ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note:

This Summary of Product Characteristics, labelling and package leaflet is the outcome of the referral procedure to which this Commission decision relates.
The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cymevene and associated names (see Annex I) 500 mg powder for concentrate for solution for infusion.
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of ganciclovir (as ganciclovir sodium).

After reconstitution with 10 mL of water for injections, each mL provides 50 mg of ganciclovir.

Excipient(s) with known effect: approximately 43 mg (2 mEq) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white solid cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cymevene is indicated in adults and adolescents from 12 years of age for the:

- treatment of cytomegalovirus (CMV) disease in immunocompromised patients;
- prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).

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

4.2 Posology and method of administration

Posology

Treatment of CMV disease in adults and adolescents from 12 years of age with normal renal function

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in whom CMV disease progresses, either while on maintenance treatment or because treatment with ganciclovir has been withdrawn, may be re-treated using the induction treatment regimen.

Prevention of CMV disease in adults and adolescents from 12 years of age with normal renal function using prophylaxis or pre-emptive therapy

- Prophylaxis:
5 mg/kg given as an intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of prophylaxis is based on the risk of CMV disease, local treatment guidelines should be consulted.

- Pre-emptive therapy:
Induction therapy: 5 mg/kg given as an intravenous infusion over one hour, every 12 hours for 7 – 14 days.
Maintenance therapy: 5 mg/kg given as an intravenous infusion over one hour, once daily on 7 days per week or 6 mg/kg once daily on 5 days per week. The duration of maintenance therapy is based on the risk of CMV disease, local treatment guidelines should be consulted.

Renal impairment

For patients with renal impairment, the dose of ganciclovir should be modified according to creatinine clearance as shown in the table below (see sections 4.4 and 5.2).

Dose modifications for patients with renal impairment:

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

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

For males: $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/L]})}$

For females: 0.85 x male value

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

Severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia

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

Caution:
Ganciclovir must be administered by intravenous infusion over 1 hour at a concentration not exceeding 10 mg/mL. Do not administer by rapid or bolus intravenous injection because the resulting excessive plasma levels may increase the toxicity of ganciclovir.

Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions (see section 4.8).

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

Cymevene is a powder for solution for infusion. After reconstitution Cymevene is a colourless to slightly yellowish solution, practically free from visible particles.

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Precaution to be taken before handling or administering the medicinal product:

Since ganciclovir is considered a potential teratogen and carcinogen in humans, caution should be taken in its handling (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or valganciclovir or to any of the excipients listed in section 6.1.

Breast-feeding (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. Caution should therefore be used when prescribing Cymevene 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 child bearing 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

Cymevene 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).

Excipients

This medicinal product contains 2 mmol (43mg) sodium per 500 mg dose. To be taken into consideration by patients on a controlled sodium diet.

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 Cymevene 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, stavudine, trimethoprim and zidovudine

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

Other antiretrovirals

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

Pharmacodynamic interactions

Imipenem – cilastatin

Convulsions have been reported in patients taking ganciclovir and imipenem–cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

Other potential drug interactions

Toxicity may be enhanced when ganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, doxorubicin, amphotericin B, mycophenolate mofetil, trimethoprim/sulphamethoxazole, and hydroxyurea) as well as nucleoside analogues (including zidovudine). Therefore, these drugs should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 4.4).

Pregnancy

The safety of ganciclovir for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. In animals studies ganciclovir was associated with reproductive toxicity and teratogenicity (see sections 4.4 and 5.3). Therefore, ganciclovir should not be used in pregnant women unless the clinical need for treatment of the woman outweighs the potential teratogenic risk to the foetus.

Contraception in males and females

As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir unless it is certain that the female partner is not at risk of pregnancy (see sections 4.4 and 5.3).

Breastfeeding

It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breastfed infant cannot be excluded. Therefore, breastfeeding must be discontinued during treatment with ganciclovir (see section 4.3).

