SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ganciclovir 500 mg Powder for Infusion*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10-ml vial contains ganciclovir sodium equivalent to ganciclovir 500 mg. Each vial contains 46 mg sodium.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Ganciclovir 500 mg Powder for Infusion is indicated for the treatment of life-threatening or sight-threatening cytomegalovirus (CMV) infection in HIV-infected patients.

4.2 Posology and method of administration

For intravenous infusion following reconstitution with 10 ml water for injection and further dilution with intravenous fluid.

Based on patient weight and therapeutic indication the calculated dose volume should be withdrawn from the vial (ganciclovir concentration 50 mg/ml) and added to an acceptable infusion fluid (typically 100 ml) for infusion over 1 hour. Infusion concentrations exceeding 10 mg/ml are not recommended. See section 6.6.

Acceptable infusion fluids include sodium chloride 0.9% intravenous infusion, dextrose 5% injection, Ringer's injection, and Lactated Ringer's injection.

Adults

Treatment of CMV infection

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. Intravenous infusion of 6 mg/kg once daily 5 days per week, or 5 mg/kg once daily 7 days per week is recommended.

Treatment of disease progression: Indefinite treatment may be required for patients with AIDS but even with continued maintenance treatment, retinitis may progress. If retinitis progresses, while on maintenance treatment or after stopping Ganciclovir 500 mg Powder for Infusion, the patient may be treated again with the induction treatment regimen.

Patients with renal impairment

Serum creatinine or creatinine clearance should be monitored carefully. The dose should be adjusted according to creatinine clearance as shown in the table below (see also section 5.2 Pharmacokinetic properties).

Estimated creatinine clearance (ml/minute) can be calculated from serum creatinine using the following formulae:

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Men: $$\text{Creatinine clearance} = \frac{72 \times (0.011 \times \text{body weight})}{\text{serum creatinine}}$$

Women: $$\text{Creatinine clearance} = 0.85 \times \frac{72 \times (0.011 \times \text{body weight})}{\text{serum creatinine}}$$

Table: **Ganciclovir dosage in renal impairment**

Creatinine clearance	Induction dose of ganciclovir
≥ 70 ml/minute	5.0 mg/kg every 12 hours
50–69 ml/minute	2.5 mg/kg every 12 hours
25–49 ml/minute	2.5 mg/kg every 24 hours
10–24 ml/minute	1.25 mg/kg every 24 hours
< 10 ml/minute	1.25 mg/kg after haemodialysis

Elderly patients

No studies on the efficacy or safety of ganciclovir in elderly patients have been conducted. Since elderly individuals often have reduced renal function, Ganciclovir 500 mg Powder for Infusion should be administered to elderly patients with special consideration for their renal status (see above).

Paediatric patients

There is limited clinical experience of treating patients aged under 12 years (see section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Patients with leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia

See section 4.4 Special warnings and precautions for use before initiation of therapy.

If blood cell counts deteriorate significantly during therapy with Ganciclovir 500 mg Powder for Infusion, treatment with haematopoetic growth factors, or dose interruption, or both should be considered (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

Method of administration

Ganciclovir 500 mg Powder for Infusion is for administration by intravenous infusion. For directions on the preparation of the infusion solution, see section 6.6l.

Ganciclovir 500 mg Powder for Infusion must be given by intravenous infusion **only**, preferably through a plastic cannula, into a vein with adequate blood flow.

Ganciclovir 500 mg Powder for Infusion must **not** be infused rapidly and it must **not** be given by bolus injection. Excessively rapid rise in plasma-gancicovir concentration can by highly toxic.

Inadvertent intramuscular or subcutaneous injection of Ganciclovir 500 mg Powder for Infusion can cause severe tissue irritation because ganciclovir solution is highly alkaline (pH about 11).

Ganciclovir 500 mg Powder for Infusion must be handled with care, see section 6.6.

4.3 Contraindications

Ganciclovir 500 mg Powder for Infusion is contraindicated in patients with hypersensitivity to ganciclovir, valganciclovir, aciclovir or valaciclovir.

