WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA515 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial contains ganciclovir sodium equivalent to ganciclovir 500 mg

Each 10 mL vial contains 43 mg sodium

3. PHARMACEUTICAL FORM

Sterile, freeze-dried powder for reconstitution with water for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA515 trade name] is indicated for the treatment of sight-threatening or life-threatening cytomegalovirus (CMV) infection in HIV-infected patients.

4.2 Posology and method of administration

Posology

Patients with CMV retinitis should ideally be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of this condition.

- Initial (induction) treatment*:* by intravenous infusion over 1 hour, 5 mg/kg every 12 hours (i.e. 10 mg/kg daily) for 14–21 days.
- Long-term (maintenance) treatment*:* For immunocompromised patients at risk of relapse of CMV retinitis, maintenance therapy may be given with [HA515 trade name] as an alternative to oral maintenance with valganciclovir. Intravenous infusion of 6 mg/kg once daily 5 days per week, or 5 mg/kg once daily 7 days per week is recommended. The duration of maintenance therapy will depend on the patient's condition and the induction of immune recovery with suitable antiretroviral therapy.
- 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in whom CMV disease progresses, either while on maintenance treatment or because treatment with ganciclovir has been withdrawn, may be treated again with the induction treatment regimen.

Special populations

Renal impairment

For patients with renal impairment, the dose of [HA515 trade name] should be modified according to creatinine clearance as shown in the table below (see also sections 4.4 and 5.2):

CrCl	Induction dose	Maintenance dose
70 mL/min or more	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
less than 10 mL/min	1.25 mg/kg 3x/wk after haemodialysis*	0.625 mg/kg 3x/wk after haemodialysis*

* [HA515 trade name] should be given shortly after completion of the hemodialysis session since hemodialysis has been shown to reduce plasma levels by approximately 50%.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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

See section 4.4 before initiation of treatment. 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 (see sections 4.4 and 4.8).

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 (see section 4.2).

Paediatric population

Information on the safety and efficacy of ganciclovir in children under 12 years of age, including neonates, is limited (see sections 4.4, 4.8 and 5.1). Currently available paediatric data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made. Therapeutic guidelines should be consulted.

Method of administration

[HA515 trade name] is given by intravenous infusion following reconstitution with water for injections and further dilution with a suitable intravenous fluid to a final concentration not exceeding 10 mg/mL. For instructions on reconstitution of [HA515 trade name] before administration, and precautions on handling, see section 6.6.

The infusion is given over 1 hour, preferably through a plastic cannula, into a vein with adequate blood flow. [HA515 trade name] must not be given by rapid or bolus intravenous injection because the resulting excessive plasma levels may increase the toxicity of ganciclovir.

Inadvertent intramuscular or subcutaneous injection of [HA515 trade name] can cause severe tissue irritation because ganciclovir solution is highly alkaline (pH about 11) (see section 4.8).

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

4.3 Contraindications

[HA515 trade name] is contraindicated in patients with hypersensitivity to ganciclovir or valganciclovir or to any of the excipients listed in section 6.1.

[HA515 trade name] is contraindicated in breastfeeding (see section 4.6).

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. Considerable caution should therefore be used when prescribing [HA515 trade name] 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, aspermatogenic, carcinogenic and to

impair fertility. It is considered likely that ganciclovir causes temporary or permanent inhibition of spermatogenesis (see sections 4.6, 4.8 and 5.3).

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 (see sections 4.6, 4.8 and 5.3).

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 (see section 4.2). Refer to treatment guidelines.

Myelosuppression

[HA515 trade name] 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 leucopenia, neutropenia, anemia, thrombocytopenia, pancytopenia and bone marrow depression 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 (see sections 4.2 and 4.8).

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. 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 (< 1000 neutrophils/µl), those who developed leucopenia during previous therapy with other myelotoxic substances, and those with renal impairment, this monitoring should be performed daily.

For patients with severe leucopenia, 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 (see sections 4.2 and 4.8).

Renal impairment

Patients with impaired renal function are at increased risk of toxicity (especially haematological toxicity). Dosage reduction is required (see sections 4.2 and 5.2).

