# Valcyte®

Valganciclovir

**Antiviral agent**

## COMPOSITION

*Active substance:* Valganciclovir (as valganciclovir HCl).

Excipients for coated tablets.

## GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Pink, convex, oval film-coated tablet with "VGC" on one side and "450" on the other side. Each tablet contains 496.3 mg valganciclovir hydrochloride, equivalent to 450 mg valganciclovir.

## INDICATIONS AND POTENTIAL USES

Valcyte is indicated for induction therapy in active CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) if these patients' vision appears to be in danger.

In patients with acquired immunodeficiency syndrome (AIDS), Valcyte may be used for maintenance therapy after induction therapy has been completed or in inactive CMV retinitis. The need to begin or continue maintenance therapy must be reviewed periodically in the light of general immune status, CD4 cell count and the response to any change in the patient's anti-HIV treatment.

Valcyte is indicated for the prophylaxis of CMV disease in solid organ transplant recipients at increased risk of CMV disease. In liver transplant recipients a higher incidence of CMV disease was observed in the valganciclovir group (900 mg once daily) than in the ganciclovir group (1 g orally three times daily). Lung transplant recipients were not investigated in the clinical studies with Valcyte.

## DOSAGE AND ADMINISTRATION

Caution – Strict adherence to dosage recommendations is essential to avoid overdose. To avoid adverse events associated with overdosage, particular care should be taken to adjust the dose in response to any decrease in renal function (e.g. in case of other severe infections).

Ganciclovir bioavailability from Valcyte tablets is significantly higher than from ganciclovir capsules; therefore, it is not possible to switch from Valcyte tablets to

ganciclovir capsules on a one-to-one basis.

**Normal dosage**

Valcyte is administered orally and should be taken with meals (see *Pharmacokinetics – Absorption* and *Pharmacokinetics in special patient populations*). Valganciclovir is rapidly and extensively converted into ganciclovir. As the bioavailability of ganciclovir from Valcyte is up to 10-fold higher than from ganciclovir capsules, the dosage and administration of Valcyte tablets as described below must be strictly followed (see *Warnings and Precautions* and *Overdosage*).

Induction therapy of CMV retinitis

For patients with active CMV retinitis the recommended dose is 900 mg (two 450 mg film-coated tablets) twice a day for 21 days. More prolonged induction treatment may increase the risk of bone marrow toxicity (see *Warnings and Precautions*).

Maintenance therapy of CMV retinitis

Following induction treatment or in patients with inactive CMV retinitis the recommended dose is 900 mg (two 450 mg film-coated tablets) once daily. Patients whose retinitis worsens may repeat induction treatment.

Prophylaxis of CMV disease in transplant patients

In renal transplant recipients, the recommended dose is 900 mg (two 450 mg film-coated tablets) once daily, starting within 10 days of transplantation and continuing until 200 days after transplantation.

In recipients of a non-renal solid organ transplant, the recommended dose is 900 mg of valganciclovir (two 450 mg film-coated tablets) once daily, starting within 10 days of transplantation and continuing until 100 days after transplantation.
If possible, the film-coated tablets should be taken with food.

**Special dosage instructions**

Patients with renal impairment

Serum creatinine or creatinine clearance must be carefully monitored. The dose should be adjusted on the basis of creatinine clearance, as shown in the table below (see *Warnings and Precautions* and *Pharmacokinetics*).

An estimate of creatinine clearance can be calculated from serum creatinine using the following formula:

$$\text{For men} = \frac{(140 - \text{age [years]}) \times (\text{body weight [kilograms]})}{(72) \times (0.011 \times \text{serum creatinine [micromoles per liter]})}$$

For women = 0.85 × value for men

| **$Cl_{CR}$ (ml/min)** | **Induction dose Valganciclovir** | **Maintenance dose** |
|---|---|---|
| ≥ 60 | 900 mg (2 film-coated tablets) twice daily | 900 mg (2 film-coated tablets) once daily |
| 40 – 59 | 450 mg (1 film-coated tablet) twice daily | 450 mg (film-coated tablet) once daily |
| 25 – 39 | 450 mg (1 film-coated tablet) once daily | 450 mg (film-coated tablet) every 2 days |
| 10 – 24 | 450 mg (1 film-coated tablet) every 2 days | 450 mg (1 film-coated tablet) twice weekly |

*Dialysis patients*

No dosage recommendation can be given for dialysis patients ($Cl_{Cr}$ < 10 ml/min). Therefore, Valcyte should not be used in these patients (see *Warnings and Precautions* and *Pharmacokinetics*).

Patients with severe leukopenia, neutropenia, anemia, thrombocytopenia and pancytopenia

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Valcyte (and 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* and *Undesirable Effects*).

Children

Safety and efficacy have not been investigated in children. The use of Valcyte in children is not recommended because the pharmacokinetic characteristics of Valcyte have not been studied in this patient population (see *Warnings and Precautions*).

Elderly patients

Safety and efficacy have not been investigated in this patient population.

Patients with liver failure

No studies have been performed in patients with liver failure.

**Method and duration of administration**

Valcyte is administered orally and should be taken with meals (see *Pharmacokinetics – Absorption*).

The film-coated tablets should not be broken or crushed. Since Valcyte is a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see *Warnings and Precautions*). Avoid direct contact of broken or crushed tablets with skin or mucous membranes and avoid inhalation of pulverised tablet material. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

The duration of administration depends on the indication (see *Dosage and Administration*).

## CONTRAINDICATIONS

Valcyte is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any other component of the product (excipient).

Due to the similar chemical structures of Valcyte, aciclovir and valaciclovir, cross-hypersensitivity reactions can occur between these drugs.

