PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

GANCLO powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of GANCLO sterile powder contains 543 mg of sterile freeze dried ganciclovir sodium equivalent to 500 mg ganciclovir.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White porous cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GANCLO is indicated for the prevention and treatment of life-threatening or sight-threatening cytomegalovirus disease (CMV) in immuno-compromised individuals and for the prevention of CMV disease in transplant recipients.

4.2 Posology and method of administration

Posology

Because of individual patient variations in the clinical response to CMV infections and the sensitivity to the myelosuppressive effects of GANCLO, the treatment of each patient should be considered individually. Changes in dose should be based

on regular clinical and haematological assessment. Due to the myelosuppressive nature of GANCLO, it is recommended that white blood cell counts be performed every two days for the first fourteen days of GANCLO administration.

Standard IV dosage for treatment of CMV retinitis

Induction treatment: 5 mg/kg infused intravenously at a constant rate, over one hour, every 12 hours (10 mg/kg/day) for 14 to 21 days for patients with normal renal function.

Maintenance treatment: 5 mg/kg given as an IV infusion over one hour, once daily for 7 days per week or 6 mg/kg once daily for 5 days per week.

Treatment of disease progression: Indefinite treatment may be required in patients with AIDS, but even with continued maintenance treatment, patients may have progression of retinitis. If this occurs, patients should be given the induction treatment again.

Standard IV dosage for prevention in transplant recipients

Induction treatment: 5 mg/kg given as an IV infusion over one hour, every 12 hours for 7 - 14 days in patients with normal renal function.

Maintenance treatment: 5 mg/kg given as an IV infusion over one hour, once daily for 7 days per week or 6 mg/kg once daily for 5 days per week.

Special populations

a) *Patients with renal impairment:* If renal function is impaired, dosage adjustments are required, as shown in the table below. Creatinine clearance can be related to serum creatinine by the following formulae:

For males = $\frac{(140 - \text{age in years}) \times \text{body weight in kg}}{72 \times (0{,}011 \times \text{serum creatinine [µmol/l]})}$

For females = 0,85 x male value

Creatinine (ml/min)	Induction dose	Maintenance dose
≥ 70 ml/min	5,0 mg/kg, 12 hourly	5,0 mg/kg/day
50 - 69 ml/min	2,5 mg/kg, 12 hourly	2,5 mg/kg/day
25 - 49 ml/min	2,5 mg/kg, daily	1,25 mg/kg/day
10 - 24 ml/min	1,25 mg/kg/day	0,625 mg/kg/day
< 10 ml/min	1,25 mg/kg 3 x a week after haemodialysis	0,625 mg/kg 3 x a week after haemodialysis

As dosage modifications are recommended in patients with renal impairment, serum creatinine or creatinine clearance levels should be monitored carefully.

b) *Patients with leukopenia, severe neutropenia, anaemia and thrombocytopenia:* Severe leucopenia neutropenia, anaemia, thrombocytopenia, bone marrow depression and aplastic anaemia 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 haemoglobin is less than 8 g/dl (see sections 4.3 and 4.4).

c) *Elderly:* Since elderly individuals often have reduced renal function, GANCLO should be administered to elderly patients with special consideration of their renal status.

d) *Paediatric population:* Safety and efficacy of ganciclovir in paediatrics have not been established, including the use for the treatment of congenital or neonatal CMV infections. The use of GANCLO in children warrants extreme caution due to potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks.

Method of administration

For intravenous use.

Preparation and administration of infusion solution

Based on patient weight and therapeutic indication, the appropriate calculated dose-volume should be removed from the vial (ganciclovir concentration 50 mg/ml) and added (normally 100 ml) to a suitable infusion fluid for delivery over the course of one hour. Infusion concentrations greater than 10 mg/ml are not recommended.

The following infusion fluids are compatible with ganciclovir:

1.Sodium chloride intravenous infusion (0,9 % w/v).

2.Dextrose 5 % in water.

3.Ringer's or lactated Ringer's solution.

GANCLO should not be mixed with other IV medicines. The infusion solution containing the reconstituted GANCLO should be used within 24 hours of adding the dose-volume from the reconstituted vial to infusion bag. This infusion solution should be refrigerated. Freezing is not recommended.

Caution - Do not administer by rapid bolus or IV injection. The toxicity of GANCLO may be increased as a result of excessive plasma levels.

Caution - IM or SC injection may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.