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 (see section 4.5).

Patients treated with ganciclovir and didanosine, medicines known to be myelosuppressive or affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5).

Ophthalmological monitoring

Indirect ophthalmoscopy of both eyes through dilated pupils should be performed at the time of diagnosis of CMV retinitis, 2 weeks after starting ganciclovir therapy, and monthly thereafter during maintenance treatment, to monitor effectiveness and detect any uveitis due to immune reconstitution syndrome from concomitant antiretroviral treatment.

This medicinal product contains 46 mg sodium per vial, equivalent to approximately 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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 [HA515 trade name] 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).

Mycophenolate mofetil, trimethoprim and zidovudine

No significant pharmacokinetic interactions were observed when ganciclovir was administered in combination with either: mycophenolate mofetil, 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 (see section 4.4).

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 (see section 4.4).

Other potential drug interactions

Toxicity may be enhanced when ganciclovir is co-administered with, or is given immediately before or after, other drugs that are known to cause renal impairment or inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, testes and germinal layers of the skin and gastrointestinal mucosa. Examples of these types of drugs are dapsone, pentamidine, flucytosine, vincristine, vinblastine, doxorubicin, amphotericin B, trimethoprim-sulphonamide combinations, nucleoside/nucleotide analogues and hydroxycarbamide (hydroxyurea).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Contraception

Women of childbearing potential must be advised to use effective contraception during treatment with ganciclovir and for at least 30 days afterwards.

Men should be advised to practice barrier contraception during treatment with ganciclovir and for at least 90 days after treatment unless it is certain that the female partner is not at risk of pregnancy (see section 5.3).

Pregnancy

There are no data on the use of ganciclovir in pregnant women. Ganciclovir readily diffuses across the human placenta. Based on its mechanism of action and reproductive toxicity in animal studies with ganciclovir (see section 5.3 Preclinical safety data), there is a risk of teratogenicity in humans.

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.

Breastfeeding

Transfer of ganciclovir into rat milk has been reported. It is not known if ganciclovir appears in human milk. A risk to the suckling child cannot be excluded. Therefore, breastfeeding must be discontinued during treatment with [HA515 trade name].

Fertility

In animal studies ganciclovir impaired fertility in male and female mice. Based on the occurrence of aspermatogenesis at ganciclovir exposures below therapeutic levels in animal studies, it is considered likely that ganciclovir may cause temporary or permanent inhibition of human spermatogenesis.

4.7 Effects on ability to drive and use machines

Ganciclovir may cause side effects, including seizures and other neurological effects (see section 4.8), that may have a major influence on the ability to drive and use machinery safely.

4.8 Undesirable effects

Summary of the safety profile

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 events

Adverse events are listed under system organ class and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

The table in this section is for adult patients only. The safety profile in children over 4 years is similar to adults with the exception of a higher frequency of gastrointestinal disorders.

Infections and infestation	
very common	candida infections including oral candidiasis and upper respiratory tract infection
common	sepsis, influenza, urinary tract infection and cellulitis
Blood and lymphatic disorders	
very common	neutropenia and anaemia
common	thrombocytopenia, leukopenia and pancytopenia

uncommon	bone marrow failure
rare	aplastic anaemia, agranulocytosis*, granulocytopenia*
Immune system disorder	
common	hypersensitivity
rare	anaphylactic reaction*
Metabolism	
very common	decreased appetite
common	weight decreased
Psychiatric disorders	
common	depression, confusional state and anxiety
uncommon	agitation, psychotic disorder, thinking abnormal and hallucinations
Nervous disorder	
very common	headache
common	insomnia, neuropathy peripheral, dizziness, paraesthesia, hypoaesthesia, seizure and dysgeusia (taste disturbance)
uncommon	tremor
Eye disorders	
common	visual impairment, retinal detachment, vitreous floaters, eye pain, conjunctivitis and macular oedema
Ear and labyrinth disorders	
common	ear pain
uncommon	deafness
Cardiac disorders	
uncommon	arrhythmia
Vascular disorders	
common	hypotension
Respiratory, thoracic and mediastinal disorders	
very common	cough and dyspnoea
Gastrointestinal disorders	

