Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valcyte 50 mg/ml powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 5.5 g valganciclovir hydrochloride per 12 g powder for oral solution.
Each ml of the reconstituted solution contains 50 mg valganciclovir (as hydrochloride).

Excipients with known effect:
This medicinal product contains 1mg/ml of sodium benzoate and a total of 0.188 mg/ml sodium (as sodium benzoate and saccharin sodium) after reconstitution (essentially 'sodium-free'). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.

The powder is a granulate with a white to slightly yellow colour.
When the powder is dissolved, it forms a clear, colourless to brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Valcyte is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS).

Valcyte is indicated for the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.

4.2 Posology and method of administration

Posology

Caution – Strict adherence to dosage recommendations is essential to avoid overdose (see sections 4.4 and 4.9).

Valganciclovir is rapidly and extensively metabolised to ganciclovir after oral dosing. Oral valganciclovir 900 mg taken twice daily is therapeutically equivalent to intravenous ganciclovir 5 mg/kg taken twice daily. The ganciclovir systemic exposure following administration of 900 mg valganciclovir oral solution is equivalent to valganciclovir 900 mg tablets.

Treatment of cytomegalovirus (CMV) retinitis

Adult patients
Induction treatment of CMV retinitis
For patients with active CMV retinitis, the recommended dose is 900 mg valganciclovir twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section 4.4).

Maintenance treatment of CMV retinitis
Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg valganciclovir once daily. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

The duration of maintenance treatment should be determined on an individual basis.

Paediatric population
The safety and efficacy of Valcyte in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in paediatric patients.

Prevention of CMV disease in solid organ transplantation

Adult patients
For kidney transplant patients, the recommended dose is 900 mg once daily, starting within 10 days post-transplantation and continuing until 100 days post transplantation. Prophylaxis may be continued until 200 days post-transplantation (see sections 4.4, 4.8 and 5.1).

For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg once daily, starting within 10 days post-transplantation and continuing until 100 days post-transplantation.

Paediatric population
In paediatric solid organ transplant patients, aged from birth, who are at risk of developing CMV disease, the recommended once daily dose of Valcyte is based on body surface area (BSA) and creatinine clearance (Clcr) derived from Schwartz formula (ClcrS), and is calculated using the equation below:
Paediatric Dose (mg) = 7 x BSA x ClcrS (see Mosteller BSA formula and Schwartz Creatinine Clearance formula below).
If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation:

where k = 0.45* for patients aged < 2 years, 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years. Refer to adult dosing for patients older than 16 years of age.
The k values provided are based on the Jaffe method of measuring serum creatinine and may require correction when enzymatic methods are used.

*For appropriate sub-populations a lowering of k value may also be necessary (e.g. in paediatric patients with low birth weight).

For paediatric kidney transplant patients, the recommended once daily mg dose (7 x BSA x ClcrS) should start within 10 days post-transplantation and continue until 200 days post-transplantation.

For paediatric patients who have received a solid organ transplant other than kidney, **the recommended once daily mg dose (7x BSA x ClcrS)** should start within 10 days post-transplantation and continue until 100 days post-transplantation.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. The oral dispenser is graduated in ml. A 50 mg dose is equivalent to 1 ml:

valganciclovir dose	Valcyte for Oral Solution to be administered
50 mg	1 ml
75 mg	1.5 ml
100 mg	2 ml
500 mg	10 ml

If the calculated dose exceeds 900 mg (2 x 9 ml), a maximum dose of 900 mg (2 x 9 ml) should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte film-coated tablets may be used if the calculated doses are within 10% of available tablet doses, and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

It is recommended to monitor serum creatinine levels regularly and consider changes in height and body weight and adapt the dose as appropriate during the prophylaxis period.
Special dosage instructions

Paediatric population

Dosing of paediatric SOT patients is individualised based on a patient's renal function, together with body surface area.

Elderly patients
Safety and efficacy have not been established in this patient population. No studies have been conducted in adults older than 65 years of age. Since renal clearance decreases with age, Valcyte should be administered to elderly patients with special consideration of their renal status (see table below).

Patients with renal impairment
Serum creatinine levels or estimated creatinine clearance should be monitored carefully.Dosage adjustment is required according to creatinine clearance, as shown in the Table below (see sections 4.4 and 5.2).

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

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 ´ male value.