The recommended dosage, frequency, or infusion rates should not be exceeded.

Handling instructions

Caution should be exercised in the handling of GANCLO. Since GANCLO is considered a potential teratogen and carcinogen in humans, caution should be observed during handling (see section 4.4). Avoid inhalation or direct contact with the skin or mucous membranes of the powder contained in GANCLO vials or GANCLO IV solutions. GANCLO solutions are alkaline (pH~11), If such contact

occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water.

4.3 Contraindications

- Patients with known hypersensitivity to ganciclovir, valganciclovir or to any of the excipients of GANCLO (see section 6.1). Due to the similarity of the chemical structure of GANCLO and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these medicines is possible.
- Pregnancy and lactation.
- Absolute neutrophil count less than 500 cells/µl, platelet count less than 25 000 cells/µl, haemoglobin less than 8 g/dl. (see section 4.4.).
- GANCLO is not indicated for the treatment of congenital or neonatal CMV infections.
- Treatment with myelosuppressive medicines.

4.4 Special warnings and precautions for use

Due to the similarity of the chemical structure of ganciclovir and that of acyclovir and penciclovir, a cross-hypersensitivity reaction between these medicines is possible. GANCLO should therefore not be prescribed to patients with known hypersensitivity to aciclovir or penciclovir (or to their prodrugs, valaciclovir or famciclovir respectively), (see section 4.3).

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with GANCLO. Therapy should not be initiated or continued 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 (see sections 4.2 and 4.3).

Impairment of fertility: In animal studies ganciclovir was found to be mutagenic, teratogenic and carcinogenic. GANCICOVIR should therefore be considered a

potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Temporary and permanent inhibition of spermatogenesis in male animals and permanent suppression of fertility in female animals have occurred. Because of the teratogenicity observed in animals, women of childbearing potential should use effective contraception during treatment. Men should be advised to practice barrier contraception during treatment and for 90 days following treatment.

It is recommended that complete blood counts and platelet counts be monitored during therapy. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see sections 4.2 and 4.3).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see section 4.2).

Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir. GANCLO should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section 4.5).

Zidovudine and GANCLO each have the potential to cause neutropenia and anaemia. Some patients may not tolerate concomitant therapy at full dosage (see section 4.5).

Didanosine plasma concentrations may increase during concomitant use with GANCLO, thus patients should be closely monitored for didanosine toxicity (see section 4.5).

Concomitant use of other medicines that are known to be myelosuppressive or associated with renal impairment with GANCLO may result in added toxicity (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

Probenecid

Probenecid, given with oral ganciclovir, resulted in statistically significant increased exposure. These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore, patients taking probenecid and GANCLO 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 (see section 4.4).

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

Convulsions have been reported in patients using GANCLO and imipenem-cilastatin concomitantly. These medicines should not be used concomitantly.

Zidovudine

Both zidovudine and GANCLO have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these medicines. Some patients may not tolerate concomitant therapy at full dosage (see section 4.4).

Other potential interactions

Toxicity may be enhanced when ganciclovir is co-administered with other medicines known to be myelosuppressive or associated with renal impairment. This includes anti-infective medicines (such as dapsone, pentamidine, flucytosine, amphotericin B, trimethoprim/sulfamethoxazole), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil) antineoplastic medicines (e.g. vincristine, vinblastine, doxorubicin and hydroxyurea) as well as nucleoside (including zidovudine, stavudine and didanosine) and nucleotide analogues (including tenofovir, adefovir). Therefore, these medicines should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks (see section 4.4).

4.6 Fertility, pregnancy and lactation

GANCLO is contraindicated in pregnancy and lactation. Please refer to sections 4.3 and 4.4.

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 (see section 4.4).

Pregnancy

In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity. Therefore, ganciclovir should not be used in pregnant women (see sections 4.3 and 4.4)

Breastfeeding

Animal data indicate that ganciclovir is excreted in the milk of lactating rats. Therefore, breastfeeding must be discontinued during treatment with ganciclovir (see section 4.3).

Fertility

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 (see section 4.4).

4.7 Effects on ability to drive and use machines

GANCLO may have a major influence on the ability to drive and use machines (see section 4.8).

Convulsions, sedation, dizziness, ataxia, confusion may occur in patients taking GANCLO. If they occur, such effects may affect tasks requiring alertness, including the patient's ability to drive and operate machinery.