Valcyte is contraindicated during pregnancy, in nursing mothers and in men who wish to father a child (see *Pregnancy and Lactation*).

## WARNINGS AND PRECAUTIONS

In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic. Valcyte should therefore be considered a potential teratogen and carcinogen in humans, which may possibly cause birth defects and cancers (see *Preclinical Data*). It is also likely that Valcyte can cause temporary or permanent inhibition of spermatogenesis (see *Pregnancy and Lactation*, *Undesirable Effects* and *Preclinical Data*).

Women of childbearing age must be advised to use effective contraception during treatment. Men must be advised to practice barrier contraception during treatment with Valcyte and for at least 90 days thereafter (see *Preclinical Data*).

Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with Valcyte (and 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 *Dosage and Administration* and *Undesirable Effects*).

The use of Valcyte in children is not recommended (see *Dosage and Administration*).

The bioavailability of ganciclovir is up to 10-fold higher than from ganciclovir capsules (Cymevene®). Valcyte must not be substituted for ganciclovir capsules in a one-to-one ratio. Patients switched to Valcyte from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte film-coated tablets (see *Dosage and Administration* and *Overdosage*).

It is recommended that full blood counts and platelet counts be monitored during treatment. In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia it is recommended that consideration be given to treatment with hematopoietic growth factors and/or treatment withdrawal (see *Dosage and Administration* and *Undesirable Effects*).

In patients with impaired renal function, dose adjustments should be made on the basis of creatinine clearance (see *Dosage and Administration* and *Pharmacokinetics in special patient populations*).

No dosage recommendation can be given for dialysis patients ($Cl_{Cr}$ < 10 ml/min). Therefore, Valcyte should not be used in these patients (see *Dosage and Administration* and *Pharmacokinetics in special patient populations*).

Convulsions have been observed in patients taking imipenem-cilastatin and ganciclovir. Valcyte should therefore not be used concomitantly with imipenem-cilastatin unless the potential benefit outweighs the potential risks (see *Interactions*).

Zidovudine and Valcyte each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy with these two drugs at full dosage (see *Interactions*).

Didanosine plasma concentrations may increase during concomitant use with Valcyte. Patients should therefore be closely monitored for didanosine toxicity (see *Interactions*).

Concomitant treatment with Valcyte and drugs known to be myelosuppressive or associated with renal impairment may lead to increased toxic effects (see *Interactions*).

No lung transplant patients were included in the controlled clinical study on valganciclovir in the prophylaxis of CMV disease after organ transplantation (see *Properties/Effects* and *Clinical efficacy*). Experience in this group of patients is therefore limited.

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of Valcyte and/or ganciclovir. Such effects may impair tasks requiring alertness, including the patient's ability to drive and operate machines (see *Effects on Ability to Drive and Operate Machines*).

# INTERACTIONS

**Pharmacokinetic/pharmacodynamic interactions**

Drug interactions with Valcyte

In a rat *in-situ* model of intestinal permeability there were no interactions between valganciclovir and valaciclovir, didanosine, nelfinavir, cyclosporin, omeprazole or mycophenolate mofetil.

Since Valcyte is metabolised to ganciclovir, the drug interactions associated with ganciclovir must be expected with Valcyte.

Drug interactions with ganciclovir

Binding of ganciclovir to plasma proteins is only about 1–2% and drug interactions involving displacement from the binding sites are not anticipated.

**Imipenem-cilastatin**

Convulsions have been reported in patients taking ganciclovir concomitantly with imipenem-cilastatin. These drugs should therefore not be used concomitantly unless the potential benefit outweighs the potential risks (see *Warnings and Precautions*).

**Probenecid**

Co-administration of probenecid with oral ganciclovir led to a statistically significant decrease in ganciclovir renal clearance (20%), resulting in statistically significantly increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Patients taking probenecid and Valcyte should therefore be closely monitored for ganciclovir toxicity.

**Zidovudine**

When zidovudine was administered together with oral ganciclovir there was a small

(19%) but statistically significant increase in the AUC of zidovudine. Administration with zidovudine was also associated with a trend towards lower (17%) ganciclovir concentrations, although this was not statistically significant. However, since both zidovudine and ganciclovir can cause neutropenia and anemia, some patients may not tolerate concomitant therapy with these two drugs at full dosage (see *Warnings and Precautions*).

**Didanosine**

Didanosine plasma concentrations were consistently raised on combined administration with ganciclovir (both intravenous and oral). An increase of 84 to 124% was observed in the AUC of didanosine at ganciclovir oral doses of 3 and 6 g/day, while an increase of 38 to 67% in didanosine AUC was observed at intravenous doses of 5 and 10 mg/kg/day. This increase cannot be explained by a mechanism involving competition for renal tubular excretion, as there was an increase in the percentage didanosine dose excreted. This increase could arise from either increased bioavailability or decreased metabolism. There was no clinically significant effect on ganciclovir concentrations. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity (see *Warnings and Precautions*).

**Mycophenolate mofetil**

Based on the results of a study with single administration of the recommended doses of oral mycophenolate mofetil (MMF) and i.v. ganciclovir and on the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co-administration of these agents (which may compete for renal tubular secretion) may lead to an increase in the phenolic glucuronide of mycophenolic acid (MPAG) and in ganciclovir concentration. No substantial change is anticipated in mycophenolic acid (MPA) pharmacokinetics and MMF dose adjustment is not required. In patients with renal impairment who are receiving MMF together with ganciclovir the dose recommendations for ganciclovir should be followed and patients carefully monitored. Since both mycophenolate mofetil and ganciclovir have the potential to cause neutropenia and leukopenia, patients should be monitored for additive toxicity.

