

# Cymevene<sup>®</sup>

Ganciclovir

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## Antiviral

## Composition

Active ingredient: ganciclovir

## Pharmaceutical form and quantity of active substance per unit

Each rubber-stoppered glass vial contains 500 mg ganciclovir as ganciclovir sodium.

## Indications and Potential Uses

Cymevene is indicated for the treatment of life-threatening or sight-threatening CMV infections in immunocompromised patients. These infections include retinitis, colitis, pneumonia, other visceral involvement and systemic infections without documented visceral involvement. The efficacy and tolerability of Cymevene have been established only in severe CMV infections, but not in congenital or neonatal CMV disease or in CMV infections in non-immunocompromised patients.

Cymevene is indicated for the prevention of CMV disease following heart, lung and heart-lung transplantation.

In order to confirm the etiological diagnosis, suitable laboratory tests (culture, demonstration of antigens, etc.) should be performed. Where retinitis is suspected, the diagnosis should be based on the presence of typical retinal damage in combination with positive cultures in blood, urine or other specimens. A diagnosis of CMV infection should not be made purely on the basis of the presence of antibodies or histological lesions such as viral inclusions in a biopsy sample.

## Dosage and Administration

### Standard dosage

#### *Initial therapy*

Adults: 5 mg/kg given as an i.v. infusion over one hour, every 12 hours (10 mg/kg/day) for 14–21 days in patients with normal renal function.

#### *Maintenance therapy*

Adults: Patients whose immune system has not recovered and who are therefore at risk of relapse may be given a dosage of 6 mg/kg/day on 5 days per week.

### Special dosage instructions

#### *Patients with renal impairment*

Depending on their creatinine clearance, patients with renal impairment receive the doses shown in the following table:

| <b>Creatinine clearance</b><br>(ml/min) | <b>Initial dose</b><br>(mg/kg)         | <b>Maintenance dose</b><br>(mg/kg) |
|-----------------------------------------|----------------------------------------|------------------------------------|
| ≥ 70 ml                                 | 5.0 (twice daily)                      | 5.0 (once daily)                   |
| 50–69                                   | 2.5 (twice daily)                      | 2.5 (once daily)                   |
| 25–49                                   | 2.5 (twice daily)                      | 1.25 (once daily)                  |
| 10–24                                   | 1.25 (once daily)                      | 0.625 (once daily)                 |
| < 10                                    | 1.25 (three times weekly hemodialysis) | 0.625 (three times weekly)         |

Creatinine clearance is calculated as follows:

#### *Men:*

$$Cl_{\text{creat}} = \{(140 - \text{age [in years]} \times \text{bodyweight [kg]})\} : \{72 \times (0.011 \times \text{serum creatinine [mmol/l]})\}.$$

#### *Women:*

$$Cl_{\text{creat}} = 0.85 \times \text{value in men.}$$

As dose adjustment is recommended in patients with impaired renal function, serum creatinine or creatinine clearance should be closely monitored.

Data from dialysis patients indicate that ganciclovir plasma levels are reduced by approximately 50% after hemodialysis.

#### *Patients with leukopenia, severe neutropenia, anemia and thrombocytopenia*

Granulocytopenia (neutropenia), anemia, thrombocytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with ganciclovir.

Treatment 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 hemoglobin level is less than 8 g/dl (see *Warnings and precautions* und *Undesirable effects*).

#### *Elderly patients*

The efficacy and tolerability of Cymevene have not been investigated in elderly patients.

As elderly patients often exhibit renal impairment, ganciclovir should be administered with particular attention to their renal function (see *Special dosage instructions: Patients with renal impairment*).

### *Children*

Ganciclovir is not as yet approved for treatment of children and adolescents under 18 years of age because of lack of clinical experience (see *Warnings and precautions*).

### *Method of administration*

**Do not administer by rapid intravenous injection, since the toxicity of Cymevene may be increased as a result of excessive plasma levels.**

Intramuscular or subcutaneous injection may result in severe tissue irritation due to the high pH (9–11) of Cymevene solution.

## **Contraindications**

Cymevene is contraindicated in patients who are hypersensitive to ganciclovir, valganciclovir or any other ingredient of the product.

Due to the similarity of the chemical structure of Cymevene with that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these medicines is possible.

Cymevene must not be given in neutropenia below 500/ $\mu$ l or in thrombocytopenia below 25,000/ $\mu$ l.

Cymevene is contraindicated during pregnancy and lactation and in men who wish to father a child.

## **Warnings and Precautions**

Because of its relatively high toxicity, ganciclovir may be used only in severe CMV infections and not in other viral diseases. Nursing staff should observe particular caution when handling ganciclovir, since it is a potential carcinogen.

In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic. Cymevene should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see *Special remarks*). It is also likely that Cymevene causes temporary or permanent inhibition of spermatogenesis (see *Preclinical data, Pregnancy and lactation and Undesirable effects*).

Neutropenia (less than 1000/ $\text{mm}^3$ ) occurs in 38% of patients treated with Cymevene and is generally observed during the first or second week of initial treatment and before administration of a cumulative dose of 200 mg/kg. The leukocyte count generally returns to normal within 3 to 7 days after cessation of treatment or after dose reduction. Since no

relationship has been found between the frequency of neutropenia and the leukocyte count before treatment, this risk cannot be predicted. Nevertheless, caution is advised in patients with a previous neutropenic reaction to other drugs.