4.7 Effects on ability to drive and use machines

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

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 reactions

Infections and infestations:	
Common (≥ 1/100, < 1/10):	Sepsis Cellulitis Urinary tract infection Candida infections including oral candidiasis.
Blood and lymphatic disorders:	
Very common (≥ 1/10):	Neutropenia Anaemia.
Common (≥ 1/100, <1/10):	Thrombocytopenia Leucopenia Pancytopenia
Uncommon (≥ 1/1000, < 1/100):	Bone marrow failure
Rare (≥ 1/10000, < 1/1000)	Agranulocytosis* Aplastic anaemia* Granulocytopenia*
Immune system disorders:	
Uncommon (≥ 1/1000, < 1/100):	Anaphylactic reaction
Metabolic and nutrition disorders:	
Common (≥ 1/100, < 1/10):	Decreased appetite Anorexia Weight decreased
Psychiatric disorders:	
Common (≥ 1/100, < 1/10):	Depression Anxiety Confusional state Thinking abnormal
Uncommon (≥ 1/1000, < 1/100):	Agitation Psychotic disorder
Rare (≥ 1/10000, < 1/1000)	Hallucinations*
Nervous system disorders:	
Common (≥ 1/100, < 1/10):	Headache Insomnia Dysgeusia (taste disturbance) Hypoaesthesia Paraesthesia Neuropathy peripheral Convulsion Dizziness
Uncommon (≥ 1/1000, < 1/100):	Tremor
Eye disorders:	
Common (≥ 1/100, < 1/10):	Macular oedema Retinal detachment Vitreous floaters Eye pain
Uncommon (≥ 1/1000, < 1/100):	Visual impairment Conjunctivitis
Ear and labyrinth disorders:	
Common (≥ 1/100, < 1/10):	Ear pain
Uncommon (≥ 1/1000, <1/100):	Deafness
Cardiac disorders:	
Uncommon (≥ 1/1000, < 1/100):	Cardiac arrhythmias
Vascular disorders:	
Uncommon (≥ 1/1000, < 1/100):	Hypotension

Respiratory, thoracic and mediastinal disorders:	
Very common (≥ 1/10):	Dyspnoea
Common (≥ 1/100, < 1/10):	Cough
Gastrointestinal disorders:	
Very common (≥ 1/10):	Diarrhoea
Common (≥ 1/100, < 1/10):	Nausea
	Vomiting
	Abdominal pain
	Abdominal pain upper
	Constipation
	Flatulence
	Dysphagia
	Dyspepsia
Uncommon (≥ 1/1000, < 1/100):	Abdominal distention
	Mouth ulceration
	Pancreatitis
Hepato-biliary disorders:	
Common (≥ 1/100, < 1/10):	Hepatic function abnormal
	Blood alkaline phosphatase increased
	Aspartate aminotransferase increased
Uncommon (≥ 1/1000, < 1/100):	Alanine aminotransferase increased
Skin and subcutaneous tissues disorders:	
Common (≥ 1/100, < 1/10):	Dermatitis
	Night sweats
	Pruritus
Uncommon (≥ 1/1000, < 1/100):	Alopecia
	Urticaria
	Dry skin
Rare (≥ 1/10000, < 1/1000)	Rash*
Musculo-skeletal and connective tissue disorders:	
Common (≥ 1/100, < 1/10):	Back pain
	Myalgia
	Arthralgia
	Muscle spasms
Renal and urinary disorders:	
Common (≥ 1/100, < 1/10):	Creatinine clearance renal decreased
	Renal impairment
	Blood creatinine increased
Uncommon (≥ 1/1000, < 1/100):	Haematuria
	Renal failure
Reproductive system and breast disorders:	
Uncommon (≥ 1/1000, < 1/100):	Male infertility
General disorders and administration site conditions:	
Common (≥ 1/100, < 1/10):	Fatigue
	Pyrexia
	Chills
	Pain
	Chest pain
	Malaise
	Asthenia
	Injection site reaction

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

** 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).

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000 /mL) 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.

Convulsions

Convulsions 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 AIDS patients treated with Cymevene for CMV retinitis.

Injection site reactions

Injection site reactions occur commonly in patients receiving ganciclovir. Cymevene 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. However, the rates of certain adverse reactions, such as pyrexia and abdominal pain, which may be characteristic of the paediatric population, occur more often in paediatric than in adult patients. Neutropenia also occurs more often in paediatric patients, but there is no correlation between neutropenia and infectious adverse reactions in the paediatric population.

