1. NAME OF THE MEDICINAL PRODUCT

[As per local approval] (For example: Cymevene 250mg capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[As per local approval] (For example: Each capsule contains 250mg of ganciclovir)

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Opaque green capsule printed with “CY 250” on the cap and two partial lines on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[As per local approval]

4.2 Posology and method of administration

Standard dosage

For patients with stable CMV retinitis following appropriate induction therapy, the recommended maintenance dose of orally administered Cymevene is 1000 mg three times per day with food. Alternatively, the dosing regimen of 500 mg six times per day may be used [58, 59, 60, 61, 62, 66]

For prevention of CMV disease, the recommended dose is 1000 mg three times per day with food [63, 64, 65].

Special dosage instructions

Patients with renal impairment:
Serum creatinine levels or creatinine clearance should be monitored carefully [68]. Dosage adjustment is required according to creatinine clearance as shown in the table below (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties). [53, 54, 55, 56, 57]

An estimated creatinine clearance (ml/min) can be related to serum creatinine by the following formulae: [67]

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

For females = 0.85 x male value

CrCl (ml/min)	Dose of ganciclovir
≥70	1000 mg three times daily
	or 500 mg every 3 h, six times daily
50 - 69	1500 mg daily or 500 mg three times daily
25 - 49	1000 mg daily or 500 mg two times daily
10 - 24	500 mg daily
<10	500 mg three times weekly, following hemodialysis [53]

Paediatric patients:
Safety and efficacy of ganciclovir in pediatrics have not been established, including use for the treatment of congenital or neonatal CMV infections (see section 4.4, Special warnings and precautions for use).

Elderly patients:
Since elderly individuals often have reduced renal function, Cymevene should be administered to elderly patients with special consideration of their renal status (see Section 4.2 Posology and method of administration, *Patients with renal impairment* [53, 54, 55, 56, 57]).

Patients with severe leucopenia, severe neutropenia, anaemia thrombocytopenia and pancytopenia:
see section 4.4 Special warnings and precautions for use before initiation of therapy.

If there is a significant deterioration of blood cell counts during therapy with Cymevene, treatment with haematopoetic growth factors and/or dose interruption should be considered [70] (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

Method of administration
Cymevene capsules are administered orally and should be taken with food (see section 5.2 Pharmacokinetic properties, Food effects).

Caution should be exercised in the handling of Cymevene.
Cymevene capsules should not be opened or crushed. Since Cymevene is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken capsules (see Section 4.4 Special warnings and precautions for use). Avoid inhalation or direct contact of the powder contained in the capsules with the skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.
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4.3 Contraindications

DO NOT CHANGE THE CURRENT NATIONAL RECOMMENDATION REGARDING THE USE OF CYMEVENE IN PREGNANCY.

Cymevene is contraindicated in patients with hypersensitivity to ganciclovir, valganciclovir or to any of the excipients.

Due to the similarity of the chemical structure of Cymevene and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible [43]. Therefore, Cymevene is contraindicated in patients with hypersensitivity to aciclovir and valaciclovir.

Cymevene is contraindicated during lactation, refer to section 4.6 Pregnancy and lactation.

4.4 Special warnings and precautions for use

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 and carcinogenic and a suppressor of female fertility [39, 68, 69]. Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 5.3 Preclinical safety data) [39]. It is also considered likely that Cymevene causes temporary or permanent inhibition of spermatogenesis [40]. 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 thereafter, 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).

The use of Cymevene capsules in children and adolescents warrants extreme caution due to the potential for long-term carcinogenicity and reproductive toxicity [71, 72]. The benefits of treatment should outweigh the risks.

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with Cymevene [58, 60, 62, 63, 64, 68, 69, 70]. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/μL, or the platelet count is less than 25000/μL, or the haemoglobin level is less than 8 g/dL [58, 60, 63, 64, 68, 70] (see section 4.2 Posology and method of administration , Special Precautions and section 4.8 Undesirable effects).

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.