Thrombocytopenia (less than 50,000/mm<sup>3</sup>) is observed in 19% of patients. This form of toxicity occurs more commonly in patients who have been treated with immunosuppressants than in AIDS patients. The risk of thrombocytopenia is greater if the initial platelet count is less than 100,000/mm<sup>3</sup>.

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Cymevene. Therefore, treatment 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 hemoglobin level is less than 8 g/dl (see *Dosage and administration*, *Special dosage instructions* and *Undesirable effects*).

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia, it is recommended that treatment with hematopoietic growth factors and/or dose interruption be considered (see *Dosage and administration* and *Undesirable effects*).

It is recommended that full blood count and platelet count be monitored during therapy.

Renal function should be regularly monitored. In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see *Dosage and administration* and *Pharmacokinetics in special patient groups*).

Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir. Therefore, Cymevene should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see *Interactions*).

Both zidovudine and Cymevene can cause neutropenia and anemia. Some patients may not tolerate concomitant full-dose therapy with these two drugs (see *Interactions*).

Since plasma concentrations of didanosine can rise during concomitant therapy with Cymevene, patients must be closely monitored for toxic effects of didanosine (see *Interactions*).

Concomitant treatment with Cymevene and medicines that are known to be myelo-suppressive or that can impair renal function can result in increased toxic effects (see *Interactions*).

Since Cymevene is eliminated via the kidneys, adequate hydration should be ensured during treatment.

Cymevene solutions have a high pH (9–11) and can cause phlebitis and/or pain at the infusion site. Therefore, in order to permit rapid dilution and distribution, they should be injected only into veins with adequate blood flow.

#### *Elderly patients*

As the efficacy and tolerability of Cymevene have not been investigated in elderly patients, the drug should be administered cautiously and with special consideration of renal function.

### *Children*

Safety and efficacy of ganciclovir in pediatric patients, including use for the treatment of congenital or neonatal CMV infections, have not been established. The use of ganciclovir in pediatrics warrants extreme caution because of the potential for long-term carcinogenicity and reproductive toxicity. The potential benefits of treatment should justify the risks (see *Pharmacokinetics in special patient groups*).

### *Precautions for preparation of the ganciclovir solution*

Because of its high pH (9–11) and carcinogenic potential, the ganciclovir solution must be prepared with caution. Use of rubber gloves and protective goggles is recommended.

Skin or mucous membrane that has come into accidental contact with the product should be washed thoroughly with soap and water; the eyes should be rinsed with water for 15 minutes. In addition, the precautions that apply to cytotoxic drugs are recommended for Cymevene.

## **Interactions**

### *Interactions with intravenous ganciclovir*

As ganciclovir is only 1–2% bound to plasma proteins, no interactions due to competition for binding sites are to be expected.

#### *(1) Didanosine*

Didanosine plasma concentrations were found to be consistently raised when the drug was 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% was observed; similarly, at intravenous doses of 5 and 10 mg/kg/day an increase in the AUC of didanosine ranging from 38 to 67% was observed. This increase cannot be explained on the basis of competition for renal tubular secretion, since the percentage of didanosine excreted increased. The increase could be due either to increased bioavailability or to reduced metabolism. There was no clinically significant effect on ganciclovir concentrations. Nevertheless, in view of the increase in didanosine plasma concentration in the presence of ganciclovir, patients should be closely monitored for toxic effects of didanosine (e.g. pancreatitis) (see *Warnings and precautions*).

#### *(2) Imipenem-cilastatin*

Convulsions have been observed in patients taking imipenem-cilastatin concomitantly with ganciclovir. Therefore, these drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see *Warnings and precautions*).

#### *(3) 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 can compete for renal tubular secretion) will result in an increase 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 who are receiving MMF and ganciclovir concomitantly, the dose recommendations for ganciclovir should be observed and the patients monitored carefully.

Since both MMF and ganciclovir can cause neutropenia and leukopenia, patients should be monitored for increased occurrence of undesirable effects.

#### *Drug interactions with oral ganciclovir*

##### *(4) Probenecid*

Concomitant administration of probenecid and 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.

##### *(5) Zidovudine (AZT)*

When zidovudine was administered concomitantly with oral ganciclovir there was a small (19%), but statistically significant, increase in the AUC of zidovudine. There was also a trend (17%) towards lower ganciclovir concentrations when ganciclovir was administered concomitantly with zidovudine, although this was not statistically significant. However, since both zidovudine and ganciclovir can cause neutropenia and anemia, some patients may not tolerate concomitant full-dose therapy with these two drugs (see *Warnings and precautions*).

##### *(6) Zalcitabine*

Zalcitabine increased the AUC<sub>0-8</sub> of oral ganciclovir by 13%. No statistically significant changes were observed in any of the other pharmacokinetic parameters that were investigated. Nor were there any clinically relevant changes in the pharmacokinetics of zalcitabine in the presence of oral ganciclovir, the only observed change being a slight increase in the elimination rate constant.