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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Management

Ganciclovir is removed by haemodialysis, therefore haemodialysis may be of benefit in reducing drug exposure in patients who receive an overdose of ganciclovir (see section 5.2).

Additional information on special populations

Renal impairment: It is expected that an overdose of ganciclovir could result in increased renal toxicity in patients with renal impairment (see section 4.4).

Paediatric population

No specific information available

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses both *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes-simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and hepatitis B virus. Clinical studies have been limited to evaluation of efficacy in patients with CMV infection.

In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. This has been shown to occur in HSV- and HCMV-infected cells, with half-lives of 18 and 6–24 hours, respectively, after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.
The virustatic activity of ganciclovir is a result of the inhibition of viral DNA synthesis by: (1) competitive inhibition of incorporation of deoxyguanosine triphosphate into DNA by DNA polymerase, and (2) incorporation of ganciclovir triphosphate into viral DNA, causing termination of, or very limited, viral DNA elongation.

Antiviral Activity

The *in vitro* antiviral activity, measured as IC50 of ganciclovir against CMV, is in the range of 0.08 μM (0.02 μg/ml) to 14 μM (3.57 μg/ml).

Clinical efficacy and safety

Viral resistance

The possibility of viral resistance should be considered in patients who repeatedly achieve a poor clinical response or experience continuous viral excretion during treatment.

Viral resistance to ganciclovir can arise by selection of mutations in the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or the viral polymerase gene (UL54). Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas viruses with mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target viral polymerase.

Paediatric population

In a prospective study, 36 severely immunocompromised paediatric patients (6 months - 16 years of age) with HIV and CMV infection received intravenous ganciclovir at a dose of 5 mg/kg per day for 2 days followed by oral ganciclovir for a median of 32 weeks. Ganciclovir was effective with a toxicity profile similar to that seen in adults. Ganciclovir was associated with a decrease in the detection of CMV by culture or polymerase chain reaction. Neutropenia was the only severe adverse drug reaction observed during the study and although none of the children required treatment cessation, 4 required granulocyte colony-stimulating factor (G-CSF) treatment to maintain absolute neutrophil counts > 400 cells/mm^3.

In a retrospective study, 122 paediatric liver transplantation recipients (16 days – 18 years of age, median age 2.5 years) received a minimum of 14 days of intravenous ganciclovir 5 mg/kg twice a day followed by pre-emptive CMV PCR monitoring. Forty-three patients were considered high-risk for CMV and 79 were routine-risk. Asymptomatic CMV infection was detected by PCR in 34.4% of subjects and was more likely in high-risk than in routine-risk recipients (58.1% vs. 21.8%, $p = 0.0001$). Twelve subjects (9.8%) developed CMV disease (8 high-risk vs. 4 routine-risk, $p = 0.03$). Three subjects developed acute rejection within 6 months of detection of CMV, but CMV was preceded by rejection in 13 subjects. There were no deaths secondary to CMV. A total of 38.5% of subjects were spared antiviral medications beyond their initial postoperative prophylaxis.

In a retrospective analysis, the safety and efficacy of ganciclovir was compared to valganciclovir in 92 paediatric kidney and/or liver transplant patients (7 months -18 years of age, median age 9 years). All children received intravenous ganciclovir 5 mg/kg twice daily for 2 weeks following transplantation. Children treated before 2004 then received oral ganciclovir 30 mg/kg/dose up to 1 g/dose three times daily ($n = 41$), while children treated after 2004 received valganciclovir up to 900 mg once daily ($n = 51$). The overall incidence of CMV was 16% (15/92 patients). Time to onset of CMV infection was comparable in both groups.