**Zalcitabine**

Zalcitabine increased the $AUC_{0–8}$ of oral ganciclovir by 13%. There were no statistically significant changes in any of the other pharmacokinetic parameters assessed. There were likewise no clinically relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir, although a small increase was observed in the elimination rate constant.

**Stavudine**

No statistically significant pharmacokinetic interaction was observed when stavudine and oral ganciclovir were given in combination.

**Trimethoprim**

Trimethoprim led to a statistically significant decrease in the renal clearance of oral ganciclovir by 16.3%. This was associated with a statistically significant decrease in the terminal elimination rate and a 15% increase in half-life. However, these changes are unlikely to be clinically significant, as $AUC_{0–8}$ and $C_{max}$ were unaffected. The only statistically significant change in the pharmacokinetic parameters of trimethoprim when co-administered with ganciclovir was an increase in $C_{min}$. However, this is probably

clinically insignificant and no dose adjustment is recommended.

**Cyclosporin**

Comparison of cyclosporin trough concentrations revealed no evidence that ganciclovir administration could affect cyclosporin pharmacokinetics. However, an increase in the maximum serum creatinine level was observed after the start of ganciclovir therapy.

**Other potential drug interactions**

Toxicity may be increased if ganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulphonamide combinations, nucleoside analogues and hydroxyurea).

Since ganciclovir is excreted through the kidneys (see *Pharmacokinetics*), toxicity may also be enhanced during co-administration of Valcyte with drugs that might reduce the renal clearance of ganciclovir and thereby increase its concentration in the body. 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.

These drugs should therefore not be used concomitantly with ganciclovir unless the possible benefit outweighs the potential risks (see *Warnings and Precautions*).

## PREGNANCY AND LACTATION

**Pregnancy**

There are no data on the use of Valcyte in pregnant women. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir (see *Preclinical Data*) there is a theoretical risk of teratogenicity in humans.

Women of childbearing age must be advised to use effective contraception during treatment. Male patients must be advised to use condoms for contraception during and for at least 90 days following treatment with Valcyte unless it is certain that the female partner is not at risk of pregnancy (see *Preclinical Data*).

Valcyte should not be used during pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the child.

**Lactation**

It is not known whether ganciclovir is excreted in breast milk, however the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, breast-feeding must be discontinued.

## EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINES

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

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of Valcyte and/or ganciclovir. Such effects impair the performance of tasks requiring

alertness, including the patient's ability to drive and operate machinery.

# UNDESIRABLE EFFECTS

**Experience from clinical studies**

Experience with Valcyte

Valganciclovir is a prodrug of ganciclovir that is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir use can therefore also be expected with Valcyte. All undesirable effects observed in clinical studies with Valcyte had been previously observed with ganciclovir.

*Treatment of CMV retinitis in AIDS patients*

The safety profiles of valganciclovir and intravenous ganciclovir were comparable during 28 days of a randomised study phase (21 days induction dose and 7 days maintenance dose) in 79 patients per group. The most frequently reported undesirable effects were diarrhea, neutropenia and pyrexia. More patients reported diarrhea, oral candidiasis, headache and fatigue in the oral valganciclovir arm, and nausea and injection site-related undesirable effects in the intravenous ganciclovir arm (see Table 1).

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

| **Adverse event** | **Valganciclovir group** | **Intravenous ganciclovir group** |
|---|---|---|
| **Adverse events per system organ class** | **n = 79**<br>% | **n = 79**<br>% |
| **Gastrointestinal disorders** | | |
| Diarrhea | 16 | 10 |
| Nausea | 8 | 14 |
| **Infections and infestations** | | |
| Oral candidiasis | 11 | 6 |
| **Nervous system disorders** | | |
| Headache | 9 | 5 |
| **General disorders** | | |
| Fatigue | 8 | 4 |
| **Vascular disorders** | | |
| Phlebitis and thrombophlebitis | – | 6 |

- Table 2 shows adverse events with an incidence ≥5% regardless of seriousness and relationship to the medicinal product observed from studies on the use of valganciclovir either in patients with CMV retinitis or in solid organ transplant recipients.

- The information in Table 2 pertaining to the patients with CMV retinitis is based on 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 a maximum of 3 weeks or 900 mg once daily as maintenance therapy. Approximately 65% of these patients received valganciclovir maintenance therapy for more than 9 months (the maximum duration was 30 months).

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

- The most frequent adverse events (% patients) – regardless of seriousness or relationship to treatment – reported on Valcyte treatment from these two clinical studies (n = 370) were diarrhea (38%), pyrexia (26%), nausea (25%), neutropenia (24%) and anemia (22%). The most frequent (≥2%) serious adverse events – regardless of seriousness or relationship to treatment – were diarrhea (4.3%), pyrexia (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 seriousness or relationship to treatment – was low, with only anemia (2.1%) showing an incidence ≥2%. The most frequently reported adverse events (% patients) – regardless of seriousness – that were considered related (remotely, possibly or probably) to Valcyte treatment by the investigator were neutropenia (21%), anemia (14%), diarrhea (13%) and nausea (9%).

*Prevention of CMV disease in transplant patients*

- Table 2 shows the adverse events (regardless of seriousness or causal relationship to the study drug) that occurred in a clinical study (up to 28 days after treatment with the study drug) with an incidence ≥5%. In this study solid organ transplant recipients were treated either with valganciclovir (n = 244) or oral ganciclovir (n = 126) starting within 10 days of transplantation and continuing up to post-transplant day 100. The most frequently reported adverse events (% patients) in patients taking Valcyte in this clinical study were diarrhea (30%), tremor (28%), graft rejection (24%), nausea (23%), headache (22%), lower limb edema (21%), constipation (20%), back pain (20%), sleep disturbance (20%), hypertension (18%) and vomiting (16%). These adverse events occurred on oral ganciclovir with approximately the same incidence. The majority of these adverse events were of mild or moderate intensity.

