Ganciclovir For Injection USP 500 mg/vial

(Lyophilized)
For IV Infusion Only
Single Dose Vial

Composition: Each vial contains:
Ganciclovir Sodium USP
Eq. to Ganciclovir 500 mg

Pharmacodynamics:
Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses both *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus 1 and 2 (HSV-1 and HSV-2), human herpesvirus 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella zoster virus (VZV), and hepatitis B virus. Clinical studies have been limited to evaluation of efficacy in patients with CMV infection.
In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. This has been shown to occur in HSV- and HCMV-infected cells, with half-lives of 18 and 6-24 hours, respectively, after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.
The virustatic activity of ganciclovir is a result of the inhibition of viral DNA synthesis by: (1) competitive inhibition of incorporation of deoxyguanosine triphosphate into DNA by DNA polymerase, and (2) incorporation of ganciclovir triphosphate into viral DNA, causing termination of, or very limited, viral DNA elongation.
Antiviral activity
The *in vitro* antiviral activity, measured as IC50 of ganciclovir against CMV, is in the range of 0.08 µM (0.02 µg/mL) to 14 µM (3.57 µg/mL).

Pharmacokinetic:
The systemic exposure ($AUC_{0-\tau}$) reported following dosing with a single 1-hour IV infusion of 5 mg/kg ganciclovir in adult liver transplant patients was on average 50.6 µg.h/mL (CV% 40).In this patient population peak plasma concentration (C_{max}) was on average 12.2 µg/mL (CV% 24).
Distribution
The volume of distribution of intravenously administered ganciclovir is correlated to body weight. The steady state volume of distribution has a range of 0.54-0.87 L/kg. Plasma protein binding was 1%-2% over ganciclovir concentrations of 0.5 and 51 µg/mL. Ganciclovir penetrates the cerebrospinal fluid, where concentrations observed reach 24%-67% of the plasma concentrations.
Biotransformation
Ganciclovir is not metabolised to a significant extent.
Elimination
Ganciclovir is predominantly eliminated by renal excretion via glomerular filtration and active tubular secretion of unchanged ganciclovir. In patients with normal renal function, more than 90% of the intravenously administered ganciclovir dose is recovered unchanged in the urine within 24 hours. The mean systemic clearance ranged from 2.64 ± 0.38 mL/min/kg (N = 15) to 4.52 ± 2.79 mL/min/kg (N = 6) and renal clearance ranged from 2.57 ± 0.69 mL/min/kg (N = 15) to 3.48 ± 0.68 mL/min/kg (N = 20), corresponding to 90%-101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from 2.73 ± 1.29 (N = 6) to 3.98 ± 1.7 hours (N = 8).
Linearity/non-linearity
Intravenous ganciclovir exhibits linear pharmacokinetics over the range of 1.6-5.0 mg/kg.
Patients with renal impairment
The total body clearance of ganciclovir is linearly correlated with creatinine clearance. In patients with mild, moderate, and severe renal impairment, mean systemic clearances of 2.1, 1 and 0.3 mL/min/kg were observed. Patients with renal impairment have an increased elimination half-life. In patients with severe renal impairment elimination half-life was increased by 10-fold.
Patients with renal impairment undergoing haemodialysis
Haemodialysis reduces plasma concentrations of ganciclovir by about 50% after intravenous administration during a 4-hour haemodialysis session.
During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42-92 mL/min, resulting in intra-dialytic half-lives of 3.3-4.5 hours. The fraction of ganciclovir removed during a single dialysis session varied from 50% to 63%. Estimates of ganciclovir clearance for continuous dialysis were lower (4.0-29.6 mL/min) but resulted in greater removal of ganciclovir over a dose interval.
Patients with hepatic impairment
The safety and efficacy of Ganciclovir Injection have not been studied in patients with hepatic impairment. Hepatic impairment should not affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made.
Paediatric population
The pharmacokinetics of IV ganciclovir (administered as 200 mg/m^2 dose) were investigated across two studies in paediatric liver (n = 18) and renal (n = 25) transplant patients aged 3 months to 16 years and evaluated using a population pharmacokinetic model.
Elderly
No studies have been conducted

Indication:
Ganciclovir Injection is indicated in adults and adolescents ≥ 12 years of age for the:
- treatment of cytomegalovirus (CMV) disease in immunocompromised patients;
- prevention of CMV disease using pre-emptive therapy in patients with drug- induced immunosuppression (for example following organ transplantation or cancer chemotherapy).

Ganciclovir Injection is also indicated from birth for the:
- prevention of CMV disease using universal prophylaxis in patients with drug- induced immunosuppression (for example following organ transplantation or cancer chemotherapy).

Consideration should be given to official guidance on the appropriate use of antiviral agents.