In a randomised, controlled study, 100 neonates (≤1 month of age) with symptomatic congenital CMV disease with CNS involvement received 6 weeks of intravenous ganciclovir 6 mg/kg every 12 hours or no treatment. Of the 100 patients enrolled, 42 met all study criteria and had both baseline and 6-month follow up audiometric evaluations. Of these, 25 received ganciclovir and 17 received no treatment. Twenty-one of 25 ganciclovir recipients had improved hearing or maintained normal hearing from baseline to 6 months compared with 10/17 control patients (84% and 59%, respectively $p = 0.06$). None of the ganciclovir recipients had worsening hearing from baseline to 6 months, compared with 7 control patients ($p < 0.01$). By one year after baseline, 5/24 ganciclovir recipients and 13/19 control patients had worsening hearing ($p < 0.01$). During the course of the study, 29/46 ganciclovir-treated

patients had neutropenia, compared with 9/43 control patients ($p < 0.1$). There were 9 deaths during the study, 3 in the ganciclovir group and 6 in the control group. No deaths were related to study medication.

In a Phase III, randomised, controlled study, 100 neonates (3-33 days of age, median age 12 days) with severe symptomatic congenital CMV with CNS involvement, received either intravenous ganciclovir 6 mg/kg twice daily for 6 weeks (n = 48) or no antiviral treatment (n = 52). Infants who received ganciclovir had improved neurodevelopmental outcomes at 6 and 12 months compared with those who did not receive antiviral treatment. Although ganciclovir recipients had fewer delays and more normal neurological outcomes, most were still behind what would be considered normal development at 6 weeks, 6 months, or 12 months of age. Safety was not assessed in this study.

A retrospective study investigated the effect of antiviral treatment on late-onset hearing loss in infants with congenital CMV infection (4-34 months of age, mean age 10.3±7.8 months, median age 8 months). The study included 21 infants with normal hearing at birth who developed late-onset hearing loss. Antiviral treatment consisted of either:

- Intravenous ganciclovir 5 mg/kg daily for 6 weeks followed by oral valganciclovir 17 mg/kg twice daily for 6 weeks then daily until 1 year of age, or
- Oral valganciclovir 17 mg/kg twice daily for 12 weeks then daily for 9 months.

None of the children required a cochlear implant and hearing loss improved in 83% of ears affected by hearing loss at baseline. Neutropenia was the only side effect reported and it was not necessary to discontinue treatment in any patient.

5.2 Pharmacokinetic properties

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

Distribution

The volume of distribution of intravenously administered ganciclovir is correlated to body weight. The steady state volume of distribution has a range of 0.54–0.87 L/kg. Plasma protein binding was 1%–2% over ganciclovir concentrations of 0.5 and 51 μg/mL. Ganciclovir penetrates the cerebrospinal fluid, where concentrations observed reach 24%–67% of the plasma concentrations.

Biotransformation

Ganciclovir is not metabolised to a significant extent.

Elimination

Ganciclovir is predominantly eliminated by renal excretion via glomerular filtration and active tubular secretion of unchanged ganciclovir. In patients with normal renal function, more than 90% of the intravenously administered ganciclovir dose is recovered unchanged in the urine within 24 hours. The mean systemic clearance ranged from 2.64 ± 0.38 mL/min/kg (N = 15) to 4.52 ± 2.79 mL/min/kg (N = 6) and renal clearance ranged from 2.57 ± 0.69 mL/min/kg (N = 15) to 3.48 ± 0.68 mL/min/kg (N = 20), corresponding to 90%–101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from 2.73 ± 1.29 (N = 6) to 3.98 ± 1.78 hours (N = 8).

Linearity/non-linearity

Intravenous ganciclovir exhibits linear pharmacokinetics over the range of 1.6–5.0 mg/kg.

Patients with renal impairment

The total plasma 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 and, depending on renal function, it ranges from about 6 to 17 hours (see section 4.2 for dose modifications required in patients with renal impairment).

Serum creatinine (μmol/L)	**Creatinine clearance (mL/min)**	**Mean Ganciclovir systemic plasma clearance (mL/min)**	**Mean Ganciclovir Plasma half-life (hours)**
< 125	≥ 70	208	3.0
125–175	50–69	102	4.8
176–350	25–49	87	5.5
> 350	10–24	34	11.5

Patients with Renal Impairment Undergoing Haemodialysis

Haemodialysis reduces plasma concentrations of ganciclovir by about 50% after intravenous administration during a 4-hour haemodialysis session.
During intermittent haemodialysis, estimates for the clearance of ganciclovir ranged from 42–92 mL/min, resulting in intra-dialytic half-lives of 3.3–4.5 hours. The fraction of ganciclovir removed during a single dialysis session varied from 50% to 63%. Estimates of ganciclovir clearance for continuous dialysis were lower (4.0–29.6 mL/min) but resulted in greater removal of ganciclovir over a dose interval.