- Adverse events not occuring in the CMV retinitis clinical studies (treatment for 100 days) and observed in the solid organ transplant clinical study at a frequency ≥2% were hypertension (18%), serum creatinine elevation (10%), metabolic disorders such as hyperkalemia (14%) and altered liver function (9%). These adverse events occurred on oral ganciclovir with approximately the same incidence and were considered a reflection of the underlying disease process.

- The most frequently reported adverse events (regardless of seriousness) in solid

organ transplant recipients treated until post-transplant day 100 which the investigator considered to bear a (remote, possible or probable) causal connection to Valcyte were (% patients) leukopenia (9%), diarrhea (7%), nausea (6%) and neutropenia (5%).

- In addition valganciclovir is associated with a higher risk of neutropenia and leukopenia than oral ganciclovir.

**Table 2 Percentage of patients with adverse events occurring in CMV retinitis patients or organ transplant recipients in clinical studies with valganciclovir**

| | **CMV retinitis patients** | **Solid organ transplant recipients: Dosing until post-transplant Day 100** | |
|---|---|---|---|
| | **Valganciclovir** | **Valganciclovir** | **Oral ganciclovir** |
| **Adverse events per system organ class** | **n = 370 %** | **n = 244 %** | **n = 126 %** |
| **Infections and infestations** | | | |
| Oral candidiasis | 20 | 3 | 3 |
| Pharyngitis/nasopharyngitis | 12 | 4 | 8 |
| Sinusitis | 10 | 3 | - |
| Upper respiratory tract infection | 9 | 7 | 7 |
| Influenza | 9 | - | - |
| Pneumonia | 7 | 4 | 2 |
| Bronchitis | 6 | - | 1 |
| *Pneumocystis carinii* pneumonia | 6 | - | - |
| Urinary tract infection | 5 | 11 | 9 |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia | 24 | 8 | 3 |
| Anemia | 22 | 12 | 15 |
| Thrombocytopenia | 5 | 5 | 5 |
| Leukopenia | 4 | 14 | 7 |
| **Immune system disorders** | | | |
| Graft rejection | - | 24 | 30 |
| **Metabolism and nutrition disorders** | | | |
| Weight loss | 9 | 3 | 3 |
| Blood creatinine elevation | 1 | 10 | 14 |
| Decreased appetite | 8 | 4 | 5 |
| Dehydration | 6 | 5 | 6 |
| Anorexia | 5 | 3 | - |
| Cachexia | 5 | - | - |
| Hyperkalemia | <1 | 14 | 14 |
| Hypokalemia | 2 | 8 | 8 |
| Hypomagnesemia | <1 | 8 | 8 |
| Hyperglycemia | 1 | 6 | 7 |
| Hypophosphatemia | <1 | 9 | 6 |

| | CMV retinitis patients | Solid organ transplant recipients: Dosing until post-transplant Day 100 | |
|---|---|---|---|
| | Valganciclovir | Valganciclovir | Oral ganciclovir |
| **Adverse events per system organ class** | **n = 370 %** | **n = 244 %** | **n = 126 %** |
| Hypocalcemia | <1 | 4 | 6 |
| **Psychiatric disorders** | | | |
| Depression | 9 | 7 | 6 |
| **Nervous system disorders** | | | |
| Headache | 18 | 22 | 27 |
| Sleep disturbance | 14 | 20 | 16 |
| Dizziness (excl. vertigo) | 9 | 10 | 6 |
| Peripheral neuropathy | 7 | 1 | 1 |
| Paresthesia | 6 | 5 | 5 |
| Tremor | 2 | 28 | 25 |
| **Eye disorders** | | | |
| Retinal detachment | 13 | - | - |
| Blurred vision | 6 | 1 | 4 |
| Macular edema | 4 | - | - |
| **Vascular disorders** | | | |
| Hypertension | 3 | 18 | 15 |
| Hypotension | 1 | 3 | 8 |
| **Respiratory organs (respiratory, thoracic and mediastinal disorders)** | | | |
| Cough | 16 | 6 | 8 |
| Dyspnea | 9 | 11 | 10 |
| Productive cough | 5 | 2 | 2 |
| Rhinorrhea | 2 | 4 | 6 |
| Pleural effusion | <1 | 7 | 8 |
| **Gastrointestinal disorders** | | | |
| Diarrhea | 38 | 30 | 29 |
| Nausea | 25 | 23 | 23 |
| Vomiting | 20 | 16 | 14 |
| Abdominal pain | 13 | 14 | 14 |
| Constipation | 6 | 20 | 20 |
| Upper abdominal pain | 6 | 9 | 6 |
| Dyspepsia | 4 | 12 | 10 |
| Abdominal distension | 2 | 6 | 6 |
| Ascites | - | 9 | 6 |
| **Hepatobiliary disorders** | | | |
| Altered liver function | 3 | 9 | 11 |
| **Skin and subcutaneous tissue disorders** | | | |
| Dermatitis | 18 | 4 | 5 |