##### *(7) Stavudine*

No statistically significant pharmacokinetic interactions were observed when stavudine and ganciclovir were administered concomitantly.

##### *(8) Trimethoprim*

Concomitant administration of trimethoprim resulted in a statistically significant decrease of 16.3% in the renal clearance of oral ganciclovir. There was also a statistically

significant decrease in the terminal elimination rate and a corresponding increase of 15% in half-life. However, these changes are probably not clinically significant, since  $AUC_{0-8}$  and  $C_{max}$  were not influenced. The only statistically significant change in the pharmacokinetic parameters of trimethoprim when administered concomitantly with ganciclovir was an increase in  $C_{min}$ . However, this increase is probably not clinically significant and no dose adjustment is recommended.

#### (9) Cyclosporine

When minimum concentrations of cyclosporine were compared there was no evidence that initiation of treatment with ganciclovir could influence the pharmacokinetics of cyclosporine. However, after initiation of treatment with ganciclovir an increase in maximum serum creatinine level was observed.

#### (10) Other potential drug interactions

Toxicity may be enhanced when ganciclovir is administered concomitantly with other drugs that are known to be myelosuppressive or to impair renal function (e.g. dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulphonamide, nucleoside analogues and hydroxyurea).

Since ganciclovir is excreted through the kidneys (see *Pharmacokinetics*), toxicity may also be enhanced when Cymevene is administered concomitantly with drugs that could reduce the renal clearance of ganciclovir and thereby increase its concentration in the body. The renal clearance of ganciclovir could 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, these drugs should not be administered concomitantly with ganciclovir unless the potential benefits outweigh the potential risks (see *Warnings and precautions*).

## Pregnancy and Lactation

No data are available on the use of Cymevene in pregnant women. Ganciclovir readily crosses the human placenta. Based on the pharmacological mechanism of action of the substance and the reproductive toxicity observed in animal experiments with ganciclovir (see *Preclinical data*), there is a risk of teratogenic effects in humans.

### Pregnancy

Since there is a risk of congenital malformations, the product is contraindicated during pregnancy.

Women of childbearing age must be instructed to take effective contraceptive measures during treatment.

Men must be instructed to use condoms for contraception during and for at least 90 days following treatment with Cymevene unless the possibility of pregnancy in their female partner is excluded (see *Preclinical data*).

### **Lactation**

It is not known whether ganciclovir is secreted in breast milk. However, since the possibility that ganciclovir may be secreted in breast milk and cause serious side effects in breastfed infants cannot be excluded, breastfeeding should be stopped.

## **Effects on Ability to Drive and Use Machines**

No relevant studies have been conducted.

Seizures, sedation, dizziness, ataxia and/or confusion have been reported with use of Cymevene. Such effects impair the performance of tasks that require alertness, such as driving vehicles and operating machinery.

## **Undesirable Effects**

The following undesirable effects can occur in patients treated with ganciclovir. Some of these effects may be attributable to the underlying disease.

Reversible neutropenia (neutrophil count  $< 1000/\mu\text{l}$ ), seen in 38% of patients, and thrombocytopenia (platelet count  $< 50,000/\mu\text{l}$ ), seen in 19% of patients, are the most conspicuous undesirable effects and are dose-limiting. Anemia and eosinophilic states occur occasionally.

Due to the frequency of leukopenia, it is recommended that a leukocyte count be performed every second day during the first 14 days of treatment. In patients who developed leukopenia after previous treatment with Cymevene or whose pretreatment leukocyte counts are less than  $2000/\text{mm}^3$ , blood counts should be performed every day.

### *Infections*

Infections, sepsis.

### *Blood and lymphatic system*

Anemia, eosinophilia, hypochromic anemia, leukopenia, myelosuppression, pancytopenia, thrombocytopenia and splenomegaly.

### *Metabolic and nutritional disturbances*

Elevated alkaline phosphatase, elevated creatinine, elevated creatine phosphokinase, reduced or elevated blood glucose, hypokalemia, elevated lactate dehydrogenase, elevated SGOT, elevated SGPT.

### *Nervous system*

Occasionally: confusion, convulsions, dizziness, headache, thought disturbances, dementia, depression, hallucinations, paresthesia, psychosis, somnolence, light-headedness, stupor. Rarely: restlessness, amnesia, anxiety, ataxia, insomnia, manic reactions, nervousness, sweating.

Abnormal dreams and thoughts, abnormal gait, coma, mouth dryness, euphoria, hypoesthesia and tremor have also been reported.

Agitation, emotional lability, hyperkinesia, loss of libido, myoclonus, neuropathy and seizures.

#### *Eyes*

Visual disturbances, amblyopia, blindness, conjunctivitis, eye pain, glaucoma, retinal detachment, retinitis and vitreous disturbances have been reported.

#### *Ear and inner ear*

Rarely: hearing impairment.

Deafness, earache and tinnitus have also been reported.

#### *Heart*

Hypotension, hypertension and tachycardia have occasionally been observed.

Angina, syncope, myocardial infarction and arrhythmia have occurred in rare cases.

#### *Blood vessels*

Hemorrhage has occasionally been observed.

Thrombophlebitis has occurred in rare cases.

