SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ganciclovir for Injection USP 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Ganciclovir USP 500 mg

3. PHARMACEUTICAL FORM

Powder for Injection
White to pale yellow colour cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ganciclovir for Injection is indicated for the treatment of life threatening or sight –treatning cytomegalovirus (CMV) infection in immunocompromised individuals. These states included acquired immunodefeciency (AIDS), iatrogenic immunosuppression associated with organ transplantation , or chemotherapy for neoplasia. Ganciclovir for injection may also be used for the prevention of CMV disease, specifically in those patients receiving immunosuppressive therapy secondary to organ transplantation.

4.2 Posology and method of administration

Posology Treatment of CMV disease in adults and adolescents from 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in whom CMV disease progresses, either while on maintenance treatment or because treatment with ganciclovir has been withdrawn, may be re-treated using the induction treatment regimen.

Prevention of CMV disease in adults and adolescents from 12 years of age with normal renal function using prophylaxis or pre-emptive therapy
- Prophylaxis: 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 prophylaxis is based on the risk of CMV disease, local treatment guidelines should be consulted.

intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days

CrCl	**Induction dose**	**Maintenance dose**
>70 mL/min	5.0 mg/kg q12h	5.0 mg/kg/day
50-69 mL/min	2.5 mg/kg q12h	2.5 mg/kg/day
25-49 mL/min	2.5 mg/kg/day	1.25 mg/kg/day
10-24 mL/min	1.25mg/kg/day	0.625 mg/kg/day
<10 mL/min	1.25 mg/kg 3x/wk after haemodialysis	0.625 mg/kg 3x/wk after haemodialysis

Estimated creatinine clearance can be calculated from serum creatinine using the following formulae:

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
As dosage modifications are recommended in patients with renal impairment, serum creatinine or estimated creatinine-clearance levels should be monitored.
Severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia

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.

Paediatric population
Information on the safety and efficacy of ganciclovir in children under 12 years of age, including neonates, is limited. But no recommendation on a posology can be made.
Therapeutic guidelines should be consulted.

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.
The infusion should be given into a vein with adequate blood flow, preferably via a plastic cannula.

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

4.4 Special warnings and precautions for use
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 for 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

Myelosuppression
Ganciclovir for 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 {rst 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

Convulsions 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 for 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.

Mycophenolate mofetil, stavudine, trimethoprim and zidovudine

No significant pharmacokinetic interactions were observed when ganciclovir was administered in combination with either: mycophenolate mofetil, stavudine, trimethoprim or zidovudine.

Other antiretrovirals

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

Pharmacodynamic interactions

Imipenem− cilastatin Convulsions 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.

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 (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, doxorubicin, amphotericin B, mycophenolate mofetil, trimethoprim/sulphamethoxazole, and hydroxyurea) as well as nucleoside analogues (including zidovudine). 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.

4.6 Fertility, pregnancy and lactation

The safety of ganciclovir for use in pregnant women has not been established.

ganciclovir readily diffuses across the human placenta.based on its pharmacological mechanism of action and reproductive toxicity observed in available animal studies with ganciclovir there is s theirethical risk if teratogenicity in human. Therefore, ganciclovir should not be given to pregnant women as there is high likehood of damage to the developing foetus.

Unless the clinical need for treatment of the woman outweighs the potential teratogenic risk to the foetus. Woman of childbearing potential much be advised to use effective contraception during 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.

It is unkown 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 nursing infant cannot be discounted. Therefore breastfeeding must be discontinues.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions

ADR (MedDRA) **System Organ Class**	**Frequency Category**
Infections and infestations:	
Candida infections including oral candidiasis	Very common
Upper respiratory tract infection	
Sepsis	Common
Influenza	
Urinary tract infection	
Cellulitis	
Blood and lymphatic disorders:	
Neutropenia	Very common
Anaemia	
Thrombocytopenia	Common
Leukopenia	
Pancytopenia	
Bone marrow failure	Uncommon
Aplastic anaemia	Rare
Agranulocytosis*	
Granulocytopenia*	
Immune system disorders:	
Hypersensitivity	Common