| | CMV retinitis patients | Solid organ transplant recipients: Dosing until post-transplant Day 100 | |
|---|---|---|---|
| | Valganciclovir | Valganciclovir | Oral ganciclovir |
| **Adverse events per system organ class** | **n = 370 %** | **n = 244 %** | **n = 126 %** |
| Night sweats | 7 | 3 | 4 |
| Pruritus | 6 | 7 | 4 |
| Acne | <1 | 4 | 6 |
| **Musculoskeletal system (locomotor apparatus, connective tissue and bone disorders)** | | | |
| Back pain | 8 | 20 | 15 |
| Arthralgia | 6 | 7 | 7 |
| Muscle cramps | 2 | 6 | 11 |
| Limb pain | 3 | 5 | 7 |
| **Renal and urinary tract disorders** | | | |
| Renal impairment | 1 | 7 | 12 |
| Dysuria | 2 | 7 | 6 |
| **General disorders** | | | |
| Pyrexia | 26 | 13 | 14 |
| Fatigue | 20 | 13 | 15 |
| Lower limb edema | 5 | 21 | 16 |
| Pain | 3 | 5 | 7 |
| Edema | 1 | 11 | 9 |
| Peripheral edema | 1 | 6 | 7 |
| Weakness | 4 | 6 | 6 |
| **Surgical and medical procedures** | | | |
| Post-operative complications | 1 | 12 | 8 |
| Post-operative pain | 2 | 13 | 7 |
| Post-operative wound infection | 1 | 11 | 6 |
| **Injury, poisoning and procedural complication** | | | |
| Increased wound drainage | -- | 5 | 9 |
| Wound dehiscence | <1 | 5 | 6 |

- Serious adverse events considered related to Valcyte treatment by the manufacturer and reported in these three clinical studies (n = 614) with a frequency of less than 5% and not mentioned in the two tables above are listed below:

- Blood and lymphatic system disorders:

- *Common:* pancytopenia.

- *Uncommon:* bone marrow depression.

- *Rare:* aplastic anemia.

- *Unknown:* potentially life-threatening thrombocytopenic hemorrhage.
- Immune system disorders:
- *Uncommon:* hypersensitivity to valganciclovir.
- Nervous system disorders:
- *Uncommon:* Seizures.
- Psychiatric disorders:
- *Uncommon:* agitation, hallucinations, confusion.
- *Unknown:* Psychosis.
- Investigations:
- *Common:* Decreased creatinine clearance.
- Table 3 lists the changes in laboratory values reported on valganciclovir or oral ganciclovir in the three clinical studies (n = 614).

**Table 3 Changes in laboratory values**

| **Changes in laboratory values** | **CMV retinitis patients** | **Solid organ transplant recipients** | |
|---|---|---|---|
| | **Valganciclovir n = 370** **%** | **Valganciclovir n = 244** **%** | **Oral ganciclovir n = 126** **%** |
| Neutropenia: ANC/µl | | | |
| <500 | 16 | 5 | 3 |
| 500–<750 | 17 | 3 | 2 |
| 750–<1000 | 17 | 5 | 2 |
| Anemia: hemoglobin g/dl | | | |
| <6.5 | 7 | 1 | 2 |
| 6.5–<8.0 | 10 | 5 | 7 |
| 8.0–<9.5 | 14 | 31 | 25 |
| Thrombocytopenia: platelets/µl | | | |
| <25,000 | 3 | 0 | 2 |
| 25,000–<50,000 | 5 | 1 | 3 |
| 50,000–<100,000 | 21 | 18 | 21 |
| Serum creatinine mg/dl | | | |
| >2.5 | 2 | 14 | 21 |
| >1.5–2.5 | 11 | 45 | 47 |

- Severe neutropenia (absolute neutrophil count [ANC] less than 500 cells/µl) was observed more frequently in CMV retinitis patients (16%) receiving valganciclovir therapy than in solid organ transplant recipients treated with valganciclovir (5%) or oral

ganciclovir (3%) until post-transplant day 100. A greater increase in serum creatinine was observed in solid organ transplant recipients treated until day 100 post-transplant with both valganciclovir and oral ganciclovir than in CMV retinitis patients. Renal impairment is a common occurrence in solid organ transplant recipients.

- Prolonging prophylaxis in high-risk renal transplant recipients to day 200 did not affect the overall safety profile of Valcyte.

*Experience with ganciclovir*

- Valcyte is rapidly converted to ganciclovir. The adverse events reported with ganciclovir that are not mentioned above are listed below:

- Infections and infestations:

- *Common:* viral infections*, sepsis.

- *Uncommon:* bacterial and fungal infections, herpes simplex, cellulitis.

- Blood and lymphatic system:

- *Common:* eosinophilia, lymphadenopathy.

- *Uncommon:* leukocytosis, splenomegaly.

- *Unknown:* iron deficiency anemia.

- Metabolism and nutrition disorders:

- *Uncommon:* diabetes mellitus, hypoproteinemia.

- Psychiatric disorders:

- *Common:* anxiety*, decreased libido*.

- *Uncommon:* pathological dreams, thought disorders, euphoria, mania, nervousness, confusion.

- *Unknown:* emotional disturbance, psychotic disturbances, hyperkinetic syndrome.

- Nervous system disorders:

- *Common:* dysgeusia*.

- *Uncommon:* ataxia, coma, myoclonus, amnesia, somnolence, migraine.

- *Unknown:* myasthenic syndrome.

- Eye disorders:

- *Common:* conjunctivitis, eye pain, visual disturbance*.

- *Uncommon:* blindness, eye hemorrhage, retinitis, vitreous disorder.

- *Unknown:* amblyopia, glaucoma.
- Ear and inner ear disorders:
- *Common:* ear pain.
- *Uncommon:* hearing loss, tinnitus.
- Cardiac disorders:
- *Uncommon:* Arrhythmia (including ventricular arrhythmia), tachycardia.
- Vascular disorders:
- *Common:* phlebitis, hemorrhage.
- *Uncommon:* deep vein thrombosis.
- *Unknown:* vasodilatation.
- Respiratory organs (respiratory, thoracic and mediastinal disorders):
- *Common:* sinus congestion.
- Gastrointestinal disorders:
- *Common:* dyspepsia, flatulence, gastrointestinal hemorrhage.
- *Uncommon:* abdominal distension, dry mouth, dysphagia, eructation, esophagitis, fecal incontinence, gastritis, gastrointestinal disorder, oral mucosa ulcers, pancreatitis, tongue disorder.
- Hepatobiliary disorders:
- *Uncommon:* cholangitis, hepatitis, jaundice.
- Skin and subcutaneous tissue disorders:
- *Common:* alopecia*, dry skin.
- *Uncommon:* photosensitivity reaction, maculopapular rash, increased sweating, urticaria.
- Musculoskeletal system (locomotor apparatus, connective tissue and bone disorders):
- *Common:* myalgia*.
- *Uncommon:* bone pain.
- Renal and urinary tract disorders:
- *Uncommon:* hematuria, renal insufficiency, urinary frequency, renal failure.