Ganciclovir 500 mg Powder for Infusion is contra-indicated during pregnancy and lactation (see section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

Teratogenicity

Before starting ganciclovir treatment, patients should be advised of the potential risks to the fetus. In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic and a suppressor of female fertility. Ganciclovir 500 mg Powder for Infusion should therefore be considered to have the potential to cause birth defects and cancers (see section 5.3 Preclinical safety data). It is also considered likely that ganciclovir inhibits spermatogenesis temporarily or permanently. Women of child-bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days afterwards, unless it is certain that the female partner is not at risk of pregnancy (see section 4.6 Pregnancy and lactation, section 4.8 Undesirable effects and section 5.3 Preclinical safety data).

Use in children

Use of Ganciclovir 500 mg Powder for Infusion in children and adolescents requires extreme caution because of its potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks.

Reported adverse events were similar to those seen in adults. Ganciclovir 500 mg Powder for Infusion is not indicated for the treatment of congenital or neonatal CMV infection.

Bone marrow suppression

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have occurred 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/µl, or the haemoglobin level is less than 8 g/dl (80 g/litre). In such patients, alternative therapy should be considered.

Ganciclovir 500 mg Powder for Infusion should be used with caution in patients with cytopenia or a history of drug-related cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood count and platelet count are monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment. In patients developing severe leucopenia, neutropenia, anaemia or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors, or dose interruption or both are considered. Alternative therapies may be considered.

Impaired renal function

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see section 4.2 and section 5.2).

Drug-drug interactions

Convulsions have been reported in patients taking imipenem–cilastatin and ganciclovir. Ganciclovir 500 mg Powder for Infusion should not be used concomitantly with imipenem–cilastatin unless the potential benefits outweigh the potential risks (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Patients treated with Ganciclovir 500 mg Powder for Infusion and didanosine, or drugs that are myelosuppressive (e.g. zidovudine), or substances affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.5 Interactions with other medicinal products and other forms of interaction

Ganciclovir may interact with other drugs which have a similar adverse effects (e.g. bone marrow suppression and renal toxicity). Furthermore, since ganciclovir is excreted by the kidneys (section 5.2), its toxicity may be enhanced by drugs that reduce its renal clearance because the co-administered drugs are either nephrotoxic or they competitively inhibit active tubular secretion.

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.

Probenecid

Probenecid given with oral ganciclovir decreased renal clearance of ganciclovir (20%) leading to statistically significantly increased exposure (40%). These changes were consistent with a mechanism involving competition for renal tubular secretion. Therefore, patients taking probenecid and Ganciclovir 500 mg Powder for Infusion should be closely monitored for ganciclovir toxicity.

Zidovudine

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, co-administration is not recommended, Alternative antiretroviral instead of zidovudine should be used (See section 4.4 Special warnings and precautions for use).

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir. Co-administration of didanosine and Ganciclovir 500 mg Powder for Infusion is not recommended; alternative antiretroviral agents other than didanosine should be used (see section 4.4 Special warnings and precautions for use).

Tenofovir

Both ganciclovir and tenofovir are cleared renally, by tubular secretion (see also below). Furthermore, both are potentially nephrotoxic, and decreased renal function may increase exposure to both agents. If concomitant use of Ganciclovir 500 mg Powder for Infusion and tenofovir disoproxil fumarate is unavoidable, renal function should be monitored weekly.

Mycophenolate Mofetil

Based on the results of a single-dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir, it is expected that co-administration may increase exposure to ganciclovir. In patients with renal impairment who receive mycophenolate mofetil and Ganciclovir 500 mg Powder for Infusion concomitantly, the dose recommendation of ganciclovir should be adhered to and the patients monitored carefully for ganciclovir toxicity,

Other antiretrovirals

No clinically significant interactions were observed when stavudine and oral ganciclovir were given in combination.

Interactions with abacavir, emtricitabine and lamivudine have not been studied. On a mechanistic basis, however, no clinically relevant interactions are expected. Metabolic interactions with, for

example, protease inhibitors and non-nucleoside reverse transcriptase inhibitors are unlikely because cytochrome P450 enzymes are not involved in the metabolism of ganciclovir.

