tell your doctor if you are pregnant or planning to become pregnant. Auro-Valganciclovir may cause birth defects and should not be used during pregnancy. If you are a woman of child-bearing potential, then you should avoid pregnancy. You must use effective contraception

during treatment and for 30 days after stopping treatment. Effective contraception includes a barrier method, such as a condom plus an additional method like birth control pills or an intrauterine device. If you are a male taking Auro-Valganciclovir with a female partner, then you should use a barrier method (e.g. condom) during treatment and for 90 days after stopping treatment. This is because Auro-Valganciclovir can cause birth defects.

Breast-feeding:
Tell your doctor if you are breast-feeding or planning to breast-feed. You should not take Auro-Valganciclovir while breast-feeding. Women who are HIV positive should not breast-feed because HIV infection can be passed to the baby via the breast milk.

Driving and using machines:
Be careful when driving a car or using machines. Auro-Valganciclovir and/or ganciclovir can cause seizures, dizziness, ataxia (unsteadiness) and confusion. You should not drive a car or use machines until you know how Auro-Valganciclovir affects you.

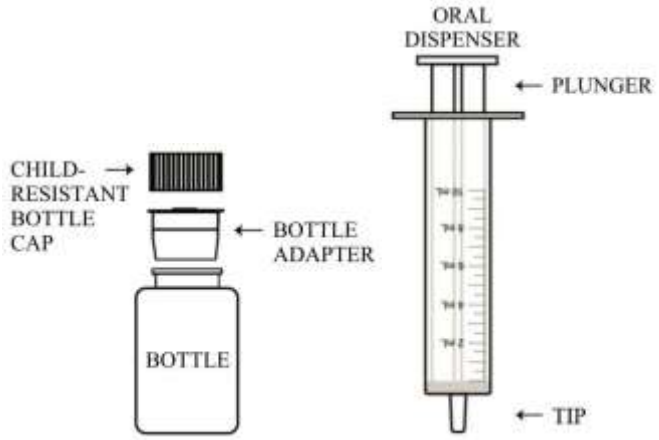
Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Auro-Valganciclovir:

- Drugs that treat AIDS such as such as zidovudine, didanosine, stavudine. These drugs may need to have their dose changed when taken with Auro-Valganciclovir.
- Drugs that reduce your immune system such as cyclosporine, tacrolimus, mycophenolate mofetil.
- Drugs that treat cancer such as vincristine, vinblastine, doxorubicin, hydroxyurea.
- Drugs that fight infections such as trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine, pegylated interferons with ribavirin.
- Drugs that stop the growth of infections such as imipenem-cilastin. Seizures have occurred in patients taking imipenem-cilastin and ganciclovir. You may discuss different options with your doctor.
- Probenecid, a medicine used to treat gout. Taking probenecid and Auro-Valganciclovir at the same time could increase the amount of ganciclovir in your blood to toxic levels.

How to take Auro-Valganciclovir:

- Take Auro-Valganciclovir exactly as your doctor has told you to.
- Do not skip any doses or take more than the recommended dose.
- Take Auro-Valganciclovir with food.
- Be careful with handling the Auro-Valganciclovir solution. Avoid getting the solution on your skin, lips, in your nose or in your eyes. If you happen to get the solution on your skin or lips, then wash the area well with soap and water. If you happen to get the solution in your eyes, rinse your eyes well with sterile water or plain tap water.
- If you have kidney problems, your doctor might prescribe a lower dose.
- If your doctor has prescribed Auro-Valganciclovir oral solution, follow the directions below to ensure proper dosing:



1. With the child-resistant cap on the bottle, shake the bottle well for 5 seconds before each use.
2. To open the bottle, press downward firmly on the child-resistant cap and turn it counter-clockwise. **Do not throw away the child-resistant cap.**
3. Push the plunger down toward the tip of the oral dispenser. With the bottle in an upright position, insert the oral dispenser into the bottle adapter opening.
4. Turn the entire unit (bottle with attached oral dispenser) upside down.
5. Slowly pull out the plunger until the desired amount of solution is withdrawn into the oral dispenser (see figure).