Deep venous thrombosis, phlebitis and vasodilatation have also occurred.

#### *Respiratory organs*

Occasionally: dyspnea.

Rarely: asthma-like symptoms, cough, epistaxis.

#### *Gastrointestinal disturbances*

Occasionally: nausea and vomiting, diarrhea, anorexia, bleeding and abdominal pain.

Rarely: sore throat, sensation of fullness, constipation and hematemesis.

Dyspepsia, dysphagia, eructation, fecal incontinence, flatulence, mouth ulcers, pancreatitis and changes in the region of the tongue have also been reported. Elevated amylase and lipase, esophagitis and gastritis.

#### *Liver and biliary tract*

Occasionally: elevation of SGOT and bilirubin levels.

Rarely: elevation of SGPT, altered liver function values, hepatitis and jaundice.

#### *Skin*

Occasionally: skin rash, pruritus and urticaria.

Rarely: alopecia and photosensitivity reactions.

Isolated cases of Stevens-Johnson syndrome have been observed.

Acne, herpes simplex, maculopapular rash, pruritus, sweating, cellulitis and skin dryness have also been reported.

#### *Musculoskeletal system*

Myalgia and myasthenia, arthralgia, back pain, bone pain and leg cramps.

#### *Kidneys and urinary tract*

Occasionally: rise in nonprotein nitrogen and plasma creatinine as a result of reduced creatinine clearance, especially in patients with pre-existing renal impairment, hyponatremia.

Rarely: hematuria, urinary incontinence.

Isolated cases of renal tubular acidosis have been observed.

Renal impairment, reduced creatinine clearance, elevated blood urea nitrogen (BUN), renal failure, pollakiuria, urinary tract infection and altered urinary frequency.

#### *Reproductive system and breast*

Impotence, breast pain.

#### *Body as a whole and injection site reactions*

Abdominal distension, anorexia, taste changes, asthenia, chest pain, chills, edema, fever, headache, migraine, malaise, pain and weight loss.

At the injection site: abscess, edema, bleeding, inflammation, pain and phlebitis.

On the basis of animal experiments it appears likely that ganciclovir causes transient or permanent inhibition of spermatogenesis. These experiments suggest that a negative effect on fertility may occur in men. Therefore, men should not father children during treatment with Cymevene and contraception is required in women.

### **Experience from clinical studies**

#### Experience with Valcyte

Valganciclovir is a prodrug of ganciclovir that is rapidly converted into ganciclovir after oral administration. The undesirable effects that are known to occur with ganciclovir are therefore also to be expected with Valcyte. All the adverse events observed in clinical studies with Valcyte had been observed previously with ganciclovir.

*Treatment of CMV retinitis in AIDS patients*

The safety profiles of valganciclovir and intravenous ganciclovir were similar during 28 days of a randomised study phase (21 days induction dosage and 7 days maintenance dosage) with 79 patients per group. The most frequently reported adverse events were diarrhea, neutropenia and fever. In the group treated with oral valganciclovir more patients reported diarrhea, oral candidiasis, headache and tiredness, while in the group treated with intravenous ganciclovir more patients reported nausea and adverse events at the injection site (see Table 1).

**Table 1: Percentage of patients with selected adverse events during the randomised study phase (first 28 days of treatment)**

| Adverse event                   | Valganciclovir group<br>n=79 | I.v. ganciclovir group<br>n=79 |
|---------------------------------|------------------------------|--------------------------------|
| Diarrhea                        | 16%                          | 10%                            |
| Oral candidiasis                | 11%                          | 6%                             |
| Headache                        | 9%                           | 5%                             |
| Tiredness                       | 8%                           | 4%                             |
| Nausea                          | 8%                           | 14%                            |
| Phlebitis and thrombo-phlebitis | —                            | 6%                             |

Table 2 shows adverse events regardless of their severity or relationship to treatment. These data are derived from two clinical studies (n=370) in which patients with CMV retinitis received Valcyte at a dosage of 900 mg twice daily as induction therapy for up to 3 weeks or 900 mg once daily as maintenance therapy. Approximately 50% of these patients received valganciclovir as maintenance therapy for more than 9 months (the longest period being 30 months).

The adverse events adjudged to be serious or life-threatening that were reported most frequently (> 1%) in AIDS patients with CMV retinitis during initial and maintenance therapy with valganciclovir were neutropenia (12.5%), anemia (7.5%), thrombocytopenia (2%), pancytopenia (1.5%), leukopenia (1.5%) and hepatic impairment (1%).

The adverse events – regardless of severity or relationship to treatment – that were reported most frequently (% of patients) in patients from these two clinical studies (n=370) during treatment with Valcyte were diarrhea (38%), fever (26%), nausea (25%), neutropenia (24%) and anemia (22%). The serious adverse events – regardless of severity or relationship to treatment – that were reported most frequently (≥ 2%) were diarrhea (4.3%), fever (4.6%), neutropenia (11.6%), anemia (7.8%), thrombocytopenia (2.2%), pneumonia (2.7%), *Pneumocystis carinii* pneumonia (3.0%) and retinal detachment (3.2%). The overall percentage incidence of life-threatening adverse events – regardless

of severity or relationship to treatment – was low, only anemia (2.1%) having an incidence of  $\geq 2\%$ . The adverse events – regardless of severity – considered by the investigating physician to be related to treatment with Valcyte (unlikely, possible or probable) that were reported most frequently (% of patients) were neutropenia (21%), anemia (14%), diarrhea(13%) and nausea (9%).