Other potential drug interactions

Toxicity may be enhanced when ganciclovir is co-administered with, or is given immediately before or after, other drugs that 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, adriamycin, amphotericin B, trimethoprim-sulphonamide combinations, nucleoside analogues and hydroxycarbamide (hydroxyurea).

Therefore, all of these drugs should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks (see section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraception in males and females

Women of childbearing potential must be advised to use effective contraception during treatment with ganciclovir. Men should be advised to practise 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 Preclinical safety data).

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 500 mg Powder for Infusion is contraindicated during pregnancy as there is a high likelihood of damage to the developing fetus (see also section 4.3.).

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 Ganciclovir 500 mg Powder for Infusion.

Fertility

Ganciclovir impairs fertility in animals (see section 4.4 and 4.6).

4.7 Effects on ability to drive and use machines

The effect of ganciclovir on the ability to drive and use machines has not been studied. Nevertheless, the clinical status of the patient and the adverse reaction profile of Ganciclovir 500 mg Powder for Infusion should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

In patients treated with ganciclovir the most common side effects were neutropenia, anaemia and thrombocytopenia.

Adverse reactions reported with intravenous ganciclovir, oral ganciclovir and valganciclovir are presented below. Valganciclovir is a prodrug of ganciclovir, and adverse reactions associated with valganciclovir can be expected to occur with ganciclovir. The frequency groupings of these adverse events are based upon the frequency recorded in clinical trials with CMV retinitis patients with AIDS and in clinical trials with solid organ transplant patients.

Adverse events considered to be at least possibly related to treatment with ganciclovir, are listed below by body system, organ class and absolute frequency. Frequencies are defined as *very common* (≥1/10), *common* (1/100–1/10), *uncommon* (1/1000–1/100), *rare* (1/10 000–1/1000) or *very rare* (≤1/10 000).

Infections and infestations:

Common: sepsis (bacteraemia, viraemia), cellulitis, urinary-tract infection, oral candidiasis

Blood and lymphatic disorders

Very common: neutropenia, anaemia

Common: thrombocytopenia, leucopenia, pancytopenia

Uncommon: bone marrow depression

Immune system disorders

Uncommon: anaphylactic reaction

Metabolic and nutrition disorders

Common: decreased appetite, anorexia

Psychiatric disorders

Common: depression, anxiety, confusion, abnormal thinking

Uncommon: agitation, psychotic disorder

Nervous system disorders

Common: headache, insomnia, dysgeusia, hypoaesthesia, paraesthesia, peripheral neuropathy, convulsions, dizziness

Uncommon: tremor

Eye disorders

Common: macular oedema, retinal detachment[†], vitreous floaters, eye pain

Uncommon: abnormal vision, conjunctivitis

Ear and labyrinth disorders

Common: ear pain

Uncommon: deafness

Cardiac disorders

Uncommon: arrhythmias

Vascular disorders

Uncommon: hypotension

Respiratory, thoracic and mediastinal disorders

Very common: dyspnoea

Common: cough

[†] Retinal detachment has occured in subjects with CMV retinitis both before and after starting ganciclovir treatment. Its relationship to therapy with ganciclovir is unknown.

Gastrointestinal disorders

Very common: diarrhoea

Common: nausea, vomiting, abdominal pain, constipation, flatulence, dysphagia, dyspepsia

Uncommon: abdominal distention, mouth ulceration, pancreatitis

Hepato-biliary disorders

Common: abnormal hepatic function, raised blood alkaline phosphatase, raised aspartate aminotransferase

Uncommon: raised alanine aminotransferase

Skin and subcutaneous tissue disorders

Common: dermatitis, night sweats, pruritus

Uncommon: alopecia, urticaria, dry skin

Musculoskeletal and connective tissue

Common: back pain, myalgia, arthralgia, muscle cramps

Renal and urinary disorders:

Common: decreased creatinine clearance, renal impairment

Uncommon: haematuria, renal failure

Reproductive system and breast disorders:

Uncommon: male infertility

General disorders and administration site conditions:

Common: fatigue, pyrexia, rigors, pain, malaise, asthenia, injection-site reaction

Investigations

Common: weight loss, raised serum creatinine

4.9 Overdose

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.

