Patient Information Leaflet **IRELAND**

Cymevene 500 mg Powder for concentrate for solution for infusion **Roche**
Ganciclovir

Please read all of this leaflet carefully before you start having this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If any of the side effects become serious or troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:
1. What Cymevene is and what it is used for
2. Before you are given Cymevene
3. How Cymevene will be given
4. Possible side effects
5. How Cymevene is stored
6. Further information

1. What Cymevene is and what it is used for

Cymevene contains a medicine called ganciclovir. This belongs to a group of medicines called 'anti-virals'.

Cymevene is used to **treat** infections caused by a virus called cytomegalovirus (CMV).
- The virus can infect any part of the body. This includes the retina of the eye where it causes problems with eye sight.
- The virus can infect anyone. However, in people who have a poor immune system because of other diseases or medicines (people who are 'immuno-compromised'), it can lead to serious infections.

Cymevene is also used to **prevent** cytomegalovirus (CMV) infection after an organ transplant.

2. Before you are given Cymevene

You must not be given Cymevene if:
- You are allergic (hypersensitive) to ganciclovir (the only ingredient in Cymevene).
- You are allergic to similar medicines called 'anti-virals'. These include valganciclovir, aciclovir and valaciclovir.
- You are pregnant or breast-feeding a baby. See the section on 'Pregnancy and breast-feeding'.

You must not be given Cymevene if any of the above apply to you. If you are not sure, talk to your doctor or nurse before having Cymevene.

Take special care with Cymevene
Check with your doctor or nurse before having Cymevene if:
- You have low numbers of white blood cells, red blood cells or platelets in your blood.
- You have had blood problems in the past that have been caused by medicines.
- You are having radiotherapy, or have recently had it.
- You have kidney problems.
- You or your partner might become pregnant during treatment. See the section on 'Pregnancy and breast-feeding'.
- Sodium content per vial is 43mg. To be taken into consideration by patients on a controlled sodium diet.

If any of the above apply to you, or if you are not sure, talk to your doctor or nurse before you have

Cymevene.

Taking other medicines
Please tell your doctor or nurse if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Cymevene can affect the way some medicines work. Also some medicines can affect the way Cymevene works.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- Probenecid (used to treat gout).
- Mycophenolate mofetil (used after an organ transplant).
- Zidovudine, didanosine, cidofovir or foscarnet (used to treat HIV).
- Imipenem-cilastatin, trimethoprim, pentamidine, flucytosine, amphotericin B or dapsone (antibiotics used to treat infections).
- Doxorubicin, vincristine, vinblastine or hydroxyurea (used to treat cancer).

Pregnancy and breast-feeding
You must not have Cymevene if you are pregnant or breast-feeding. Cymevene will damage an unborn baby.

- If you are a man and your partner is at an age where she could get pregnant, you must use condoms during your treatment with Cymevene and for 90 days after the end of treatment.
- If you are a woman at an age where you could get pregnant, you must use contraception (birth control) during your treatment.

If you are not sure if you are protected (have adequate contraception), talk to your doctor or nurse before having Cymevene.

Driving and using machines
Ganciclovir can make you feel dizzy, sleepy or confused. It can also cause fits and loss of co-ordination. If any of these happen to you, do not drive or use any tools or machines.

3. How Cymevene will be given

Cymevene will be given to you by a doctor or nurse. It will be given to you through a small tube into one of your veins (called an 'intravenous infusion'). It usually takes one hour for the medicine to be given.

- The dose of Cymevene varies from one patient to another. It depends on your age, weight, how well your kidneys are working and what you need the medicine for. The doctor will work out how much to give you.
- How often you have Cymevene and how long you keep having it for also varies from one patient to another. You will usually start by having one infusion every 12 hours for up to 21 days. After that you may have one infusion a day.
- Your doctor will see how you respond to this medicine, you may need to have regular blood tests. If necessary your dose might be changed of your treatment stopped.

If you are given more Cymevene than you should
- If you are given too much Cymevene you may get changes to your blood, problems with your liver or kidneys, stomach pain, being sick, diarrhoea, fits and shaking.
- If you think you have been given too much Cymevene, tell your doctor or nurse.

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

4. Possible side effects

Like all medicines, Cymevene can cause side effects, although not everyone will get them.

Allergic reactions (uncommon, affect less than 1 in 100 people)
If you have an allergic reaction, **tell a doctor straight away**.
The signs may include:

- A raised itchy skin rash (hives).
- Difficulty breathing or swallowing caused by sudden swelling of the throat, face, lips and mouth.
- Sudden swelling of the hands, feet and ankles.

