Composition

Active ingredient: ganciclovir.
One vial contains 500 mg of ganciclovir in the form of the sodium salt.

Properties

Ganciclovir is a synthetic nucleoside analogue of guanine that inhibits replication of herpes viruses both in vitro and in vivo. In vitro it is 10-30 times more active than aciclovir against various strains of cytomegalovirus.

After penetrating infected cells, ganciclovir is transformed, by kinase into ganciclovir triphosphate, which inhibits viral DNA synthesis by (1) competitively inhibiting the incorporation of deoxyguanosine triphosphate (dGTP) and (2) through direct incorporation into DNA, resulting in inhibition of viral replication. Sensitive human viruses include cytomegalovirus (CMV), herpes simplex virus (HSV) types I and II, Epstein-Barr virus (EBV) and varicella-zoster virus (VZV). The median inhibitory concentration (IC₅₀) of ganciclovir in vitro varies depending on the strain of CMV tested. The average value is 4 µmol/l.

By contrast, it is a far less potent inhibitor of mammalian cell proliferation in vitro. The IC₅₀ in the most sensitive cell type, bone marrow colony forming cells, is 39.0 mmol/l.

Pharmacokinetics

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

Absorption

Plasma concentrations of between 3.1 and 21.7 mg/l (mean 8.3 mg/l) are reached after infusion of 5 mg/kg bodyweight over one hour.

Distribution

The precise distribution of ganciclovir to the various tissues and body fluids in man is not known. At autopsy ganciclovir has been found to be concentrated in the kidneys, with smaller quantities in the liver, lungs and testes.

Concentrations of ganciclovir in the cerebrospinal fluid are 7-67% of the maximum plasma concentrations. The steady-state volume of distribution is 33-45 l/1.73 m² in patients with normal renal function. Plasma protein binding is 1-2%. It is not known if ganciclovir is excreted in human breast milk.

Metabolism and Elimination

Apart from undergoing phosphorylation, ganciclovir is not metabolized. It is mainly excreted unchanged via the kidneys (about 90% in patients with normal renal function). The plasma half-life is 2.9±1.3 hours, depending on renal status. Plasma clearance is about 3.6 ml/min/kg (which correlates well with creatinine clearance).

Pharmacokinetics in special clinical situations.

Renal impairment: The plasma half-life is prolonged and the plasma concentration increased in patients with a creatinine clearance <50 ml/min.

Elderly patients: Dose adjustment may be required depending on renal status.

Dialysis patients: Ganciclovir is dialysable (hemodialysis and peritoneal dialysis). Hemodialysis may reduce ganciclovir plasma concentrations by about 50%.

Indications

Cymevene is indicated for the treatment of life- or sight-threatening CMV disease in immunocompromised individuals. This includes retinitis, colitis, pneumonia and other visceral disease of systemic infection without confirmed visceral disease. The safety and efficacy of Cymevene have been confirmed only in severe CMV infections; they have not been confirmed in congenital or neonatal CMV infections or in CMV infections in non-immunocompromised patients. Appropriate laboratory tests (culture, antigens, etc.) should be carried out to confirm
the etiologic diagnosis. Where retinitis is suspected, the diagnosis should be based on the presence of typical retinal lesions, supported by positive culture from blood, urine or other sites. A diagnosis of CMV infection should not be made solely on the basis of a positive antibody test or histological confirmation of viral inclusions in a biopsy sample.

**Contraindications**
Cymevene is contraindicated during pregnancy and in patients with hypersensitivity to ganciclovir or aciclovir. Cymevene must not be given if the neutrophil count is less than 500 cells/µl and/or the platelet count is less than 25,000 cells/µl. Ganciclovir is not approved for treatment of children and adolescents under 18 years of age, because of the lack of clinical experience with the drug in these age groups.

**Side Effects**

*Hematology:* Reversible neutropenia (neutrophils <1000 cells/µl), seen in 38% of patients and thrombocytopenia (platelets <50,000 cells/µl), seen in 19% of patients, are the most conspicuous adverse reactions and are dose limiting.