It is recommended that complete blood counts and platelet counts be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment. In patients developing severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered [70] (see section 4.2 Posology and method of administration, Special dosage instructions and section 4.8 Undesirable effects).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required [53, 54, 55, 56, 57] (see section 4.2 Posology and method of administration, Special dosage instructions and section 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations).

Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir [65]. Cymevene 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 Cymevene and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity [13, 44, 77] (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction

Imipenem-cilastatin
Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly [74]. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4 Special warnings and precautions for use).

Probenecid
Probenecid given with oral ganciclovir resulted in statistically significantly decreased renal clearance of ganciclovir (20%) leading to statistically significantly increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for renal tubular secretion. Therefore, patients taking probenecid and Cymevene should be closely monitored for ganciclovir toxicity. [44, 53, 81].

Zidovudine
When zidovudine was given in the presence of oral ganciclovir there was a small (17%), but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. [81]. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage [44, 81, 82, 83] (see section 4.4 Special warnings and precautions for use).

Didanosine
Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6 g/day, an increase in the AUC of didanosine ranging from 84 to 124% has been observed, and likewise 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 [44, 81] (see section 4.4 Special warnings and precautions for use).

Mycophenolate Mofetil
Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co-administration of these agents (which have the potential to compete for renal tubular secretion) will result in increases in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid (MPA) pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment to whom MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed and the patients monitored carefully [84, 85].

Zalcitabine
No clinically significant pharmacokinetic changes were observed after concomitant administration of ganciclovir and zalcitabine. Both valganciclovir and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events. [44].

Stavudine
No clinically significant interactions were observed when stavudine and oral ganciclovir were given in combination. [44].

Trimethoprim
No clinically significant pharmacokinetic interaction was observed when trimethoprim and oral ganciclovir were given in combination. However, there is a potential for toxicity to be enhanced since both drugs are known to be myelosuppressive and therefore both drugs should be used concomitantly only if the potential benefits outweigh the risks. [44].

Other antiretrovirals
At clinically relevant concentrations, there is unlikely to be either a synergistic or antagonistic effect on the inhibition of either HIV in the presence of ganciclovir or CMV in the presence of a variety of antiretroviral drugs. Metabolic interactions with, for example, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are unlikely due to the lack of P450 involvement 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/sulpha combinations, nucleoside analogues and hydroxyurea.

Since ganciclovir is excreted through the kidney (section 5.2), toxicity may also be enhanced during co-administration of ganciclovir with drugs that might reduce the renal clearance of ganciclovir and hence increase its exposure. The renal clearance of ganciclovir might be inhibited by two mechanisms: (a) nephrotoxicity, caused by drugs such as cidofovir and foscarnet, and (b) competitive inhibition of active tubular secretion in the kidney by, for example, other nucleoside analogues.

Therefore, all of these drugs should be considered for concomitant use with ganciclovir only if the potential benefits outweigh the potential risks [13, 77, 86] (see section 4.4 Special warnings and precautions for use).

4.6 Pregnancy and lactation

The safety of Cymevene for use in human pregnancy has not been established. Ganciclovir readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir (see section 5.3 Preclinical safety data), there is a theoretical risk of teratogenicity in humans [71].

Women of childbearing potential should must be advised to use effective contraception during treatment. Male patients should must be advised to practise barrier contraception during, and or at least 90 days following treatment unless it is certain that the female partner is not at risk of pregnancy [71, 72] (see section 5.3 Preclinical safety data).