4.8 Undesirable effects

a. 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. Therefore, adverse drug reactions reported with 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 (see section 4.4). 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: frequent, less frequent and frequency unknown.

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.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Candida infections including oral candidiasis, upper respiratory tract infection, sepsis, influenza, urinary tract infection, cellulitis
Blood and lymphatic	Frequent	Neutropenia, anaemia,

MedDRA system organ class	**Frequency**	**Adverse reactions**
system disorders		thrombocytopenia, leucopenia, pancytopenia
	Less frequent	Bone marrow failure, aplastic anaemia
	Frequency unknown	Agranulocytosis, granulocytopenia
Immune system disorders	Frequent	Hypersensitivity
	Frequency unknown	Allergic reaction
Metabolic and nutritional disorders	Frequent	Decreased appetite (anorexia), decreased weight
Psychiatric disorders	Frequent	Depression, confusional state anxiety
	Less frequent	Agitation, psychotic disorder, abnormal thinking, hallucinations
Nervous system disorders	Frequent	Insomnia, peripheral neuropathy, dizziness, paraesthesia, hypoaesthesia, seizure, headache, dysgeusia
	Less frequent	Tremor
Eye disorders	Frequent	Visual impairment, retinal detachment, vitreous floaters, eye pain, conjunctivitis, macular oedema
Ear and labyrinth	Frequent	Ear pain

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders	Less frequent	Deafness
Cardiac disorders	Less frequent	Dysrrhythmia
Vascular disorders	Frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, dyspnoea
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, abdominal pain, dyspepsia, flatulence, upper abdominal pain, constipation, mouth ulceration, dysphagia, abdominal distention, pancreatitis
Hepato-biliary disorders	Frequent	Increased blood alkaline phosphatase, abnormal hepatic function, increased aspartate aminotransferase, increased alanine aminotransferase
Skin and subcutaneous tissue disorders	Less frequent	Night sweats, pruritus, rash, dermatitis, alopecia
	Less frequent	Dry skin, urticaria
Musculoskeletal and connective tissue disorders	Frequent	Muscle spasms, back pain, myalgia, arthralgia
Renal and urinary disorders	Frequent	Renal impairment, decreased renal creatinine clearance, increased blood creatinine

MedDRA system organ class	Frequency	Adverse reactions
	Less frequent	Renal failure, haematuria
Reproductive system and breast disorders	Frequent	Male infertility
General disorders and administration site conditions	Frequent	Pyrexia, fatigue, injection site reaction, pain, chills, malaise, asthenia
	Less frequent	Chest pain

c. 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 medicine 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 medicines 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 (see sections 4.4 and 4.5).

Retinal detachment

This adverse reaction has only been reported in studies in HIV patients treated with ganciclovir as contained in GANCLO for CMV retinitis.

Injection site reactions

Injection site reactions occur commonly in patients receiving ganciclovir. GANCLO 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 medicine 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 (see section 4.4).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

Haematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia

Hepatotoxicity: hepatitis, liver function disorder

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

Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting

Neurotoxicity: generalised tremor, convulsion.

In addition, one adult received an excessive volume of IV ganciclovir solution by intravitreal injection, and experienced temporary loss of vision and central retinal

artery acclusion secondary to increased intraocular pressure related to the injected fluid volume.

Management

Haemodialysis and hydration may be of benefit in reducing medicine exposure in patients who receive an overdose of ganciclovir (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.8 - Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB06.

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. Clinical studies have been limited to assessment 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 of ganciclovir 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 hours and between 6 and 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 due to the inhibition of viral DNA synthesis by ganciclovir triphosphate competitively inhibiting the incorporation of deoxyguanosine triphosphate into DNA by DNA polymerase and incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, viral DNA elongation. Typical anti-viral IC_{50} against CMV *in vitro* is in the range 0,14 µM (0,04 µg/ml to 14 µM (3,5 µg/ml).

The current working definition of CMV resistance to ganciclovir, based on *in vitro* assays, is a median inhibitory concentration (IC_{50}) > 1,5 µg/ml (6,0 µM). CMV resistance to ganciclovir is uncommon (~ 1 %). It has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. During the first 6 months of treatment for CMV retinitis with ganciclovir IV, viral resistance is detected in 3 % to 8 % of patients. Most patients with worsening CMV retinitis while on treatment do not shed resistant CMV. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir IV. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

The possibility of viral resistance should be considered in patients who repeatedly show poor clinical response or experience persistent viral excretion during therapy. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described that contain mutations in the UL97 gene of CMV that controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir, and virus with this mutation may be resistant to other CMV medicines.