- Reproductive system and breast disorders:
- *Uncommon:* impotence.
- *Unknown:* Breast pain.
- General disorders:
- *Uncommon:* asthenia, malaise, mucous membrane disorder, pain, rigor, weakness.
- Investigations:
- *Common:* serum lactate dehydrogenase elevation, serum alkaline phosphatase elevation.
- *Uncommon:* aspartate aminotransferase elevation, alanine aminotransferase elevation, blood urea nitrogen elevation, serum creatine phosphokinase elevation, hypoglycemia.
- * Borderline between *common* and *uncommon*.

**Post-marketing experience**

Experience with ganciclovir and/or valganciclovir

Undesirable effects of intravenous and oral ganciclovir from spontaneous reports in the post-marketing period that are not mentioned in any section above and for which a causal relationship cannot be excluded are listed below. As Valcyte is rapidly and extensively converted to ganciclovir, such undesirable effects could also occur with Valcyte.

- Anaphylaxis
- Decreased fertility in males
- Isolated cases of decreased prothrombin level have been reported.

The undesirable effects reported during the post-marketing period are consistent with those seen in clinical trials with Valcyte and ganciclovir.

# OVERDOSAGE

Experience with valganciclovir overdose

One adult developed fatal bone marrow depression (marrow aplasia) after several days at a dosage at least 10-fold higher than that recommended for the patient's degree of renal impairment (decreased creatinine clearance).

Potentially increased nephrotoxicity must also be expected after overdosage with valganciclovir (see *Dosage and Administration* and *Warnings and Precautions*).

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

Experience with intravenous ganciclovir overdosage

Reports of overdoses with intravenous ganciclovir are available from clinical trials and post-marketing experience. In some of these cases no undesirable effects were reported. Most patients experienced one or more of the following undesirable effects:

*Hematological toxicity:* pancytopenia, bone marrow depression, bone marrow aplasia, leukopenia, neutropenia, granulocytopenia

*Hepatotoxicity:* hepatitis, hepatic impairment

*Nephrotoxicity:* exacerbation 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

# PROPERTIES/EFFECTS

**ATC code**

J05AB14

**Mechanism of action / pharmacodynamics**

Pharmacotherapeutic group: antiviral agent for systemic use.

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that is rapidly converted to ganciclovir by intestinal and hepatic esterases after oral administration. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive viruses in man include human cytomegalovirus (HCMV), herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), human herpes viruses 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus.

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 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 deoxyguanosine triphosphate incorporation into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA, which leads to termination of the viral DNA chain or permits only very limited further elongation of this DNA chain.

Antiviral activity

The typical antiviral $IC_{50}$ of ganciclovir against CMV *in vitro* is in the range 0.08 µM (0.02 µg/ml) to 14.32 µM (3.58 µg/ml).

The clinical antiviral effect of Valcyte has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis (clinical trial WV15376). CMV shedding

was decreased in urine from 46% (32/69) of patients at study entry to 7% (4/55) of patients following four weeks of Valcyte treatment.

**Clinical efficacy**

Treatment of CMV retinitis

Clinical studies of Valcyte have been conducted in patients with AIDS and CMV retinitis. The efficacy of Valcyte for induction treatment in CMV retinitis has been shown to be comparable to that of intravenous ganciclovir. In a randomised, open-label controlled study 160 patients with AIDS and newly diagnosed CMV retinitis were randomised to receive treatment with either Valcyte film-coated 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). The median age was 39 years, the median baseline HIV-1 RNA was 4.9 $\log_{10}$ and the median CD4 cell count was 23 cells/$mm^3$. A determination of CMV retinitis progression by masked review of retinal photographs taken at baseline and week 4 was the primary outcome measurement of the three-week induction therapy. Table 4 shows the outcomes at four weeks.

**Table 4 Week 4 masked review of retinal photographs in study WV15376**

| | **Cymevene® i.v.** | **Valcyte** |
|---|---|---|
| Determination of CMV retinitis progression at week 4 | n=80 | n=80 |
| Progression | 7 | 7 |
| No progression | 63 | 64 |
| Death | 2 | 1 |
| Discontinuations due to adverse events | 1 | 2 |
| Failed to return | 1 | 1 |
| CMV not confirmed at baseline or no interpretable baseline photos | 6 | 5 |

Maintenance therapy of CMV retinitis

No clinical comparative data on the efficacy of Valcyte in the maintenance treatment of CMV retinitis are available, since in study WV15376 Valcyte was administered in open fashion to all patients after the fourth week. Nevertheless, the area under the plasma concentration versus time curve (AUC) for ganciclovir after once-daily administration of

900 mg valganciclovir (Valcyte) is similar to that after once-daily intravenous administration of 5 mg/kg ganciclovir (Cymevene®). Although the $C_{max}$ value for ganciclovir after administration of valganciclovir is lower than that after intravenous administration of ganciclovir, it is higher than the $C_{max}$ value obtained after oral administration of ganciclovir. Therefore, the use of valganciclovir for maintenance treatment is supported by a plasma concentration versus time profile similar to that of two preparations that have been approved for use in the maintenance treatment 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 treatment with Valcyte and 219 (126) days in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with Valcyte.