It is unknown if ganciclovir is excreted in breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, breastfeeding must be discontinued.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Convulsion, sedation, dizziness, ataxia and/or confusion have been reported with the use of Cymevene [58, 60, 73, 74, 75, 76]. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

4.8 Undesirable effects

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

Other relevant adverse reactions reported with i.v. or oral ganciclovir are presented in the table below. The frequency groupings of these adverse events are based upon the frequency recorded in clinical trials with patients with AIDS and in clinical trials with solid organ transplant patients. [103]

Infections and infestations:	
Common (≥1/100, <1/10):	Sepsis (bacteremia, viraemia), cellulitis, urinary tract infection, 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 depression.
Immune system disorders:	
Uncommon (≥1/1000, <1/100):	anaphylactic reaction.
Metabolic and nutrition disorders:	
Common (≥1/100, <1/10):	appetite decreased, anorexia.
Psychiatric disorders:	
Common (≥1/100, <1/10):	depression, anxiety, confusion, abnormal thinking.
Uncommon (≥1/1000, <1/100):	agitation, psychotic disorder
Nervous system disorders:	
Common (≥1/100, <1/10):	headache, insomnia, dysgeusia (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, convulsions, dizziness (excluding vertigo).
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):	vision abnormal, 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):	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 ulcerations, 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.
Musculo-skeleta and connective tissue disorders:	
Common (≥1/100, <1/10):	back pain, myalgia, arthralgia, muscle cramps.
Renal and urinary disorders:	
Common (≥1/100, <1/10):	creatinine clearance renal decreased, renal impairment.
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, rigors, pain, chest pain, malaise, asthenia, injection site reaction (intravenous ganciclovir only).
Investigations:	
Common (≥1/100, <1/10):	weight decreased, blood creatinine increased.

4.9 Overdose

Overdose experience with oral ganciclovir
There have been no reports of overdosage with orally administered Cymevene. Doses as high as 6000 mg/day did not result in overt toxicity other than transient neutropenia [87].

Hemodialysis 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*).

Overdose experience with intravenous ganciclovir [87]

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:

- *Hematological toxicity*: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia
- *Hepatotoxicity*: hepatitis, liver function disorder
- *Renal toxicity:* worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine.
- *Gastrointestinal toxicity*: abdominal pain, diarrhea, vomiting
- *Neurotoxicity*: generalised tremor, convulsion

Overdose experience with valganciclovir [87]
One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J 05 A B 06 (anti-infectives for systemic use, antivirals for systemic use, direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors).

Mechanism of action
Ganciclovir is a synthetic analogue of 2'-deoxyguanosine which inhibits replication of herpes viruses in vitro [2, 3, 4, 5, 6] and in vivo [5, 7]. 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 [8], HHV-8 [9]), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus [10, 11, 12, 13]. 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, pUL97 [14, 15]. Further phosphorylation occurs by several cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly [16, 17]. Triphosphate metabolism has been shown to occur in HSV- and HCMV- infected cells with half-lives of 18 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 [17, 18].

The virustatic activity of ganciclovir is due to the inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine triphosphate into DNA by DNA polymerase [19, 20, 21], and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, viral DNA elongation [22].

Antiviral Activity

The *in vitro* anti-viral activity, measured as IC_{50} of ganciclovir against CMV, is in the range of 0.08 μM (0.02 μg/mL) [23] to 14 μM (3.5 μg/mL) [24].

Viral Resistance

The current working definition of CMV resistance to ganciclovir, based on in vitro assays, is a median inhibitory concentration (IC_{50}) >1.5 μg/mL (6.0 μM). CMV resistance to ganciclovir is uncommon (~1%). It has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. During the first 6 months of treatment for CMV retinitis with Cymevene vials or Cymevene capsules, viral resistance is detected in 3% to 8% of patients [25, 26]. Most patients with worsening CMV retinitis while on treatment do not shed resistant CMV. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with Cymevene vials. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis [27, 28].

The possibility of viral resistance should be considered in patients who repeatedly show poor clinical response or experience persistent viral excretion during therapy [14, 15, 27, 29, 30, 31, 32, 33, 34]. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described that contain mutations in the UL97 gene of CMV that controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir, and virus with this mutation may be resistant to other anti-CMV drugs [35, 36, 37, 38].