very common	diarrhoea, nausea, vomiting and abdominal pain
common	dyspepsia, flatulence, abdominal pain upper, constipation, mouth ulceration, dysphagia, abdominal distention and pancreatitis
Hepato-biliary disorders	
common	blood alkaline phosphate increased, hepatic function abnormal, aspartate aminotransferase increased and alanine aminotransferase
Skin and subcutaneous tissue disorders	
very common	dermatitis, night sweats, pruritis, rash and alopecia
uncommon	dry skin and urticaria
Musculoskeletal and connective tissue disorders	
common	back pain, myalgia, arthralgia and muscle spasms
Renal and urinary disorders	
common	renal impairment, creatine clearance renal decreased
uncommon	renal failure and haematuria
Reproductive system and breast disorders	
uncommon	infertility male
General disorders and administration site conditions	
very common	pyrexia and fatigue
common	injection site reaction, pain, chills, malaise, asthenia and chest pain

***** 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 (see sections 4.4 and 4.5).

Retinal detachment

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

Injection site reactions

Injection site reactions occur commonly in patients receiving ganciclovir. [HA515 trade name] 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 under 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 (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

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

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, 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 intravenous ganciclovir solution by intravitreal injection and had temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

Management

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of ganciclovir (see section 5.2 Pharmacokinetic properties, Patients undergoing haemodialysis).

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 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. 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 (3.5 μg/mL).

Clinical studies

Clinical efficacy

In patients with AIDS and CMV retinitis, immediate treatment with ganciclovir has been shown to increase the time to disease progression, and to improve survival.

Viral resistance

The possibility of viral resistance should be considered for patients who repeatedly show poor clinical response or experience persistent viral excretion during therapy. CMV resistant to ganciclovir can arise after prolonged treatment or prophylaxis with ganciclovir by selection of mutations in either the viral protein kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or, but less frequently, in the viral polymerase gene (UL54). Virus with mutations in the UL97 gene are resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals with a similar mechanism of action.

The working definition of CMV resistance to ganciclovir based on in vitro antiviral assays is an IC_{50} value ≥ 12 μM with values of 6–12 μM indicating intermediate resistance. By these definitions up to 4% of untreated patients have CMV isolates with IC_{50} values that meet the criteria for either resistance or intermediate resistance.

In a prospective study of 76 previously untreated severely immunocompromised AIDS patients with CMV retinitis starting therapy with ganciclovir (intravenous induction and maintenance or intravenous induction and oral maintenance), the number of patients carrying resistant virus (IC_{50} > 6 μM) increased with time of treatment; 3.7%, 5.4%, 11.4% and 27.5% of those still on treatment at

baseline, 3, 6 and 12 months respectively. Similarly, in another study of AIDS patients with CMV retinitis treated for 3 months or longer with intravenous ganciclovir, 7.8% of patients carried virus with $IC_{50} \geq 12$ μM. Combined data from 4 clinical studies of the treatment of CMV retinitis indicated an incidence of resistance ($IC_{50} > 6$ μM) of 3.2% (median exposure 75 days) for intravenous ganciclovir and 6.5% (median exposure 165 days) for oral ganciclovir.

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for [HA515 trade name], as it is regarded as essentially the same as the WHO-accepted comparator product Cytovene® (MAH) in qualitative terms and with respect to the ratio of active and other ingredients.

Pharmacokinetics of ganciclovir

Absorption	
Absorption	After 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1 ±3.2 (n=16) and 26.8 ± 6.1 μg·hr/mL (n=16) and Cmax ranged between 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 μg/mL (n=16).
Distribution	
Volume of distribution (mean)	0.59-0.89 L/kg
Plasma protein binding *in vitro*	1-2%
Tissue distribution	CSF; 0.31 to 0.68 μg/mL representing 24 to 70% of plasma concentration.
Metabolism	
Metabolism	Not metabolized to a significant amount
Elimination	
Elimination half life	2.6-4.4 hours
Mean systemic clearance (Cl/F)	2.7-4.3 mL/min/kg
% of dose excreted in urine	90% unchanged excreted in urine.
% of dose excreted in faeces	NA
Pharmacokinetic linearity	Exhibits linear pharmacokinetics over the range of 1.6-5.0 mg/kg

Special populations

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 (see section 4.2 for dose modifications required in patients with renal impairment).