Although no direct comparative data are available, Valcyte provides 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. Ganciclovir AUC has been shown to correlate with time to progression of CMV retinitis.

Prophylaxis of CMV disease in transplant patients

A double-blind, double-dummy, comparative clinical study was conducted in heart, liver and kidney transplant patients (lung transplant patients were not included in the study) at high risk of CMV disease (D+/R-). The patients received either Valcyte (900 mg once daily) or oral ganciclovir (1000 mg three times daily) starting within 10 days after transplantation and continuing until day 100 post-transplant. The incidence of CMV disease (CMV syndrome + tissue invasive disease) during the first 6 months post-transplant was 12.1% in the Valcyte arm (n=239) compared with 15.2% in the oral ganciclovir arm (n=125) as assessed by an endpoint committee. The great majority of cases occurred following cessation of prophylaxis (i.e. after day 100), with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm.

In terms of transplantation organ, valganciclovir and oral ganciclovir achieved the following results:

| Incidence of CMV disease by organ type (ITT, EC) | | | |
|---|---|---|---|
| | Oral ganciclovir (n=125) % | Valganciclovir (n=239) % | Total (n=364) % |
| All organs (n=364) | 15.2 (19) | 12.1 (29) | 13.2 (48) |
| Heart (n=56) | 9.5 (2) | 5.7 (2) | 7.1 (4) |
| Liver (n=177) | 11.9 (7) | 18.6 (22) | 16.4 (29) |
| Kidneys (n=120) | 23.1 (9) | 6.2 (5) | 11.7 (14) |
| Kidneys-pancreas (n=11) | 16.7 (1) | 0 | 9.1 (1) |

The incidence of acute rejection in the first 6 months was 29.7% in patients randomised to valganciclovir compared with 36.0% in the oral ganciclovir arm. The incidence of

graft loss was the same (0.8%) in both arms.

Prolongation of Valcyte prophylaxis of CMV for 200 days after transplantation in high-risk renal transplant recipients proved superior to treatment for 100 days in preventing CMV disease in the first 12 months after transplantation.

A double-blind placebo-controlled study in 326 renal transplant recipients at high risk of CMV disease (D+/R-) evaluated the efficacy and safety of prolonging Valcyte prophylaxis of CMV from 100 to 200 days after transplantation. After randomisation (1:1), patients received Valcyte film-coated tablets (900 mg once daily); treatment was started within 10 days of transplantation, continued for 200 or 100 days after transplantation, then followed by the administration of placebo for 100 days.

Table 5 shows the proportion of patients developing CMV disease in the first 12 months after transplantation.

**Table 5 Proportion of renal transplant recipients developing CMV disease[1], ITT population after 12 months**

| | Valganciclovir 900 mg once daily, 100 days | Valganciclovir 900 mg once daily, 200 days | p (Cochran-Mantel-Haenszel) |
|---|---|---|---|
| Patients developing confirmed or suspected CMV disease[2] | 71/163 (43.6%) | 36/155 (23.2%) | 0.0001 |
| Patients developing confirmed CMV disease | 60/163 (36.8 %) | 25/155 (16.1%) | < 0.0001 |

*[1]CMV disease was defined as a CMV syndrome or CMV with tissue invasion. [2]Confirmed CMV was a clinically confirmed case of CMV disease. CMV was suspected if there were no data in these patients at the week 52 visit or if CMV disease had not been confirmed before this date.*

Twelve months after transplantation, graft survival rates were 98.1% (160/163) on the 100-day treatment and 98.2% (152/155) on the 200-day treatment. The rates of biopsy-confirmed acute rejection 12 months after transplantation were 17.2% (28/163) on the 100-day treatment and 11.0 % (17/155) on the 200-day treatment.

Viral resistance

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

Treatment of CMV retinitis

Genotypic analysis of CMV in polymorphonuclear leukocytes (PMNL) isolated from 148

patients enrolled in a clinical study on CMV retinitis showed that 2.2%, 6.5%, 12.8% and 15.3% contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment. Phenotypic resistance was not identified, however very few CMV culture isolates were available for analysis.

Prophylaxis of CMV disease in transplant patients

Resistance was studied by genotypic analysis of CMV in polymorphonuclear leukocyte samples collected a) on day 100 (end of study drug prophylaxis) and b) in cases of suspected CMV disease up to 6 months after transplantation. From the 245 patients randomised to receive valganciclovir, 198 day-100 samples were available for testing and no ganciclovir resistance mutations were observed. This compares with 2 ganciclovir resistance mutations detected in the 103 samples tested (1.9%) for patients in the oral ganciclovir comparator arm.

Of the 245 patients randomised to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 127 patients randomised to the ganciclovir comparator arm, samples from the 29 patients with suspected CMV disease were tested, from which two resistance mutations were observed, giving an incidence of resistance of 6.9%.

# PHARMACOKINETICS

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

The parameters that control exposure to ganciclovir from valganciclovir are bioavailability and renal function. The bioavailability of ganciclovir from valganciclovir is similar across all patient populations studied. The systemic exposure of heart, kidney and liver transplant recipients to ganciclovir was similar after oral administration of valganciclovir in accordance with the renal function dosing algorithm.

**Absorption**

Valganciclovir is a prodrug of ganciclovir that is well absorbed from the gastrointestinal tract after oral administration and rapidly metabolised in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low; $AUC_{24}$ and $C_{max}$ values are approximately 1% and 3% of those of ganciclovir, respectively.