5.2 Pharmacokinetic properties

Absorption [44, 46, 47, 48]

The absolute bioavailability of ganciclovir capsules under fasting conditions ranged from 3 to 13%. At the recommended dose, food increased the steady state AUC by 20%, increased the C_{max} slightly and delayed the time taken to reach peak concentration. The absolute bioavailability of ganciclovir under fed conditions averaged 6% to 9%. When ganciclovir was administered orally with food at a total daily dose of 3 g/day (500 mg q3h, 6 times daily and 1000 mg t.i.d.), the steady-state absorption as measured by area under the serum concentration vs time curve (AUC) over 24 hours and maximum serum concentrations (C_{max}) were similar following both regimens with an AUC 0-24 of 15.9 ± 4.2 and 15.4 ± 4.3 μg·hr/ml and C_{max} of 1.02 ± 0.24 and 1.18 ± 0.36 μg/ml, respectively (N=16).

Food effects [46]

When Cymevene capsules were given with a meal containing 602 calories and 46.5% fat at a dose of 1000 mg every 8 hours to 20 HIV-positive subjects, the steady-state AUC increased by 20% (range: -10 % to 31 %) and there was a significant prolongation of time to peak serum concentrations (T_{max})

from 1.8 ± 0.8 to 3.0 ± 0.6 hours and a higher C_{max} (0.85 ± 0.25 vs 0.96 ± 0.27 µg/ml) (N=20) [44, 46].

Distribution [44, 49]
For Cymevene capsules, no correlation was observed between AUC and reciprocal body weight (range: 55-128 kg); therefore oral dosing according to weight is not required. Binding to plasma proteins was 1-2% over ganciclovir concentrations of 0.5 and 51 µg/ml.

Metabolism [50]
Following oral administration of a single 1000 mg dose of 14 C-labelled ganciclovir, 86 ± 3% of the administered dose was recovered in the feces and 5 ± 1% was recovered in the urine (n = 4). No single metabolite recovered in excreta accounted for more than 3.5% of the radioactivity[44].

Elimination [44]
When administered orally, ganciclovir exhibits linear kinetics up to a total daily dose of 4 g/day provided each unit dose does not exceed 1 g. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. After oral administration of ganciclovir, steady state is achieved within 24 hours. Renal clearance following oral administration ranged from 2.33 ± 0.86 ml/min/kg (N=9) [51] to 4.54 ± 1.39 ml/min/kg (N=10) [52]. Half-life ranged from 3.06 ± 0.78 hours (N=3) to 7.34 ± 1.46 (N=2) [52] following oral administration.

Pharmacokinetics in special clinical situations

Patients with renal impairment [53, 54, 55, 56, 57]
The pharmacokinetics following oral administration of Cymevene capsules were evaluated in 8 solid organ transplant recipients; dose was modified according to estimated creatinine clearance.

Patients undergoing hemodialysis
Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both i.v. and oral administration [53, 55] (see Section 4.9 Overdose).

During intermittent hemodialysis, estimates for the clearance of ganciclovir ranged from 42 to 92 mL/min, resulting in intra-dialytic half-lives of 3.3 to 4.5 hours. Estimates of ganciclovir clearance for continuous dialysis were lower (4.0 to 29.6 mL/min) but resulted in greater removal of ganciclovir over a dose interval. For intermittent hemodialysis, the fraction of ganciclovir removed in a single dialysis session varied from 50 to 63% [44].

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 [39, 40].

Ganciclovir causes impaired fertility and teratogenicity in animals [41] (see section 4.4 Special warnings and precautions for use).

Based upon animals studies where aspermatogenesis was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir could cause inhibition of human spermatogenesis [42, 43].

Data obtained using 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 [44, 45].

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[As per local approval]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[As per local approval]

6.4 Special precautions for storage

[As per local approval]

6.5 Nature and contents of container

[As per local approval]

6.6 Instructions for use and handling, and disposal

Caution should be exercised in the handling of Cymevene, see section 4.2 Posology and method of administration, Method of administration.

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

7. MARKETING AUTHORISATION HOLDER

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

REFERENCES

See Cymevene Capsules CDS version 1.2.

"Cymevene Capsules
Expert report incl ref.