Anemia and eosinophilic disorders occur occasionally. Due to the frequency of leukopenia, it is recommended that leukocyte counts be performed every two days during the first two weeks of therapy. Blood counts should be performed daily in patients in whom Cymevene has previously resulted in leukopenia or who have pretreatment leukocyte counts of less than 2000 cells/µl.

*Cardiovascular system:* Occasionally: hypotension, hypertension, tachycardia, hemorrhage. Rarely: angina-like pain, syncope, myocardial infarction, arrhythmia, thrombophlebitis.

*Central nervous system:* Occasionally: confusion, seizures, dizziness, headache, abnormal thoughts, dementia, depression, hallucinations, paresthesia, psychosis, somnolence, light-headedness, stupor. Rarely: restlessness, amnesia, ataxia, insomnia, manic reactions, nervousness, sweating.

*Sensory organs:* Rarely: deafness, retinal detachment in AIDS patients with CMV retinitis (possibly related to treatment).

**Respiratory system:** Occasionally: dyspnea. Rarely: asthma-like symptoms, cough, nosebleeds.

**Gastrointestinal tract:** Occasionally: nausea, vomiting, diarrhea, anorexia, bleeding, abdominal pain. Rarely: throat pain, sensation of fullness, constipation, hematemesis.

**Liver function:** Occasionally: increased SGOT and bilirubin. Rarely: increased SGPT.

**Renal function:** Occasionally: increased nonprotein nitrogen and plasma creatinine due to reduced creatinine clearance (particularly in patients with pre-existing renal impairment), hyponatremia. Rarely: hematuria, urinary frequency.

**Hypersensitivity Reactions:** Occasionally: skin rash, pruritus, urticaria. Rarely: alopecia.

Based on the results of animal studies it is considered likely that ganciclovir causes temporary or permanent inhibition of spermatogenesis. These studies also indicate that suppression of fertility in men may occur. Because of this, during treatment with Cymevene men must not father children and women must use effective contraception.

**Warnings**
Because of its relatively high toxicity, ganciclovir may be used only in severe CMV infections and not in other viral diseases. Due to its carcinogenic potential, medical staff should handle ganciclovir with caution.

**Precautions**
Neutropenia (neutrophils <1000 cells/µl) has been observed in 38% of patients treated with Cymevene. It generally appears during the first or second week of treatment and before a cumulative dose of 200 mg/kg has been given. The leukocyte count usually returns to normal 3-7 days after discontinuation of treatment or dose reduction. As no correlation has been established between the frequency of neutropenia and pretreatment leukocyte counts, it is not possible to predict the potential risk. Nonetheless, caution is required in patients...
with previous neutropenic reactions to other medications. Thrombocytopenia (platelets <50,000 cells/µl) has been observed in 19% of patients treated with Cymevene. This reaction occurs more often in patients treated with immunosuppressant drugs than in AIDS patients. The risk of thrombocytopenia is greater if the pretreatment platelet count is less than 100,000 cells/µl. As Cymevene is eliminated via the kidneys, adequate hydration should be maintained during treatment. If renal function is impaired, the dosage must be adjusted in accordance with the creatinine clearance (see Dosage and Administration). Due to their high pH (9-11), Cymevene solutions may cause phlebitis and/or pain at the site of infusion. Veins with adequate blood flow should therefore be chosen to permit rapid dilution and distribution. The safety and efficacy of Cymevene have not been evaluated in elderly patients. Caution should be exercised if Cymevene is administered to such patients and special consideration given to their renal status.

**Pregnancy, Nursing Mothers**

Ganciclovir is contraindicated during pregnancy and nursing.

The animal studies performed to date indicate that Cymevene has mutagenic and teratogenic properties. In one 18-month study in mice ganciclovir was found to be carcinogenic at oral doses of 20 and 1000 mg/kg/day. With the exception of histiocytic sarcoma of the liver, all ganciclovir-induced tumors were epithelial or vascular in origin. No carcinogenic effect was observed with a dose of 1 mg/kg/day. Cymevene must be considered a potential carcinogen in humans.