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.

Hepatic impairment

The safety and efficacy of Cymevene 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 (see section 4.2).

Paediatrics

Ganciclovir pharmacokinetics were studied in 10 children, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir are similar after single and multiple (every 12 hours) intravenous doses (5 mg/kg). After the 5 mg/kg single dose, exposure as measured by mean AUC∞ was 19.4 ± 7.1 μg·hour/ml, the steady-state volume of distribution reported was 0.68 ± 0.20 l/kg, Cmax was 7.59 ± 3.21 μg/ml, systemic clearance was 4.66 ± 1.72 ml/minute/kg, and half-life was 2.49 ± 0.57 hours. The pharmacokinetics of intravenous ganciclovir in children are similar to those in adults.

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

None

6.2 Incompatibilities

The dry powder should not be reconstituted with bacteriostatic water containing parabens, because parabens are incompatible with ganciclovir powder and may cause precipitation.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

Undiluted vials: Do not store above 30°C. Protect from light. Single use vials. Discard unused portion.

From a microbiological point of view, the product should be used immediately after reconstitution and dilution. If the product is not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user.

In-use storage time for the reconstituted vial should be no longer than 12 hours. Do not refrigerate.

In-use storage time for the infusion solution should be no longer than 24 hours when stored in a refrigerator at 2–8°C. The diluted solution should not be frozen.

6.5 Nature and contents of container

10-ml clear borosilicate Type I glass vial with grey bromobutyl stopper and aluminium seal with a plastic flip-off top. Cartons of 10.

6.6 Special precautions for disposal and other handling

Ganciclovir 500 mg Powder for Infusion should be handled with care.

Since ganciclovir is considered a potential teratogen and carcinogen in humans, it should be handled with care (see section 4.4 Special warnings and precautions for use). Avoid inhalation or direct contact of the powder in the vials or direct contact of the reconstituted solution with the skin or mucous membranes. Ganciclovir solutions are alkaline (pH approximately 11). If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, rinse eyes thoroughly with sterile water, or potable water if sterile water is unavailable.

Method of preparation of ganciclovir solution

1. Lyophilised Ganciclovir 500 mg Powder for Infusion should be reconstituted by introducing 10 ml sterile Water for Injections into the vial. Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), because they are incompatible with ganciclovir and may cause precipitation.
2. The vial should be shaken to dissolve the drug. The reconstituted solution contains ganciclovir 50 mg/ml.
3. Reconstituted solution should be inspected for particulate matter before preparing the solution for infusion.
4. Reconstituted solution in the vial is stable at room temperature for 12 hours. It should not be refrigerated.

Preparation and administration of infusion solution

The dose volume calculated on the basis of the patient's weight should be withdrawn from the vial containing ganciclovir solution (ganciclovir 50 mg/ml) and added to an acceptable infusion fluid. Sodium chloride 0.9% intravenous infusion, dextrose 5% injection, Ringer's injection, and Lactated Ringer's injection are determined to be compatible with ganciclovir sodium for injection. Infusion concentrations greater than ganciclovir 10 mg/ml are not recommended. Reconstituted solution and the solution for intravenous infusion should be clear. Do not use if particles are present.

Ganciclovir sodium for injection should not be mixed with other intravenous products.

Because Ganciclovir 500 mg Powder for Infusion is reconstituted with non-bacteriostatic sterile water, the infusion solution should be used as soon as possible and within 24 hours of dilution in order to reduce the risk from bacterial contamination.

The infusion solution may be refrigerated. The infusion solution should not be frozen.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA515

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

June 2024

References

US NIH Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, page 173 ff. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

UK SmPC for Cymevene

https://www.medicines.org.uk/emc/product/10242/smpc#about-medicine

European harmonised SmPC

https://www.ema.europa.eu/en/documents/referral/cymevene-article-30-referral-annex-iii_en.pdf

US prescribing information for Cytovene

http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019661s030lbl.pdf

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products