6. Turn the entire unit right side up and slowly remove the oral dispenser from the bottle.
7. Place the tip of the oral dispenser directly into mouth. Slowly push down the plunger until the oral dispenser is empty. Swallow the solution. Do not mix with any liquid prior to swallowing.
8. Use the child-resistant cap to close the bottle. Return the bottle to the refrigerator (see Storage).
9. After each use:
   Remove the plunger from the oral dispenser by pulling the plunger all the way out. Rinse the oral dispenser and plunger under running tap water and air dry before next use.

- It is important that you use the oral dispenser provided in the box to measure the amount of Auro-Valganciclovir solution.

- Each box contains two oral dispensers, in case one of them gets lost or damaged. Each oral dispenser is designed to measure up to a 10 mL amount of Auro-Valganciclovir solution. Remember to take the amount of Auro-Valganciclovir as prescribed by your doctor.
- Reach out to your doctor or pharmacist if both oral dispensers become lost or damaged. They will tell you how to take your Auro-Valganciclovir solution.

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 18 mL of Auro-Valganciclovir solution taken twice a day for 21 days. Use the oral dispenser provided and take two 9 mL amounts of the solution in the morning and two 9 mL amounts in the evening.
- The usual dosage for adults to help keep CMV retinitis under control (maintenance therapy) is 18 mL Auro-Valganciclovir solution taken once a day. Use the oral dispenser provided and take two 9 mL amounts of solution once a day. You should try to take the solution at the same time each day.

Prevention of CMV Disease in Solid Organ Transplantation

- The usual dosage to prevent CMV in adults who received a solid organ transplant is 18 mL Auro-Valganciclovir solution taken once a day. Treatment starts within 10 days of transplant and continues until 100 days after the transplant. Use the oral dispenser provided and take two 9 mL amounts of solution once a day.

Patients with kidney problems: If your kidneys are not working properly, your doctor may instruct you to take a lower dose of Auro-Valganciclovir solution each day. It is very important that you follow the dose prescribed by your doctor.

Overdose:

If you think you, or a person you are caring for, have taken too much Auro-Valganciclovir, particularly accidental oral ingestion, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take a dose of Auro-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. Do not take two doses of Auro-Valganciclovir at the same time.
- Do not let your Auro-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.

What are possible side effects from using Auro-Valganciclovir?

These are not all the possible side effects you may have when taking Auro-Valganciclovir. If you

experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea, nausea, vomiting
- Constipation
- Fever
- Headache
- Trembling
- Swelling of the legs
- Back pain
- Insomnia (sleeplessness)
- High blood pressure
- Dizziness, unsteadiness
- Confusion
- Increased potassium in the blood.

Other side effects. Auro-Valganciclovir causes cancer in animals and may cause cancer in people.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Graft Rejection – Transplant tissue is destroyed by your immune system: discomfort, feeling ill, pain or swelling in the area of the tissue, fever, flu-like symptoms.		✓	
COMMON			
Blood Problems – Reduced number of white blood cells: chills, fever, fatigue, sore mouth, cough, redness, pain or swelling of any area of your body, pain or burning when you pass your urine.	✓		
Blood Problems – Reduced number of red blood cells: tiredness and weakness, paleness, shortness of breath.	✓		
Blood Problems – Reduced number of platelets: increased bruising and bleeding, fatigue, weakness.	✓		
Seizures: uncontrolled movements, loss of consciousness, staring, fits.		✓	
UNCOMMON			
Kidney Problems: decrease in amount of urine produced, lower back pain or side pain, swelling of feet or lower legs, pain or discomfort when urinating.	✓		
Infertility in Men - Inability for a man to cause pregnancy: not able to produce sperm, lower sperm count.	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

- Keep out of reach and sight of children.
- Store Auro-Valganciclovir oral solution in its original labelled container in a refrigerator at 2-8°C. The pharmacist will write the date of expiration on the bottle label.
- Keep the bottle tightly closed.
- Do not use medication after the expiry date on the package.
- Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

If you want more information about Auro-Valganciclovir:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.); the importer's website http://www.auropharma.ca, or by calling 1-855-648-6681.

This leaflet was prepared by Auro Pharma Inc.

Last Approved: February 14, 2023