**Overdosage**

Eleven cases of short-term ganciclovir overdose have been reported, with reversible neutropenia observed in three patients. There is no specific treatment for overdosage. Systematic and supportive therapy such as hemodialysis and forced diuresis may be effective in accelerating elimination of ganciclovir. Measures must be taken to protect the patient against neutropenia until marrow recovery is assured.

**Special Remarks**

**Incompatibilities**

Solutions containing parabens cause precipitation of ganciclovir.

**Stability**

This medicine should not be used after the expiry date (EXP) shown on the pack. After preparation from the powder, keep the Cymevene solution at room temperature (15º-25ºC) and use within 12 hours. After dilution, refrigerate the infusion solution (2º-8ºC) and use within 24 hours.

**Drug Interactions**

It is possible that probenecid, like other drugs that inhibit renal tubular secretion or resorption, may reduce renal clearance of ganciclovir and prolong its plasma half-life. It is also possible that concomitant administration of cytostatics (dapsone, pentamidin, fluocytosine, vincristine, vinblastine, doxorubicin), amphotericin B, sulfonamide/trimethoprim combinations or other nucleoside analogues may potentiate the toxic effect of Cymevene. Concomitant administration of zidovudine during induction therapy with Cymevene in AIDS patients is NOT recommended. Current data show that concomitant administration of zidovudine and Cymevene at the recommended dosages during maintenance treatment with Cymevene results in severe neutropenia in most patients. Concomitant treatment with ganciclovir and high doses of β-lactam antibiotics may lead to generalized seizures.

**Dosage and Administration**

**Normal Dosage**

*Induction treatment (adults):* In patients with normal function, 5 mg/kg given as an intravenous infusion over one hour, every 12 hours (10 mg/kg/day) for 14-21 days.

*Maintenance treatment (adults):* In patients whose immune status remains depressed, and who are thus at risk of relapse, a dose of 6 mg/kg/day, five days per week, may be used.
The following infusion fluids are compatible with Cymevene: physiological saline, dextrose 5% and Ringer’s or lactated Ringer’s solution. The infusion solution must be used within 24 hours of dilution and should be refrigerated (2º-8ºC). Do not freeze.

**Special Dosage Instruction (adults)**

For patients with renal impairment the dosage should be adjusted as shown in the following table:

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min/1.73 m²)</th>
<th>Dose (mg/kg)</th>
<th>Dose interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>5.0</td>
<td>12</td>
</tr>
<tr>
<td>25-50</td>
<td>2.5</td>
<td>12</td>
</tr>
<tr>
<td>10-25</td>
<td>2.5</td>
<td>24</td>
</tr>
<tr>
<td>0-10</td>
<td>1.25</td>
<td>24</td>
</tr>
</tbody>
</table>

For maintenance treatment half the corresponding dose used for induction treatment should be given once daily.

**Administration**

- Do not administer by rapid intravenous injection. 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 solutions.

**Precautions during preparation of ganciclovir solutions:** Due to the high pH (9-11) ganciclovir solutions must be prepared with caution. Use of rubber gloves and protective eye glasses is recommended. If accidental contact with the skin or mucous membranes occurs, wash the affected area thoroughly with soap and water; if the product comes into contact with the eyes, rinse with plain water for 15 minutes. In addition, the same precautions as for cytostatic agents are recommended for Cymevene.

**Reconstituted solution:** Dissolve the contents of one vial of lyophilized Cymevene (500 mg) by adding 10 ml of sterile water for injection and shaking vigorously. The solution must be clear. Do not use bacteriostatic water for injection containing parabens, as these are incompatible with Cymevene and may cause precipitation. The solution is stable at room temperature for 12 hours. It should not be refrigerated.

**Infusion solution:** The appropriate dose volume of reconstituted sodium (concentration 50 mg/ml) should be added to an infusion fluid (normally 100 ml); the infusion concentration should not be greater than 10 mg/ml) for infusion over one hour.