**Table 2: Percentage of patients with CMV retinitis in whom adverse events occurred in clinical studies with valganciclovir**

|                                       | <b>Patients with CMV retinitis</b> |
|---------------------------------------|------------------------------------|
|                                       | <b>Valganciclovir</b>              |
| <b>Adverse events by organ system</b> | <b>n=370</b>                       |
|                                       | <b>%</b>                           |
| <b>Gastrointestinal tract</b>         |                                    |
| Diarrhea                              | 38                                 |
| Nausea                                | 25                                 |
| Oral candidiasis                      | 20                                 |
| Vomiting                              | 20                                 |
| Abdominal pain                        | 13                                 |
| Upper abdominal pain                  | 6                                  |
| Constipation                          | 6                                  |
| <b>Body as a whole</b>                |                                    |
| Fever                                 | 26                                 |
| Tiredness                             | 20                                 |
| Headache                              | 18                                 |
| Influenza                             | 9                                  |
| Weight loss                           | 9                                  |
| Reduced appetite                      | 8                                  |
| Back pain                             | 8                                  |
| Dehydration                           | 6                                  |

|                                       | <b>Patients with CMV retinitis</b> |
|---------------------------------------|------------------------------------|
|                                       | <b>Valganciclovir</b>              |
| <b>Adverse events by organ system</b> | <b>n=370</b><br><b>%</b>           |
|                                       |                                    |
| Anorexia                              | 5                                  |
| Cachexia                              | 5                                  |
| Leg edema                             | 5                                  |
| <b>Blood and lymph system</b>         |                                    |
| Neutropenia                           | 24                                 |
| Anemia                                | 22                                 |
| Thrombocytopenia                      | 5                                  |
| <b>Skin and appendages</b>            |                                    |
| Dermatitis                            | 18                                 |
| Night sweats                          | 7                                  |
| Pruritus                              | 6                                  |
| <b>Airways</b>                        |                                    |
| Cough                                 | 16                                 |
| Pharyngitis/nasopharyngitis           | 12                                 |
| Upper respiratory tract infection     | 9                                  |
| Dyspnea                               | 9                                  |
| Pneumonia                             | 7                                  |
| Bronchitis                            | 6                                  |
| <i>Pneumocystis carinii</i> pneumonia | 6                                  |
| Productive cough                      | 5                                  |

|                                              | <b>Patients with CMV retinitis</b> |
|----------------------------------------------|------------------------------------|
|                                              | <b>Valganciclovir</b>              |
| <b>Adverse events by organ system</b>        | <b>n=370</b><br><b>%</b>           |
|                                              |                                    |
|                                              |                                    |
| <b>Central and peripheral nervous system</b> |                                    |
| Sleep disturbances                           | 14                                 |
| Dizziness                                    | 9                                  |
| Depression                                   | 9                                  |
| Peripheral neuropathy                        | 7                                  |
| Paresthesia                                  | 6                                  |
| Tremor                                       | 2                                  |
| <b>Sense organs</b>                          |                                    |
| Macular edema                                | 4                                  |
| Retinal detachment                           | 13                                 |
| Sinusitis                                    | 10                                 |
| Blurred vision                               | 6                                  |
| <b>Locomotor apparatus</b>                   |                                    |
| Arthralgia                                   | 6                                  |
| <b>Urogenital tract</b>                      |                                    |
| Dysuria                                      | 2                                  |
| Urinary tract infection                      | 5                                  |
|                                              |                                    |
| <b>Hepatobiliary disturbances</b>            |                                    |

|                                       | <b>Patients with CMV retinitis</b> |
|---------------------------------------|------------------------------------|
|                                       | <b>Valganciclovir</b>              |
| <b>Adverse events by organ system</b> | <b>n=370</b><br><b>%</b>           |
|                                       |                                    |
| Hepatic impairment                    | 3                                  |
|                                       |                                    |

The following serious adverse events were considered by the manufacturer to be related to treatment with Valcyte, were reported to have occurred with a frequency of less than 5% in these two clinical studies (n= 370), and are not included in either of the above two tables:

*Blood and lymph system:* leukopenia, pancytopenia, bone marrow depression, aplastic anemia.

*Urogenital tract:* reduced creatinine clearance.

*Infections:* events associated with bone marrow depression and impairment of the immune system such as local and systemic infections and sepsis.

*Bleeding complications:* potentially life-threatening bleeding in association with thrombocytopenia.

*Central and peripheral nervous system:* convulsions, psychosis, hallucinations, confusion, agitation.

*Body as a whole:* hypersensitivity to valganciclovir.

The changes in laboratory values that occurred in association with treatment with valganciclovir in the two clinical studies (n=370) are listed in Table 3.