Paediatric Population

The pharmacokinetics of intravenous ganciclovir were investigated in neonates aged 2–49 days following doses of 4 mg/kg (N = 14) and 6 mg/kg (N = 13). Mean C_{max} was 5.5 ± 6 μg/mL at 4 mg/kg and 7.0 ± 1.6 μg/mL at 6 mg/kg. Mean values for the steady state volume of distribution (0.7 L/kg) and systemic clearance (3.15 ± 0.47 mL/min/kg at 4 mg/kg and 3.55 ± 0.35 mL/min/kg at 6 mg/kg) were comparable to those observed in adults with normal renal function.

Pharmacokinetics of intravenous ganciclovir were also studied in infants and children with normal renal function and aged 9 months–12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) 5 mg/kg intravenous doses. Exposure as measured by mean $AUC_{0-\infty}$ on Days 1 and 14 were 19.4 ± 7.1 and 24.1 ± 14.6 μg.h/mL, respectively, and the corresponding C_{max} values were 7.59 ± 3.21 μg/mL (Day 1) and 8.31 ± 4.9 μg/mL (Day 14). The range of exposures was comparable to those observed in adults. The corresponding values of mean systemic clearance, mean renal clearance, and mean elimination half-life were 4.66 ± 1.72 mL/min/kg, 3.49 ± 2.40 mL/min/kg, and 2.49 ± 0.57 h, respectively. The pharmacokinetics of intravenous ganciclovir in infants and children were consistent with those observed in neonates and adults.

Elderly

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. Based upon animal studies where aspermatogenesis 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

Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.. Do not use bacteriostatic water for injections containing parabens (para-hydroxybenzoates) since these are incompatible with Cymevene and may cause precipitation.

6.3 Shelf life

3 years

After reconstitution:
Chemical and physical in-use stability has been demonstrated for the reconstituted product for 12 hours at 25°C after dissolving with water for injections. Do not refrigerate or freeze.
From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 – 8°C (do not freeze).
From a microbiological point of view, the Cymevene infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Single-dose glass vials of 10 mL with fluoro-resin laminated rubber stopper and aluminum closure with flip-off cap.
Available in packs of 1 vial or 5 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Caution should be exercised in the handling of Cymevene.
Since Cymevene is considered a potential teratogen and carcinogen in humans, caution should be observed in its handling. Avoid inhalation or direct contact of the powder contained in the vials or direct contact of the reconstituted solution with the skin or mucous membranes. Cymevene solutions are alkaline (pH ~11). If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water.

Preparation of the reconstituted concentrate

Aseptic technique should be used throughout to reconstitute lyophilised Cymevene.

1. The flip-off cap should be removed to expose the central portions of the rubber stopper. Draw 10 mL of water for injection into a syringe, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. **Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene.**

2. The vial should be gently swirled in order to ensure complete wetting of the product.

3. The vial should be gently rotated/ swirled for some minutes to obtain a clear reconstituted solution.

4. The reconstituted solution should be checked carefully to ensure that the product is in solution and practically free from visible particles prior to dilution with compatible solvent. Reconstituted solutions of Cymevene range in colour from colourless to light yellow.

For storage conditions of the reconstituted concentrate, see sections 6.3.

Preparation of final diluted solution for infusion

Based on patient weight the appropriate volume should be removed with a syringe from the vial and further diluted into an appropriate infusion solution. Add a volume of 100ml of diluent to the reconstituted solution. Infusion concentrations greater than 10mg/mL are not recommended. Sodium chloride, dextrose 5%, Ringer's or lactated Ringer's solutions are determined chemically or physically compatible with Cymevene.

Cymevene should not be mixed with other intravenous products.

The diluted solution should then be infused intravenously over 1 hour as directed in section 4.2. Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solution.

For storage conditions of the diluted solution for infusion, see section 6.3.