Systemic exposure to ganciclovir after oral administration of 900 mg of valganciclovir is 24.9 ± 4.5 µg·h/ml compared to 25.6 ± 5.1 µg·h/ml after 5 mg/kg ganciclovir. The corresponding figures for peak concentrations are 5.15 ± 1.2 µg/ml and 9.31 ± 2.1 µg/ml respectively.

Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir to HIV+, CMV+ patients in the dose range 450 to 2625 mg was demonstrated only after food intake. When valganciclovir was taken at a dose of 875 mg (the recommended dose is 900 mg) with a standard breakfast containing bacon and scrambled eggs, increases were seen in both mean ganciclovir $AUC_{24}$ (by approximately 30%) and mean ganciclovir $C_{max}$ (by approximately 14%) compared to the fasting state. It

is therefore recommended that Valcyte be taken with meals (see *Dosage and Administration*).

Pharmacokinetic results from a study in HIV+, CMV+ subjects which included severely ill patients were similar to those in the less affected population.

*Valganciclovir in HIV+, CMV+ patients*

Systemic exposure of HIV+, CMV+ patients after twice-daily administration of ganciclovir and Valcyte for one week is:

| Parameter | Ganciclovir (5 mg/kg, i.v.) n = 18 | Valcyte (900 mg valganciclovir, p.o.) n = 25 | |
|---|---|---|---|
| | | Ganciclovir | Valganciclovir |
| $AUC_{(0-12)}$ (µg·h/ml) | 28.6 ± 9.0 | 32.8 ± 10.1 | 0.37 ± 0.22 |
| $C_{max}$ (µg/ml) | 10.4 ± 4.9 | 6.7 ± 2.1 | 0.18 ± 0.06 |

The efficacy of ganciclovir in increasing the time to progression of CMV retinitis has been shown to correlate with systemic exposure (AUC).

*Valganciclovir in organ transplant recipients*

Steady-state systemic exposure of solid organ transplant recipients to ganciclovir after daily oral administration of ganciclovir and valganciclovir is:

| Parameter | Ganciclovir (1000 mg 3 times daily) n = 82 | Valcyte (900 mg valganciclovir once daily) n = 161 |
|---|---|---|
| | | Ganciclovir |
| $AUC_{(0-24)}$ (µg·h/ml) | 28.0 ± 10.9 | 46.3 ± 15.2 |
| $C_{max}$ (µg/ml) | 1.4 ± 0.5 | 5.3 ± 1.5 |

The systemic exposure of heart, kidney and liver transplant recipients to ganciclovir was the same after oral administration of valganciclovir in accordance with the renal function dosing algorithm.

**Distribution**

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of Valcyte was not determined. Plasma protein binding of ganciclovir was 1–2% at concentrations of 0.5 and 51 µg/ml. The steady-state volume of distribution of ganciclovir after intravenous administration was 0.680 ± 0.161 l/kg.

**Metabolism**

Valganciclovir is rapidly hydrolysed to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabelled ganciclovir (1000 mg single dose) accounted for more than 1–2% of the radioactivity recovered in the feces or urine.

**Elimination**

The major route of elimination of valganciclovir after Valcyte administration is renal excretion as ganciclovir by glomerular filtration and active tubular secretion. Typically, renal clearance (2.23 ml/min/kg) accounts for approximately 75% of ganciclovir's systemic clearance (3.00 ml/min/kg).

**Pharmacokinetics in special patient populations**

Renal failure

Renal impairment was accompanied by decreased clearance of ganciclovir from valganciclovir, with a corresponding increase in terminal half-life.

| Creatinine clearance (ml/min) | Number of subjects | AUC$_{(0-\infty)}$ (µg·h/ml) | $C_{max}$ (µg/ml) | $T_{½}$ (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 |

Dose adjustment is, therefore, required in patients with impaired renal function (see *Dosage and Administration* and *Warnings and Precautions*).

*Dialysis patients*

No dosage recommendation can be given for dialysis patients ($Cl_{Cr}$ < 10 ml/min), since the individual dose of Valcyte required for these patients corresponds to a strength of less than 450 mg/film-coated tablet. Therefore, Valcyte should not be used in these 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 cross-over study (n = 28). The absolute bioavailability of ganciclovir from valganciclovir after a single 900 mg dose of valganciclovir, taken with a meal, was approximately 60%, which accords with estimates obtained in other patient populations. Ganciclovir $AUC_{0–24}$ was comparable to that achieved with 5 mg/kg of intravenous ganciclovir in liver transplant recipients.

# PRECLINICAL DATA

Valganciclovir is a prodrug of ganciclovir, therefore effects observed with ganciclovir can be expected to occur with valganciclovir. The toxicity of valganciclovir observed in preclinical studies corresponded to that of ganciclovir and was precipitated by ganciclovir concentrations corresponding to or less than the induction dose administered in humans.

These findings were gonadotoxicity (testicular cell loss) and nephrotoxicity (uremia, cell degeneration), which were irreversible, and myelotoxicity (anemia, neutropenia, lymphocytopenia) and gastrointestinal toxicity (mucosal cell necrosis), which were reversible.

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

# SPECIAL REMARKS

**Instructions for handling and disposal**

The film-coated tablets must not be broken or crushed. Since Valcyte is potentially teratogenic and carcinogenic in man, broken tablets must be handled with care (see *Warnings and Precautions*). Direct contact of broken or crushed tablets with skin or mucous membranes or inhalation of powder components must be avoided. If such contact occurs, wash thoroughly with soap and water and rinse eyes thoroughly with plain water only.

Any medicinal product remaining unused after the end of treatment or by the expiry date should be properly disposed of.

**Stability**

This medicine should not be used after the expiry date (EXP) shown on the pack

# PACKS

Film-coated tablets 450 mg 60

**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.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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