**Table 3: Changes in laboratory values**

| <b>Changes in laboratory values</b> | <b>Patients with CMV retinitis</b>    |
|-------------------------------------|---------------------------------------|
|                                     | <b>Valganciclovir</b><br><b>n=370</b> |
| Neutropenia: ANC/ $\mu$ l           |                                       |
| <500                                | 16%                                   |
| 500 – <750                          | 17%                                   |

| Changes in laboratory values         | Patients with CMV retinitis           |
|--------------------------------------|---------------------------------------|
|                                      | <b>Valganciclovir</b><br><b>n=370</b> |
| 750 – <1000                          | 17%                                   |
| Anemia: hemoglobin g/dl              |                                       |
| <6.5                                 | 7%                                    |
| 6.5 – <8.0                           | 10%                                   |
| 8.0 – <9.5                           | 14%                                   |
| Thrombocytopenia: platelets/ $\mu$ l |                                       |
| <25,000                              | 3%                                    |
| 25,000 – <50,000                     | 5%                                    |
| 50,000 – <100,000                    | 21%                                   |
| Serum creatinine mg/dl:              |                                       |
| >2.5                                 | 2%                                    |
| >1.5 – 2.5                           | 11%                                   |

## Postmarketing experience

### *Experience with ganciclovir and/or valganciclovir*

Adverse effects of intravenous and oral ganciclovir from spontaneous reports in the postmarketing phase which are not mentioned in any of the above sections and for which a causal relationship cannot be excluded are listed below. Since Valcyte is rapidly and extensively converted to ganciclovir, such adverse effects could also occur with Valcyte:

- Anaphylaxis
- Male infertility
- Acute renal failure, oliguria, anuria
- There have been isolated reports of a reduction in prothrombin level.

The adverse effects reported in the postmarketing phase correspond to those that were observed in the clinical studies with Valcyte and ganciclovir.

## Overdosage

### *Overdose experience with intravenous ganciclovir*

Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during postmarketing 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, leukopenia, neutropenia, granulocytopenia

*Hepatotoxicity:* hepatitis, hepatic impairment

*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

In addition, one adult received an excessive volume of i.v. ganciclovir solution by intravitreal injection and experienced temporary loss of vision and central retinal artery occlusion secondary to increased intraocular pressure related to the injected fluid volume.

Hemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who have received an overdose of oral ganciclovir (see *Pharmacokinetics in special patient groups*).

#### *Overdose experience with valganciclovir*

One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least tenfold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).

It is to be expected that overdosage of valganciclovir might also result in severe renal toxicity (see *Dosage and administration* and *Warnings and precautions*).

Hemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who have received an overdose of valganciclovir (see *Pharmacokinetics in special patient groups – Dialysis patients*).

## **Properties and Effects**

**ATC code: J05AB06**

### **Mechanism of action and pharmacodynamics**

Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses *in vitro* and *in vivo*.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase UL97. Further phosphorylation occurs by 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 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 inhibition of viral DNA synthesis by two mechanisms:

- a) competitive inhibition of incorporation of deoxyguanosine triphosphate into DNA by viral DNA polymerase and
- b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, viral DNA elongation.

#### *Antiviral activity*

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.

*In-vitro* antiviral activity, measured as IC<sub>50</sub> of ganciclovir against CMV, is in the range of 0.08 µM (0.02 µg/ml) to 14.32 µM (3.58 µg/ml).

#### *Viral resistance*

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

#### *Treatment of CMV retinitis*

A genotypic analysis of CMV in polymorphonuclear leukocyte (PMNL) isolates from 148 patients enrolled in a clinical study on CMV retinitis found that 2.2%, 6.5%, 12.8% and 15.3% of isolates contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of treatment with valganciclovir. Phenotypic resistance was not identified, however very few CMV culture isolates were available for analysis.

### **Clinical efficacy**

#### *Treatment of CMV retinitis*

Clinical studies with Valcyte were performed in patients with AIDS and CMV retinitis. The efficacy of Valcyte in induction therapy of CMV retinitis was found to be similar to that of intravenous ganciclovir. In a randomised, controlled study, 160 patients with AIDS and newly diagnosed CMV retinitis were randomised to receive treatment with either Valcyte tablets (900 mg twice daily for 21 days, then 900 mg once daily for 7 days) or intravenous ganciclovir solution (5 mg/kg twice daily for 21 days, then 5 mg/kg once daily for 7 days). Median age was 39 years, median HIV-1 RNA level at baseline was

4.9 log<sub>10</sub> and median CD4 cell count was 23 cells/mm<sup>3</sup>. CMV retinitis progression as determined by masked assessment of fundus photographs at baseline and at week 4 formed the primary assessment criterion for the three-week induction therapy. Table 4 shows the results at week 4.