Disposal

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name and associated names (see Annex I) strength pharmaceutical form}
[See Annex I - To be completed nationally]

Ganciclovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains ganciclovir sodium equivalent to 500 mg ganciclovir

3. LIST OF EXCIPIENTS

This medicinal product contains sodium. Read the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial
5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid direct contact with or inhalation of the powder contained in the vial or direct contact of the solution with skin or mucous membranes.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{(Invented) name and associated names (see Annex I) strength pharmaceutical form}
[See Annex I - To be completed nationally]

Ganciclovir
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 mg

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Cymevene and associated names (see Annex I) 500 mg powder for concentrate for solution for infusion

[See Annex I - To be completed nationally]
ganciclovir

Read all of this leaflet carefully before you start using this medicine – because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cymevene is and what it is used for

What Cymevene is
Cymevene contains the active substance ganciclovir. This belongs to a group called anti-viral medicines.

What Cymevene is used for
Cymevene is used to treat diseases caused by a virus called cytomegalovirus (CMV) in patients who have a weak immune system. It is also used to prevent CMV infection after an organ transplant or during chemotherapy.
It is used in adults and adolescents 12 years and older.
- The virus can affect any part of the body. This includes the retina at the back of the eye – this means the virus can cause problems with eye sight.
- The virus can affect anyone, but it is a particular problem in people with a weak immune system. In these people the CMV virus can lead to a serious disease. A weak immune system may be caused by other diseases (such as AIDS) or by medicines (such as chemotherapy or immunosuppressants).

2. What you need to know before you use Cymevene

Do not use Cymevene if:
- you are allergic to ganciclovir, valganciclovir or any of the other ingredients of this medicine (listed in section 6)
- you are breast-feeding (see Breast-feeding subsection).

Do not use Cymevene if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before using Cymevene.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Cymevene if:
- you are allergic to aciclovir, valaciclovir, penciclovir or famciclovir – these are other medicines used for viral infections
- you have low white blood cell, red blood cell or platelet counts – your doctor will do blood tests before you start and during your treatment
- you have had problems with your blood cell counts caused by medicines in the past
- you have kidney problems – your doctor will need to give you a lower dose and check your blood cell counts more often during treatment
- you are having radiotherapy.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using Cymevene.

Look out for side effects
Cymevene can cause some serious side effects that you need to tell your doctor about straight away. Look out for these while you are taking Cymevene – your doctor may tell you to stop taking Cymevene and you may need urgent medical treatment:
- low white blood cell counts – with signs of infection such as sore throat, mouth ulcers or a fever
- low red blood cell counts – signs include feeling short of breath or tired, palpitations or pale skin
- low level of platelets – signs include bleeding or bruising more easily than usual, blood in urine or stools or bleeding from gums, the bleeding could be severe
- allergic reaction – the signs may include red itchy skin, swelling of the throat, face, lips or mouth, difficulty swallowing or breathing.

Tell your doctor straight away if you notice any of the serious side effects above. See Serious side effects at the top of section 4 for more information.

Tests and checks
While you are using Cymevene your doctor will do regular blood tests. This is to check the dose you are having is right for you. For the first 2 weeks these blood tests will be done often. After that the tests will be done less often.

Children and adolescents
There is limited information on how safe or effective Cymevene is in children under 12 years.

Other medicines and Cymevene
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- imipenem/cilastatin – used for bacterial infections,
- pentamidine – used for parasite or lung infections,
- flucytosine, amphotericin B – used for fungal infections,
- trimethoprim, trimethoprim/sulfamethoxazole, dapsone – used for bacterial infections,
- probenecid – used for gout,
- mycophenolate mofetil – used after an organ transplant,
- vincristine, vinblastine, doxorubicin – used for cancer,
- hydroxyurea – used for a problem called polycythemia, sickle cell disease and cancer,
- didanosine, stavudine, zidovudine or any other medicines used for HIV.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using Cymevene.

Pregnancy, breast-feeding and fertility

Pregnancy
Cymevene should not be used by pregnant women unless the benefits to the mother outweigh the possible risks to the unborn baby.
If you are pregnant or think you might be pregnant, do not use this medicine unless your doctor tells you to. This is because Cymevene may harm the unborn baby.

Contraception
You should not become pregnant while using this medicine. This is because it may affect the unborn baby.