Dosage & Administration:
Posology
Treatment of CMV disease
Adults and paediatric population ≥ 12 years of age with normal renal function:
- Induction treatment: 5 mg/kg given as an intravenous infusion over one hour, every 12 hours for 14 - 21 days.
- Maintenance treatment: For immunocompromised patients at risk of relapse maintenance therapy may be given. 5 mg/kg given as an intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of maintenance treatment should be determined on an individual basis, local treatment guidelines should be consulted.
- Treatment of disease progression: Any patient, in whom CMV disease progresses, either while on maintenance treatment or because treatment with ganciclovir has been withdrawn, may be re-treated using the induction treatment regimen.

Special dosage instructions
Renal impairment
Paediatric patients (from birth to ≤ 16 years of age) with renal impairment receiving a prophylactic dose of ganciclovir calculated using the 3 x BSA x CrCLS dosing algorithm do not require further dose modification because this dose is already adjusted for creatinine clearance.
If the blood cell counts are significantly reduced during therapy with ganciclovir, treatment with haematopoietic growth factors and/or discontinuation of treatment should be considered.
Elderly
No studies on the efficacy or safety of ganciclovir in the elderly have been conducted. Since renal function decreases with age, ganciclovir should be administered to the elderly with special consideration for their renal status.
Method of administration
Caution:
Ganciclovir must be administered by intravenous infusion over 1 hour at a concentration not exceeding 10 mg/mL. Do not administer by rapid or bolus intravenous injection because the resulting excessive plasma levels may increase the toxicity of ganciclovir.
Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.
The recommended dosage, frequency and infusion rates should not be exceeded.
Ganciclovir Injection is a powder for solution for infusion. After reconstitution Ganciclovir Injection is a colourless to slightly yellowish solution, practically free from visible particles.
The infusion should be given into a vein with adequate blood flow, preferably via a plastic cannula.
Preparation of reconstituted solution:
To be reconstituted with 10ml of Water for Injection.

Preparation of final diluted solution for infusion
Depending on the patient's body weight, withdraw the required volume from the vial into a syringe and then dilute it with an appropriate infusion fluid. Add a volume of 100 ml of the solvent to the reconstituted solution. Infusion concentrations greater than 10 mg/ml are not recommended. Sodium Chloride Solutions, 5% Dextrose, Ringer's Injection, and Lactated Ringer's Injection, have been shown to be chemically or physically compatible with Ganciclovir For Injection USP 500 mg.

Contraindications:
Hypersensitivity to the active substance or valganciclovir or to any of the excipients listed.

Breastfeeding
It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be excluded. Animal data indicate that ganciclovir is excreted in the milk of lactating rats.

Warning:
Cross-hypersensitivity
Due to the similarity of the chemical structure of ganciclovir and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these drugs is possible. Caution should therefore be used when prescribing Ganciclovir Injection to patients with known hypersensitivity to aciclovir or penciclovir (or to their prodrugs, valaciclovir or famciclovir respectively).
Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception
Prior to initiation of ganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. Based on clinical and nonclinical studies it is considered likely that ganciclovir causes temporary or permanent inhibition of spermatogenesis. Ganciclovir should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Therefore, women of childbearing potential must be advised to use effective contraception during treatment and for at least 30 days thereafter. Men must be advised to practice barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy.
The use of ganciclovir warrants extreme caution, especially in the paediatric population due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should be carefully considered in each case and should clearly outweigh the risks. Refer to treatment guidelines.
Myelosuppression
Ganciclovir Injection should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.
Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia and bone marrow failure have been observed in patients treated with ganciclovir. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µL or the platelet count is less than 25,000 cells/µL or the haemoglobin is less than 8 g/dL.
It is recommended that complete blood counts including platelet counts be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and in neonates and infants. During the first 14 days of administration it is recommended that white blood cell count (preferably as a differential test) is conducted every second day; in patients with low baseline neutrophil levels (< 1,000 neutrophils/µl), those who developed leukopenia during previous therapy with other myelotoxic substances, and those

with renal impairment, this monitoring should be performed daily.

For patients with severe leukopenia, neutropenia, anaemia and/or thrombocytopenia it is recommended to consider the use of treatment with haematopoietic growth factors and/or the interruption of ganciclovir therapy.

Renal impairment

Patients with impaired renal function are at increased risk of toxicity (especially haematological toxicity). Dosage reduction is required.

Use with other medicines

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

Patients treated with ganciclovir and didanosine, medicines known to be myelosuppressive or affecting renal function, should be closely monitored for signs of added toxicity.

Pregnancy & Lactation:

Fertility

A small clinical study with renal transplant patients receiving Valcyte for CMV prophylaxis for up to 200 days demonstrated an impact of valganciclovir/ganciclovir on spermatogenesis, with decreased sperm density and motility measured after treatment completion. This effect appears to be reversible and approximately six months after Valcyte discontinuation, mean sperm density and motility recovered to levels comparable to those observed in the untreated controls.

In animal studies, ganciclovir impaired fertility in male and female mice and has shown to inhibit spermatogenesis and induce testicular atrophy in mice, rats and dogs at doses considered clinically relevant.

Based on clinical and nonclinical studies, it is considered likely that ganciclovir may cause temporary or permanent inhibition of human spermatogenesis.

Pregnancy

The safety of ganciclovir for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity. Therefore, ganciclovir should not be used in pregnant women unless the clinical need for treatment of the woman outweighs the potential teratogenic risk to the foetus.