**Table 4: Masked assessment of fundus photographs at week 4 of study WV15376**

|                                                                                                 | Cymevene <sup>®</sup> i.v. | Valcyte |
|-------------------------------------------------------------------------------------------------|----------------------------|---------|
| Assessment of CMV retinitis progression at Week 4                                               | n=80                       | n=80    |
| Progression                                                                                     | 7                          | 7       |
| No progression                                                                                  | 63                         | 64      |
| Death                                                                                           | 2                          | 1       |
| Treatment stopped because of adverse events                                                     | 1                          | 2       |
| Did not attend for review                                                                       | 1                          | 1       |
| CMV not confirmed at baseline examination or photographs not assessable at baseline examination | 6                          | 5       |

#### *Maintenance therapy of CMV retinitis*

No comparative clinical data are available regarding the efficacy of Valcyte in the maintenance therapy of CMV retinitis, since in study WV15376 Valcyte was administered in open fashion to all patients after week 4. Nevertheless, the area under the plasma-concentration-versus-time curve (AUC) of ganciclovir after administration of 900 mg valganciclovir (Valcyte) once daily is similar to that after intravenous administration of 5 mg/kg ganciclovir (Cymevene<sup>®</sup>) once daily. Although the C<sub>max</sub> of ganciclovir after administration of valganciclovir is lower than that after intravenous administration of ganciclovir, it is higher than the C<sub>max</sub> achieved after oral administration of ganciclovir. The use of valganciclovir for maintenance therapy is thus supported by a plasma-concentration-versus-time profile that is similar to that of two products that are licensed for use in the maintenance therapy of CMV retinitis.

The mean (median) time from randomisation to progression of CMV retinitis was 226 (180) days in the group receiving induction and maintenance therapy with Valcyte and 219 (126) days in the group receiving induction therapy with intravenous ganciclovir and maintenance therapy with Valcyte.

Although no directly comparable data are available, use of Valcyte can achieve a systemic exposure to ganciclovir similar to that achieved with recommended doses of intravenous ganciclovir, which has been shown to be effective in the treatment of CMV

retinitis. The AUC of ganciclovir has been shown to correlate with time to progression of CMV retinitis.

## Pharmacokinetics

Because of the relatively high toxicity, no pharmacokinetic studies have been performed in healthy volunteers. Consequently, all data are from patients.

### Absorption

The systemic exposure ( $AUC_{0-24}$ ) reported following dosing with a single 1-hour intravenous infusion of 5 mg/kg ganciclovir in HIV+/CMV+ patients or in adult AIDS patients ranged from  $21.4 \pm 3.1$  (n=16) to  $26.0 \pm 6.06$  (n=16)  $\mu\text{g}\cdot\text{h}/\text{ml}$ . In this patient population peak plasma concentration ( $C_{\text{max}}$ ) ranged from  $7.59 \pm 3.21$  (n=10) and  $8.27 \pm 1.02$  (n=16) to  $9.03 \pm 1.42$  (n=16)  $\mu\text{g}/\text{ml}$ .

### Distribution

After intravenous administration of ganciclovir the volume of distribution is correlated with body weight. Values for the steady-state volume of distribution ranged from  $0.536 \pm 0.078$  (n=15) to  $0.870 \pm 0.116$  (n=16) l/kg. Cerebrospinal fluid concentrations obtained 0.25–5.67 hours post-dose in two patients who received 2.5 mg/kg ganciclovir every 8 hours or every 12 hours ranged from 0.50 to 0.68  $\mu\text{g}/\text{ml}$ , representing 24–67% of the respective plasma concentrations. The precise distribution to the various tissues and body fluids in man is not known, however at autopsy ganciclovir has been found to be concentrated in the kidneys, with smaller quantities in the liver, lungs and testes. Binding to plasma proteins was 1–2% for ganciclovir concentrations between 0.5 and 51  $\mu\text{g}/\text{ml}$ .

### Metabolism and elimination

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,  $89.6 \pm 5.0\%$  (n=4) of intravenously administered ganciclovir was recovered unmetabolised in the urine. In subjects with normal renal function, systemic clearance ranged from  $2.64 \pm 0.38$  ml/min/kg (n=15) to  $4.52 \pm 2.79$  ml/min/kg (n=6) and renal clearance ranged from  $2.57 \pm 0.69$  ml/min/kg (n=15) to  $3.48 \pm 0.68$  ml/min/kg (n=20), corresponding to 90%–101% of administered ganciclovir. Half-lives in subjects without renal impairment ranged from  $2.73 \pm 1.29$  (n=6) to  $3.98 \pm 1.78$  hours (n=8).

## Pharmacokinetics in Special Patient Groups

### *Patients with renal impairment*

Renal impairment resulted in decreased clearance of ganciclovir from valganciclovir and a corresponding increase in terminal half-life.

| Creatinine clearance (ml/min) | Number of subjects | AUC <sub>(0-∞)</sub> (µg·h/ml) | C <sub>max</sub> (µg/ml) | t <sub>1/2</sub> (h) |
|-------------------------------|--------------------|--------------------------------|--------------------------|----------------------|
| > 70                          | 8                  | 27.8 ± 7.0                     | 5.56 ± 1.61              | 3.46 ± 0.66          |
| 51–70                         | 6                  | 50.5 ± 23.2                    | 6.88 ± 2.54              | 4.85 ± 1.36          |
| 21–50                         | 6                  | 99.7 ± 54.8                    | 7.08 ± 1.62              | 10.2 ± 4.4           |
| 11–20                         | 6                  | 252 ± 63                       | 8.54 ± 1.20              | 21.8 ± 5.2           |

Therefore, dosage adjustment is required for renally impaired patients (see *Dosage and administration* and *Warnings and precautions*).