Women
If you are a woman who could get pregnant – use contraception while you are using Cymevene. Also do this for at least 30 days after Cymevene has been stopped.

Men
If you are a man whose female partner could get pregnant – use a barrier method of contraception (such as condoms) while you are using Cymevene. Also do this for at least 90 days after Cymevene has been stopped.

If you or your partner becomes pregnant while using Cymevene, talk to your doctor straight away.

Breast-feeding
Do not use Cymevene if you are breast-feeding. If your doctor wants you to start using Cymevene you must stop breast-feeding before you start using the medicine. This is because Cymevene may pass into breast milk.

Fertility
Cymevene may affect fertility. Cymevene may temporarily or permanently stop men from producing sperm. If you are planning to have a baby, talk to your doctor or pharmacist before using Cymevene.

Driving and using machines
You may feel sleepy, dizzy, confused or shaky, or you may lose your balance or have fits while using Cymevene. If this happens, do not drive or use any tools or machines.

Cymevene contains sodium
Cymevene contains 43 mg of sodium in each 500mg dose. This should be taken into consideration by patients on a controlled sodium diet.

3. How to use Cymevene

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine
Cymevene will be given to you by a doctor or nurse. It will be given through a tube into your vein. This is called an intravenous infusionand it will usually take one hour.

The dose of Cymevene varies from one patient to another. Your doctor will work out how much you need. It will depend on:
- your weight
- your age
- how well your kidneys are working
- your blood counts
- what you are using the medicine for.

How often you will have Cymevene and how long you keep using it will also vary.
- You will usually start by having one or two infusions every day.
- If you have two infusions a day, this will continue for up to 21 days.
- After that the doctor may prescribe the infusion once a day.

People with kidney or blood problems
If you have any kidney or blood problems your doctor might suggest a smaller dose of Cymevene and check your blood cell counts more often during treatment.

If you use more Cymevene than you should
If you think you have been given too much Cymevene talk to your doctor or go to hospital straight away. You may get the following symptoms if you have too much:
- stomach pain, diarrohea or being sick
- shaking or fits
- blood in your urine
- kidney or liver problems
- changes in blood cell counts.

If you stop using Cymevene
Do not stop using Cymevene without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Serious side effects
Tell your doctor straight away if you notice any of the following serious side effects – your doctor may tell you to stop taking Cymevene and you may need urgent medical treatment:

Very common: may affect more than 1 in 10 people
- low white blood cell counts – with signs of infection such as sore throat, mouth ulcers or a fever
- low red blood cell counts – signs include feeling short of breath or tired, palpitations or pale skin.

Common: may affect up to 1 in 10 people
- low level of platelets – signs include bleeding or bruising more easily than usual, blood in urine or stools or bleeding from gums, the bleeding could be severe.

Uncommon: may affect up to 1 in 100 people
- allergic reaction – the signs may include, red itchy skin, swelling of the throat, face, lips or mouth, difficulty swallowing or breathing.

Tell your doctor straight away if you notice any of the side effects above.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common: may affect more than 1 in 10 people
- diarrhoea
- feeling short of breath.

Common: may affect up to 1 in 10 people
- headache
- trouble sleeping
- fever, chills or night sweats

- feeling tired, dizzy, weak or generally unwell
- feeling depressed, anxious, confused or having abnormal thoughts
- pain
- ear pain
- hands or feet feeling weak or numb, which may affect your balance
- muscle pain or spasms
- back, chest or joint pain
- sight problems or eye pain
- eczema, skin problems, itching
- changes to your sense of touch, tingling, tickling, pricking or burning feeling
- fits
- cough
- feeling or being sick
- problems swallowing
- changes to the way things taste
- loss of appetite, anorexia or weight loss
- stomach pain, constipation, wind, indigestion
- urine infection – signs include fever, passing urine more often, pain when passing urine
- thrush and oral thrush
- bacterial skin infection – signs include red, painful or swollen skin
- blood poisoning (sepsis)
- changes in blood cell counts
- liver and kidney problems shown in tests
- a skin reaction where the medicine was injected – such as inflammation, pain and swelling.