Contraception in males and females

As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir unless it is certain that the female partner is not at risk of pregnancy.

Breastfeeding

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be excluded. Animal data indicate that ganciclovir is excreted in the milk of lactating rats. Therefore, breastfeeding must be discontinued during treatment with ganciclovir.

Effects on ability to drive and use machines:

Ganciclovir may have a major influence on the ability to drive and use machines.

Drug Interaction & Incompatibilities:

Pharmacokinetic interactions

Probenecid

Probenecid given with oral ganciclovir resulted in statistically decreased renal clearance of ganciclovir and led to clinically significant increased exposure. Such an effect is also anticipated during concomitant administration of intravenous ganciclovir and probenecid. Therefore, patients taking probenecid and Ganciclovir Injection should be closely monitored for ganciclovir toxicity.

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir. At intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38% to 67% has been observed. There was no clinically significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity.

Other antiretrovirals

Cytochrome P450 isoenzymes play no role in ganciclovir pharmacokinetics. Consequently, pharmacokinetic interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are not anticipated.

Pharmacodynamic interactions

Imipenem-cilastatin

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks.

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these drugs. Some patients may not tolerate concomitant therapy at full dosage.

Other potential drug interactions

Toxicity may be enhanced when ganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment. This includes anti-infective agents (such as dapsone, pentamidine, flucytosine, amphotericin B, trimethoprim/sulfamethoxazole), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil) antineoplastic agents (e.g. vincristine, vinblastine, doxorubicin and hydroxyurea) as well as nucleoside (including zidovudine, stavudine and didanosine) and nucleotide analogues (including tenofovir, adefovir). Therefore, these drugs should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks.

Paediatric population

Interaction studies have only been performed in adults.

Do not use bacteriostatic water for injections containing parabens (para-hydroxybenzoates) since these are incompatible with Ganciclovir Injection and may cause precipitation.

Side Effects:

Summary of the safety profile

Valganciclovir is a pro-drug of ganciclovir, and adverse reactions associated with valganciclovir can be expected to occur with ganciclovir. Oral ganciclovir is no longer available but adverse reactions reported with its use can also be expected to occur in patients receiving intravenous ganciclovir. Therefore, adverse drug reactions reported with intravenous or oral ganciclovir or with valganciclovir are included in the table of adverse reactions.

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

The frequencies presented in the table of adverse reactions are derived from a pooled population of HIV-infected patients (n = 1,704) receiving maintenance therapy with ganciclovir or valganciclovir. Exception is made for agranulocytosis, granulocytopenia and anaphylactic reaction; the frequencies of which are derived from post-marketing experience. Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: 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. Intravenous ganciclovir is associated with a lower risk of diarrhoea compared to oral valganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC < 500/μL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

ADR (MedDRA) System Organ Class and frequency category :

Infections and infestations:

Very common

- Candida infections including oral candidiasis
- Upper respiratory tract infection

Common

- Sepsis, Influenza, Urinary tract infection, Cellulitis

Immune system disorders:

Common

Hypersensitivity

Rare

Anaphylactic reaction

Metabolic and nutrition disorders:

Very common

Decreased appetite

Common

Weight decreased

Psychiatric disorders:

Common

Depression, Confusional state, Anxiety

Uncommon

Agitation, Psychotic disorder, Thinking abnormal, Hallucinations

Nervous system disorders:

Very common

Headache

Common

Headache, Insomnia, Neuropathy peripheral, Dizziness, Paraesthesia, Hypoaesthesia, Seizure, Dysgeusia (taste disturbance)

Uncommon

Tremor

Cardiac disorders:

Uncommon

Arrhythmia

Renal and urinary disorders:

Common

Renal impairment, Creatinine clearance renal decreased, Blood creatinine increased, Renal failure, Blood creatinine increased

Uncommon

Haematuria

Overdosage:

Symptoms

Reports of overdoses with i.v. ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. The majority of the reports were either not associated with any adverse reactions, or included one or more of the adverse reactions listed below:

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

– Hepatotoxicity: hepatitis, liver function disorder

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

– Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting

– Neurotoxicity: generalised tremor, seizure

Management

Ganciclovir is removed by haemodialysis, therefore haemodialysis may be of benefit in reducing drug exposure in patients who receive an overdose of ganciclovir.

Additional information on special populations

Renal impairment: It is expected that an overdose of ganciclovir could result in increased renal toxicity in patients with renal impairment.

Paediatric population

No specific information available

Caution:

To be handled with great care because it is a potent cytotoxic agent and suspected carcinogen.

Storage: Store below 30°C,
Protect from light & moisture.

Presentation:

1 vials packed in a carton along with pack insert.

Keep out of the reach of children.

Prescription Only medicine.

Manufactured by: Kwality Pharmaceuticals Ltd.
1-A Industrial Area, Nurpur,Raja ka Bagh (HP), India.

Marketed by:
RemDcion
Healthcare International
Navi Mumbai, India.

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