Other possible side effects:

Very common (affect more than 1 in 10 people)

- Low numbers of one type of white blood cell (called neutrophils). The signs include infections of the mouth, gums, throat and lungs. Your doctor may want you to have blood tests.
- Low numbers of red blood cells (anaemia). The signs include feeling tired, pale skin, palpitations (a fluttering sensation in the heart) and being short of breath.
- Difficulty breathing.
- Diarrhoea.

Common (affect less than 1 in 10 people)

- Infections of the blood, skin, urinary tract and mouth. The signs include high temperature (fever), chills, feeling tired, redness and swelling of the skin, pain on passing water and creamy white spots in the mouth.
- Low numbers of all types of white blood cells. The signs include infections of the mouth, gums, throat and lungs.
- Low numbers of platelets in your blood. The signs include bruising easily and nose bleeds.
- Low numbers of all the types of cells in your blood. The signs include feeling tired, bruising easily, being short of breath and nose bleeds.
- Loss of appetite.
- Depression, anxiety, feelings of confusion and abnormal thinking.
- Headache.
- Difficulty in sleeping.
- Changes to the way things taste.
- Dizziness.
- Fits (‘convulsions’).
- Changes in your skin sensitivity (such as numbness, pins and needles, burning sensations).
- Changes to your eye-sight (vision), loss of vision or eye pain.
- Pain in your ears.
- A cough.
- Feeling or being sick, pain in your stomach, constipation, wind and difficulty swallowing.
- Problems with your liver, shown in a blood test.
- Skin rashes (including inflammation, redness and blistering), itchiness and sweating at night.
- Pain in your back, joints, muscles or chest or muscle cramps.
- Problems with your kidneys. This may affect the amount of water (urine) that you pass.
- Feeling tired, unwell or weak, high temperature (fever), shivering, weight loss.
- A reaction where Cymevene was given into your vein.

Uncommon (affect less than 1 in 100 people)

- Changes to your bone marrow (which may affect how your body produces some blood cells).
- Disturbances of the mind, including feeling agitated and losing contact with reality.
- Shaking or trembling that you cannot control.
- Infection of the eye (conjunctivitis).

- Deafness.
- Uneven heart beat.
- Low blood pressure. The signs include feeling dizzy or light-headed.
- Mouth ulcers, swelling of the abdomen (tummy) and pancreatitis. The signs of pancreatitis include severe pain in the stomach which spreads to your back.
- Loss of hair and dry skin.
- Serious kidney disease.
- Blood in your urine (water).
- Infertility in men. Cymevene may stop men from producing sperm. This can be temporary or permanent.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below).

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How Cymevene is stored

- Your doctor or pharmacist are responsible for storing Cymevene. They are also responsible for disposing of any unused Cymevene correctly.
- Keep out of the reach and sight of children.
- Do not store Cymevene above 30°C.
- Do not use Cymevene after the expiry date printed on the carton or vial after EXP.

6. Further information

What Cymevene contains
The active substance in Cymevene powder for infusion is ganciclovir. Each glass vial contains 500 mg (milligrams) ganciclovir as ganciclovir sodium 543mg. Sodium content per vial is 43 mg.

There are no other ingredients in Cymevene.

What Cymevene looks like and contents of the pack
Cymevene is a white to off-white powder, supplied in a glass vial. Before it is given, Cymevene is made into a solution by adding sterile water to the vial. The correct dose is then taken out of the vial and added to the bag of infusion solution to be given to the patient.

Vials of Cymevene are supplied in packs of 5 or 25. Not all packs may be marketed.

Marketing Authorisation Holder
Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City, AL7 1TW
United Kingdom.

Manufacturer
Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

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This information is intended for medical or healthcare professionals only.
The tear-off portion above is intended for the patient

INFORMATION FOR HEALTHCARE PROFESSIONALS

Cymevene® 500 mg Powder for concentrate for solution for infusion
Ganciclovir

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

Posology and method of administration

For intravenous infusion following reconstitution with 10ml Water for Injections BP. Based on patient weight the appropriate calculated dose volume should be removed from the vial (ganciclovir concentration 50mg/ml) and added to an acceptable infusion fluid (typically 100ml) for delivery over the course of 1 hour. Infusion concentrations greater than 10mg/ml are not recommended. (For further information see *Instructions for use/handling and disposal*).

Adults
Treatment of CMV infection
Initial (induction) treatment: 5mg/kg infused at a constant rate over 1 hour every 12 hours (10mg/kg/day) for 14 to 21 days.