#### *Liver transplant recipients*

The pharmacokinetics of valganciclovir in stable liver transplant recipients were investigated in an open-label four-part crossover study (n=28). The absolute bioavailability of ganciclovir from valganciclovir following a single dose of 900 mg valganciclovir taken with a meal was approximately 60%, in agreement with estimates obtained in other patient populations. Ganciclovir AUC<sub>0-24</sub> was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant recipients.

#### *Dialysis patients*

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both intravenous and oral administration (see *Overdosage*).

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%.

#### *Neonates*

The pharmacokinetics of ganciclovir were investigated in 27 neonates aged from 2 to 49 days after intravenous administration of 4 mg/kg (n=14) and 6 mg/kg (n=13). Mean C<sub>max</sub> was 5.5 ± 6 µg/ml and 7.0 ± 1.6 µg/ml with the low and the high dose, respectively. The mean steady-state volume of distribution (0.7 l/kg) and the systemic clearance (3.15 ± 0.47 ml/min/kg with 4 mg/kg and 3.55 ± 0.35 ml/min/kg with 6 mg/kg) were comparable to those of adults with normal renal function.

#### *Children*

Ganciclovir pharmacokinetics were also studied in 10 children with normal renal function aged between 9 months and 12 years. The pharmacokinetic parameters of ganciclovir were the same after single and multiple (every 12 hours) intravenous doses (5 mg/kg). Exposure as measured by mean AUC<sub>∞</sub> on days 1 and 14 was 19.4 ± 7.1 and 24.1 ± 14.6

$\mu\text{g}\cdot\text{h}/\text{ml}$ , respectively. The corresponding  $C_{\text{max}}$  values were  $7.59 \pm 3.21 \mu\text{g}/\text{ml}$  (day 1) and  $8.31 \pm 4.9 \mu\text{g}/\text{ml}$  (day 14). This range of exposure is comparable to that observed in adults. The steady-state volume of distribution after a single dose on day 1 and at the end of the period of multiple-dose administration (day 14) was  $0.68 \pm 0.20 \text{ l/kg}$ . Systemic clearance on the same days of this study was  $4.66 \pm 1.72 \text{ ml/min/kg}$  (day 1) and  $4.86 \pm 2.96 \text{ ml/min/kg}$  (day 14). The corresponding mean values for renal clearance (0–12 h) were  $3.49 \pm 2.40$  (day 1) and  $3.49 \pm 1.19 \text{ ml/min/kg}$  (day 14). The corresponding mean values for  $t_{1/2}$  were  $2.49 \pm 0.57$  hours (day 1) and  $2.22 \pm 0.76$  hours (day 14). The pharmacokinetics of ganciclovir in this study corresponded to those of neonates and adults.

### *Elderly patients*

No studies were performed in adults over 65 years of age.

## **PRECLINICAL DATA**

### **Toxicity, mutagenicity and carcinogenicity**

The toxicity observed in preclinical studies consisted of irreversible gonadotoxicity (testicular cell loss) and nephrotoxicity (uremia, cell degeneration) and reversible myelotoxicity (anemia, neutropenia, lymphocytopenia) and gastrointestinal toxicity (mucosal cell necrosis).

Further preclinical studies have shown ganciclovir to be mutagenic, carcinogenic, teratogenic, embryotoxic and aspermatogenic (i.e. impairs male fertility) and to impair female fertility.

## **Additional information**

### **Incompatibilities**

Ganciclovir precipitates in paraben-containing solutions.

### **Stability**

This product must not be used after the expiry date (EXP) shown on the pack. After dissolution of the dry substance, the solution should be kept at room temperature (15–25°C) and used within 12 hours. The diluted infusion solution should be kept in a refrigerator (2–8°C) and used within 24 hours.

### **Special precautions for storage**

Do not store the product (dry substance) above 30°C.

### **Instructions for use and handling**

Because of its carcinogenic and mutagenic potential, Cymevene should be handled with care. Avoid inhalation or direct contact of the powder or direct contact of the reconstituted solution with the skin or mucous membranes. Cymevene solutions are

alkaline (pH approximately 11). Use of rubber gloves and protective goggles is recommended. In the event of contact with the skin or mucous membranes, wash thoroughly at once with soap and water. For eye exposure rinse thoroughly with plain water for 15 minutes.

*Reconstituted solution:* Dissolve the content of one vial of lyophilised Cymevene (500 mg) in 10 ml of water for injection by vigorous shaking. Check the clarity of the reconstituted solution. Do not use paraben-containing bacteriostatic water for injection, since it is incompatible with the sterile lyophilised active substance of Cymevene and may cause precipitation. The reconstituted solution is stable at room temperature for 12 hours. Do not store in a refrigerator.

*Infusion solution:* Withdraw the required volume of reconstituted solution (50 mg/ml) and add it to the infusion solution (usually 100 ml, concentration no higher than 10 mg/ml) for administration over the course of one hour. The following infusion fluids are compatible with Cymevene: physiological saline, 5% dextrose, Ringer's injection and lactated Ringer's injection. The infusion solution is to be used within 24 hours after preparation and should be kept in a refrigerator (2–8°C) (do not freeze).

## Packs

Vial containing 500 mg of the sterile lyophilised drug

1

### This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

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