Anaphylactic reaction*	Rare
Metabolic and nutrition disorders:	
Decreased appetite	Very common
Weight decreased	Common
Psychiatric disorders:	
Depression	Common
Confusional state	
Anxiety	
Agitation	Uncommon
Psychotic disorder	
Thinking abnormal	
Hallucinations	
Nervous system disorders:	
Headache	Very common
Insomnia	Common
Neuropathy peripheral	
Dizziness	
Paraesthesia	
Hypoaesthesia	
Seizure	
Dysgeusia (taste disturbance)	
Tremor	Uncommon
Eye disorders:	
Visual impairment	Common
Retinal detachment	
Vitreous floaters	
Eye pain	
Conjunctivitis	
Macular oedema	
Ear and labyrinth disorders:	
Ear pain	Common
Deafness	Uncommon
Cardiac disorders:	
Arrhythmia	Uncommon
Vascular disorders:	
Hypotension	Common
Respiratory, thoracic and mediastinal disorders:	
Cough	Very common
Dyspnoea	
Gastrointestinal disorders:	
Diarrhoea	Very common
Nausea	
Vomiting	
Abdominal pain	

Dyspepsia	Common
Flatulence	
Abdominal pain upper	
Constipation	
Mouth ulceration	
Dysphagia	
Abdominal distention	
Pancreatitis	
Hepato-biliary disorders:	
Blood alkaline phosphatase increased	Common
Hepatic function abnormal	
Aspartate aminotransferase increased	
Alanine aminotransferase increased	
Skin and subcutaneous tissue disorders:	
Dermatitis	Very common
Night sweats	Common
Pruritus	
Rash	
Alopecia	
Dry skin	Uncommon
Urticaria	
Musculoskeletal and connective tissue disorders:	
Back pain	Common
Myalgia	
Arthralgia	
Muscle spasms	
Renal and urinary disorders:	
Renal impairment	Common
Creatinine clearance renal decreased	
Blood creatinine increased	
Renal failure	Uncommon
Haematuria	
Reproductive system and breast disorders:	
Infertility male	Uncommon
General disorders and administration site conditions:	
Pyrexia	Very common
Fatigue	
Injection site reaction	Common
Pain	
Chills	
Malaise	
Asthenia	
Chest pain	Uncommon

** The frequencies of these adverse reactions are derived from post-marketing experience; all other frequency categories are based on the frequency recorded in clinical trials.*

Description of selected adverse reactions

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 and following administration of a cumulative dose of ≤ 200 mg/kg. The cell count usually normalises within 2 to 5 days after discontinuation of the drug or dose reduction (see section 4.4).

Severe neutropenia

Severe neutropenia was reported more frequently in HIV patients (14%) receiving maintenance therapy with valganciclovir, oral or intravenous ganciclovir (n = 1,704) than in organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia was 10%.

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000/µL) 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 AIDS (see section 4.4). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Seizures

Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir.

Retinal detachment

This adverse reaction has only been reported in studies in HIV patients treated with Ganciclovir for Injection for CMV retinitis.

Injection site reactions

Injection site reactions occur commonly in patients receiving ganciclovir. Ganciclovir for Injection should be administered as recommended in section 4.2 to reduce the risk of local tissue irritation.

Paediatric population

Formal safety studies with ganciclovir have not been conducted in children < 12 years of age but based on experience with valganciclovir, a pro-drug of ganciclovir, the overall safety profile of the active drug is similar in paediatric and adult patients. Neutropenia occurs more often in paediatric patients, but there is no correlation between neutropenia and infectious adverse reactions in the paediatric population. A higher risk of cytopenias in neonates and infants warrants the careful monitoring of blood counts in these age groups.

Only limited data are available in neonates or infants with HIV/AIDS or symptomatic congenital CMV infection treated with valganciclovir or ganciclovir, however the safety profile appears to be consistent with the known safety profile of valganciclovir/ganciclovir.

4.9 Overdose

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 bene{t 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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antivirals for systemic use, direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB06.
Mechanism of action
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 herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and hepatitis B virus.

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.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of ganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis, and in solid organ transplant patients.

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 ± 1.78 hours (N = 8).

5.3 Preclinical safety data

Ganciclovir was mutagenic in mouse lymphoma cells and clastogenic in mammalian cells. Such results are consistent with the positive mouse carcinogenicity study with ganciclovir.
Ganciclovir is a potential carcinogen.
Ganciclovir causes impaired fertility and teratogenicity in animals. Based upon animal studies where inhibition of spermatogenesis was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir causes inhibition of human spermatogenesis

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injection, Sodium Hydroxide, Mannitol

6.2 Incompatibilities

Not known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container and special equipment for use, administration or implantation

10ml Flint glass vial USP type-I and sealed by 20mm grey butyl rubber plugs with 20mm flip off aluminium seal.

6.6 Special precautions for disposal <and other handling>

None.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.
C- 1101 /1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway, Goregaon (East)
Mumbai- 400 063, India.

8. MARKETING AUTHORISATION NUMBER(S)

06330/08585/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25.07.2021

10. DATE OF REVISION OF THE TEXT

14/07/2023

11. Reference

https://www.medicines.org.uk/emc/product/10242/smpc#gref