5.2 Pharmacokinetic properties

Absorption

The systemic exposure (AUC_{0-24}) reported following dosing with a single 1-hour IV infusion of 5 mg/kg ganciclovir in HIV+/CMV+ patients or in adult AIDS patients ranged from 21,4 ± 3,1 (N = 16) to 26,0 ± 6,06 (N = 16) µg.h/ml. In this patient population peak plasma concentration (C_{max}) ranged from 7,59 ± 3,21 (N = 10), 8,27 ± 1,02 (N = 16) to 9,03 ± 1,42 (N = 16) µg/ml.

Distribution

For IV ganciclovir, volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0,536 ± 0,078 (N = 15) to 0,870 ± 0,116 (N = 16) L/kg. Cerebrospinal fluid concentrations obtained 0,25 - 5,67 hours post-dose in 2 patients who received 2,5 mg/kg ganciclovir IV eight or twelve hourly, ranged from 0,31 - 0,68 µg/ml, representing 24 - 70 % of the respective plasma concentrations.

Biotransformation

Ganciclovir is not metabolised to a significant extent.

Elimination

When administered IV, ganciclovir exhibits linear pharmacokinetics over the range of 1,6 - 5,0 mg/kg and when administered orally, ganciclovir exhibits linear kinetics up to a total daily dose of 4 g/day, provided each unit dose does not exceed 1 g. Renal excretion of unchanged medicine by glomerular filtration and active tubular secretion is the major route of elimination. In patients with normal renal function, 91,3 ± 5,0 % of IV administered ganciclovir was recovered unmetabolised in the urine. In subjects with normal renal function, 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).

Pharmacokinetics in special populations

Patients with renal impairment: Both plasma half-life as well as peak plasma levels of ganciclovir are increased in patients with a decreased creatinine clearance. Dosage adjustments based on creatinine clearance are necessary in patients with impairment of renal function.

Patients undergoing haemodialysis: Haemodialysis reduces plasma concentrations of ganciclovir by about 50 % after IV administration.

During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42 to 92 ml/min, resulting in intra-dialytic half-lives of 3,3 to 4,5 hours. Estimates of ganciclovir clearance for continuous dialysis were lower (4,0 to 29,6 ml/min), but resulted in greater removal of ganciclovir over a dose interval. For intermittent haemodialysis, the fraction of ganciclovir removed in a single dialysis session varied from 50 to 63 %.

Elderly: No studies have been conducted in adults older than 65 years of age.

Children: The pharmacokinetics of IV ganciclovir in neonates and children are similar to those observed in adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 4.2.

6.3 Shelf life

60 months.

After reconstitution:

Chemical and physical in-use stability has been demonstrated for the reconstituted medicine for 12 hours at or below 25 °C after dissolving with water for injections. Do not refrigerate or freeze.

After dilution:

Chemical and physical in-use stability in 4 diluents (0,9 % sodium chloride injection, 5 % glucose injection, Ringer's injection, and Lactated Ringer's injection) and the reconstituted solution have been demonstrated for 4 hours at or below 25 °C and 24 hours at 2 – 8°C (do not freeze).

6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after reconstitution and after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

10 ml Type 1 glass vial with a 20 mm bromobutyl rubber stopper and a 20 mm aluminium-plastic overseal.

Vials of GANCLO are supplied in packs of 1 or 10 in an outer cardboard box. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution of the vial

1. The contents of the vial should be reconstituted by the addition of 10 ml sterile water for injection immediately before being used for preparation of the infusion solution. Do not use bacteriostatic water for injection containing

parahydroxybenzoates, since these are incompatible with ganciclovir sterile powder and may cause precipitation.

2. The vial should be shaken to dissolve the medicine.
3. Reconstituted solution should be inspected for particulate matter prior to proceeding with admixture preparation.
4. Reconstituted solution in the vial is stable at room temperature for 12 hours (i.e. the appropriate dose-volume must be removed from the vial and added to the infusion bag within 12 hours). It should not be refrigerated.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

Address: 106 16th Road, Midrand, Gauteng, 1686.

Contact No.: +27 (0)10 045 2500

PV Email Address: pv@kahmagroup.co.za

8 REGISTRATION NUMBER

57/20.2.8/0619

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 August 2025

10 DATE OF REVISION OF THE TEXT

To follow