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: ATC code: J05AB06 (anti-infectives for systemic use, antivirals for systemic use, direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors).

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine which inhibits replication of herpes viruses 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 and varicella–zoster virus 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 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: (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 IC_{50} of ganciclovir against CMV, is in the range of 0.08 μM (0.02 μg/ml) to 14 μM (3.5 μg/ml).

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} ≥ 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

Systemic exposure

The systemic exposure ($AUC_{0–24}$) following a single 1-hour intravenous infusion of ganciclovir 5 mg/kg in patients infected with HIV and CMV ranged from 21.4 ± 3.1 µg·hour/ml (n = 16) to 26.0 ± 6.06 µg·hour/ml (n = 16). In these patients peak plasma concentration (C_{max}) ranged from 8.27 ± 1.02 µg/ml (n = 16) to 9.03 ± 1.42 µg/ml (n = 16).

Distribution

For intravenous ganciclovir, the volume of distribution is correlated with body weight with values for the steady-state volume of distribution ranging from 0.536 ± 0.078 l/kg (n = 15) to 0.870 ± 0.116 l/kg (n = 16). Cerebrospinal fluid concentrations 0.25–5.67 hours post-dose in 2 patients who received 2.5 mg/kg intravenous ganciclovir every 8 hours or every 12 hours ranged from 0.50 to 0.68 µg/ml representing 24–67% of the respective plasma concentrations. Binding to plasma proteins was 1–2% over ganciclovir concentrations of 0.5 and 51 µg/ml.

Intra-ocular concentrations of ganciclovir range from 40 to 200% of those measured simultaneously in plasma following administration of intravenous ganciclovir. Average intravitreal concentrations following induction and maintenance dosing with intravenous ganciclovir were 1.15 and 1.0 µg/ml respectively. Half-life of ganciclovir within the eye is much longer than that in plasma with estimates ranging from 13.3 to 18.8 hours.

Metabolism and elimination

When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6–5.0 mg/kg. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, 89.6 ± 5.0% (n = 4) of intravenous ganciclovir was recovered unmetabolised in the urine. In subjects with normal renal function, systemic clearance ranged from 2.64 ± 0.38 ml/minute/kg (n = 15) to 4.52 ± 2.79 ml/minute/kg (n = 6) and renal clearance ranged from 2.57 ± 0.69 ml/minute/kg (n = 15) to 3.48 ± 0.68 ml/minute/kg (n = 16), corresponding to 90–101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from 2.73 ± 1.29 hours (n = 6) to 3.98 ± 1.78 hours (n = 8).

Special populations

Renal impairment

Renal impairment leads to altered kinetics of ganciclovir as indicated by the study data below.

Serum creatinine	Ganciclovir	
	Systemic plasma clearance	Plasma half-life
< 124 µmol/l (n = 22)	3.64 ml/minute/kg	2.9 hours
125–225 µmol/l (n = 9)	2.00 ml/minute/kg	5.3 hours
226–398 µmol/l (n = 3)	1.11 ml/minute/kg	9.7 hours
> 398 µmol/l (n = 5)	0.33 ml/minute/kg	28.5 hours

Patients on haemodialysis

During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42 to 92 ml/minute, 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/minute) 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%.

Paediatric population

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, C_{max} 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.

Older people

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

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 (see section 4.4 Special warnings and precautions for use).

Based on animal studies where aspermatogenesis was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir could inhibit human spermatogenesis.

Data from an ex vivo human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1 to 10 mg/ml and occurred by passive diffusion.

The transfer of ganciclovir into rat milk has been reported. The milk:plasma ratio for ganciclovir in rats was about 1.6.

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, wash thoroughly with soap and water, 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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Reference list

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

This SmPC text is primarily based on the UK SmPCs for Cymevene and on the US prescribing information for Cytovene. These documents are available at
http://www.medicines.org.uk/emc/medicine/3497 and
http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019661s030lbl.pdf, respectively.