Uncommon: may affect up to 1 in 100 people

- hair loss
- deafness
- mouth ulcers
- hives, dry skin
- feeling agitated or nervous
- eye infection (conjunctivitis)
- abnormal thoughts or feelings, losing contact with reality
- blood in urine
- tremor, shaking
- swollen stomach
- uneven heartbeat
- low blood pressure, which may make you feel dizzy or faint
- serious kidney problems shown in tests
- low red blood cell counts shown in tests
- infertility in men – see 'Fertility' section
- pancreatitis – signs are severe stomach pain which spreads into your back.

Rare: may affect up to 1 in 1,000 people

- rash
- hallucinations – hearing or seeing things that are not real.

Side effects in children and adolescents

The following side effects are more likely in children:

- fever
- stomach pain
- low white blood cell counts.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cymevene

Keep this medicine out of the sight and reach of children.

Powder: Does not require any special storage conditions. It should not be used after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

After reconstitution:
Chemical and physical in-use stability has been demonstrated for the reconstituted product for 12 hours at 25°C after dissolving with water for injections. Do not refrigerate or freeze.
From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

After dilution in infusion solutions (sodium chloride 0.9%, dextrose 5%, Ringer's or lactated Ringer's solution for injection) :
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 – 8°C (do not freeze).
From a microbiological point of view, the Cymevene infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cymevene contains
- The active substance is ganciclovir. Each glass vial contains 500 mg ganciclovir as ganciclovir sodium. Following reconstitution of the powder, 1ml solution contains 50 mg ganciclovir.
- The other ingredients are sodium hydroxide and hydrochloric acid.

What Cymevene looks like and contents of the pack
Cymevene is a white to off white powder for concentrate for solution for infusion, supplied in a single-dose glass vial, with a rubber stopper and aluminium closure with flip-off cap. Reconstituted solutions of Cymevene range in colour from colourless to light yellow.

Vials of Cymevene are supplied in packs of 1 or 5. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

This medicinal product is authorised in the Member States of the EEA under the following names:
<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

INSTRUCTIONS FOR USE AND HANDLING

Please refer to the Summary of Product Characteristics for full prescribing information.

Method of administration

Caution:
Ganciclovir must be administered by intravenous infusion over 1 hour at a concentration not exceeding 10 mg/mL. Do not administer by rapid or bolus intravenous injection because the resulting excessive plasma levels may increase the toxicity of ganciclovir.

Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.

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

Cymevene is a powder for solution for infusion. After reconstitution Cymevene is a colourless to slightly yellowish solution, practically free from visible particles.

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

Caution should be exercised in the handling of Cymevene.
Since Cymevene is considered a potential teratogen and carcinogen in humans, caution should be observed in its handling. Avoid inhalation or direct contact of the powder contained in the vials or direct contact of the reconstituted solution with the skin or mucous membranes. Cymevene solutions are alkaline (pH ~11). If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water.

Preparation of the reconstituted concentrate

Aseptic technique should be used throughout to reconstitute lyophilised Cymevene.

1. The flip-off cap should be removed to expose the central portions of the rubber stopper. Draw 10 mL of water for injection into a syringe, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. **Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene.**

2. The vial should be gently swirled in order to ensure complete wetting of the product.

3. The vial should be gently rotated/ swirled for some minutes to obtain a clear reconstituted solution.

4. The reconstituted solution should be checked carefully to ensure that the product is in solution and practically free from visible particles prior to dilution with compatible solvent. Reconstituted solutions of Cymevene range in colour from colourless to light yellow.

Preparation of final diluted solution for infusion

Based on patient weight the appropriate volume should be removed with a syringe from the vial and further diluted into an appropriate infusion solution. Add a volume of 100ml of diluent to the reconstituted solution. Infusion concentrations greater than 10mg/mL are not recommended. Sodium chloride, dextrose 5%, Ringer's or lactated Ringer's solutions are determined chemically or physically compatible with Cymevene.

Cymevene should not be mixed with other intravenous products.

The diluted solution should then be infused intravenously over 1 hour as directed in section 4.2. Do not administer by intramuscular or subcutaneous injection because this may result in severe tissue irritation due to the high pH (~11) of ganciclovir solution.

Disposal

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.