Long-term (maintenance) treatment: For immunocompromised patients at risk of relapse of CMV retinitis a course of maintenance therapy may be given. Intravenous infusion of 6mg/kg once daily 5 days per week, or 5mg/kg once daily 7 days per week is recommended.

Treatment of disease progression: Indefinite treatment may be required in patients with AIDS, but even with continued maintenance treatment, patients may have progression of retinitis. Any patient in whom the retinitis progresses, either while on maintenance treatment or because treatment with Cymevene has been withdrawn, may be re-treated using the induction treatment regimen.

Prevention of CMV disease
Induction regimen: 5mg/kg infused every 12 hours (10mg/kg/day) for 7 to 14 days.

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

Special dosage instructions

Patients with renal impairment:
Serum creatinine levels or creatinine clearance should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in the table below.

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

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

For females = 0.85 x male value

CrCl	Induction dose of ganciclovir
≥ 70 ml/min	5.0mg/kg every 12 hours
50 – 69 ml/min	2.5mg/kg every 12 hours
25 – 49 ml/min	2.5mg/kg/day
10 – 24 ml/min	1.25mg/kg/day
< 10 ml/min	1.25mg/kg 3x/week after haemodialysis

CrCl	Maintenance dose of ganciclovir
≥ 70 ml/min	5.0mg/kg/day
50 – 69 ml/min	2.5mg/kg/day
25 – 49 ml/min	1.25mg/kg/day
10 – 24 ml/min	0.625mg/kg/day
< 10 ml/min	0.625mg/kg 3x/week after haemodialysis

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

Paediatric patients
There has been limited clinical experience in treating patients under the age of 12 years. Reported adverse events were similar to those seen in adults.

However, the use of Cymevene in children warrants extreme caution due to the potential for long-term carcinogenicity and reproductive toxicity. The benefits of treatment should outweigh the risks. Cymevene is not indicated for the treatment of congenital or neonatal CMV infections.

Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia
Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with Cymevene. 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 8g/dL.

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.

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.

Method of administration
Cymevene is a powder for solution for intravenous infusion. For directions on the preparation of the infusion solution, see *Instructions for use/handling, and disposal*.

Cymevene must only be given by intravenous infusion, preferably via a plastic cannula, into a vein with adequate blood flow.

Caution - do not administer by rapid or bolus i.v. injection! The toxicity of Cymevene may be increased as a result of excessive plasma levels.

Caution - i.m. or s.c. injection may result in severe tissue irritation due to the high pH (~11) of ganciclovir solutions.
The recommended dosage, frequency, or infusion rates should not be exceeded.

Instructions for use/handling and disposal

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

Method of Preparation of Cymevene solution
Each vial contains ganciclovir sodium equivalent to 500mg ganciclovir. Reconstitution with 10ml of sterile Water for Injections BP gives a ganciclovir concentration of 50mg/ml. Further dilution in an appropriate intravenous solution must be performed before infusion (see below).

1. Lyophilized Cymevene should be reconstituted by injecting 10ml of sterile Water for Injections into the vial. **Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with Cymevene sterile powder and may cause precipitation.**

2. The vial should be shaken to dissolve the drug.

3. Reconstituted solution should be inspected for particulate matter prior to proceeding with the admixture preparation. Only solutions which are colourless or light yellow, and free of particles should be used. For in-use storage times for the reconstituted vial, see section ‘Special precautions for storage’.

   The whole preparation should be performed under aseptic conditions

4. Reconstituted solution in the vial is stable at room temperature for 12 hours. It should not be refrigerated.

Preparation and administration of infusion solution

Based on patient weight the appropriate calculated dose volume should be removed from the Cymevene vial (concentration 50mg/ml) and added to an acceptable infusion fluid. Normal saline, dextrose 5% in water, Ringer's or lactated Ringer's solution are determined chemically or physically compatible with Cymevene. Infusion concentrations greater than 10mg/ml are not recommended.

Cymevene should not be mixed with other iv products.

Because Cymevene is reconstituted with nonbacteriostatic sterile water, the infusion solution should be used as soon as possible and within 24 hours of dilution in order to reduce the risk of bacterial contamination.

The infusion solution should be refrigerated. Freezing is not recommended.

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

Shelf life

Unopened vial: 3 years.

Special precautions for storage

- Undiluted vials: Do not store above 30ºC.
- In-use storage times for the reconstituted vial should not be longer than 12 hours. Do not refrigerate.
- In-use storage time for the infusion solution should not be longer than 24 hours when stored in a refrigerator at 2 - 8°C. Freezing is not recommended.

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