Clcr (ml/min)	Induction dose of valganciclovir	Maintenance/Prevention dose of valganciclovir
³ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	225 mg once daily
10 – 24	225 mg once daily	125 mg once daily
<10	200 mg three times a week after dialysis	100 mg three times a week after dialysis

Dosage for patients with renal impairment:

valganciclovir dose	Valcyte for Oral Solution to be administered
125 mg	2.5 ml
225 mg	4.5 ml
450 mg	9 ml

Patients undergoing haemodialysis:
Dosage adjustment is necessary for patients on haemodialysis (Clcr <10ml/min) (see sections 4.4 and 5.2) and a dosing recommendation is given in the Table above.

Patients with hepatic impairment
Safety and efficacy of Valcyte have not been established in patients with hepatic impairment (see section 5.2).

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia:
See section 4.4before initiation of therapy. If there is a significant deterioration of blood cell counts during therapy with Valcyte, treatment with haematopoietic growth factors and/or dose interruption should be considered (see section 4.4).

Method of administration

Valcyte is administered orally, and whenever possible, should be taken with food (see section 5.2).

Precautions to be taken before handling or administering the medicinal product
Valcyte powder for oral solution requires reconstitution prior to oral administration. Two oral dosing dispensers that are graduated to 10 ml (500 mg), with 0.5 ml (25 mg) graduations are provided. It is recommended that patients use the dispenser.

The maximum duration of use for one dispenser is specified for 20 applications. For instructions on reconstitution of the medicinal product before administration, see sections 4.4 and 6.6.

4.3 Contraindications

Valcyte is contraindicated in patients with hypersensitivity to valganciclovir, ganciclovir or to any of the excipients listed in section 6.1.

Valcyte is contraindicated during breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Cross-hypersensitivity
Due to the similarity of the chemical structure of ganciclovir and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these drugs is possible. Caution should therefore be used when prescribing Valcyte to patients with known hypersensitivity to aciclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively).

Precautions to be taken before handling
Owing to the teratogenic character, the Valcyte powder and reconstituted solution should be handled with caution. Inhalation should be avoided. If the powder or solution make direct contact with skin, the area should be washed thoroughly with soap and water. If the solution gets into the eye, the eye should be thoroughly washed with water immediately (see section 6.6).

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception
Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies, ganciclovir was found to be mutagenic, teratogenic, carcinogenic, and a suppressor of fertility. Valcyte should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 5.3). Based on clinical and nonclinical studies it is also considered likely that Valcyte causes temporary or permanent inhibition of spermatogenesis. Women of child bearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy (see sections 4.6, 4.8 and 5.3).

Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long term.

Myelosuppression
Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anaemia have been observed in patients treated with Valcyte (and ganciclovir). 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 (see sections 4.2 and 4.8).

When extending prophylaxis beyond 100 days the possible risk of developing leukopenia and neutropenia should be taken into account (see sections 4.2, 4.8 and 5.1).

Valcyte should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood counts and platelet counts should be monitored regularly during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and paediatrics, at a minimum each time the patient attends the transplant clinic. In patients developing severe leukopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see sections 4.2 and 4.8).

Renal impairment
In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections 4.2 and 5.2).

Use with other medicines

Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. Valcyte should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section 4.5).

Patients treated with Valcyte and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5).

The controlled clinical study using valganciclovir for the prophylactic treatment of CMV disease in transplantation, as detailed in section 5.1, did not include lung and intestinal transplant patients. Therefore, experience in these transplant patients is limited.

Controlled diet
For patients on a sodium-controlled diet, this medicinal product contains a total of 0.188 mg/ml sodium (essentially 'sodium-free').

Benzoic acid and benzoates (sodium benzoate)
This medicine contains 100mg of sodium benzoate in each 12g bottle, which is equivalent to 1mg/ml after reconstitution. Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions with valganciclovir

In-vivo drug interaction studies with Valcyte have not been performed. Since valganciclovir is extensively and rapidly metabolised to ganciclovir; drug interactions associated with ganciclovir will be expected for valganciclovir.

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

Didanosine
Didanosine plasma concentrations were found to be consistently raised when given with IV ganciclovir. At intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67% has been observed, confirming a pharmacokinetic interaction during the concomitant administration of these drugs.There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity e.g pancreatitis (see section 4.4)

Other antiretrovirals
Cytochrome P450 isoenzymes play no role in ganciclovir pharmacokinetics. As a consequence, pharmacokinetic interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are not anticipated.

Pharmacodynamic interactions
Imipenem-cilastatin
Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantlyand a pharmacodynamic interaction between these two drugs cannot be discounted. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

Zidovudine
Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these drugs. Some patients may not tolerate concomitant therapy at full dosage (see section 4.4).

Potential drug interactions
Toxicity may be enhanced when ganciclovir/valganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment. This includes nucleoside (e.g. zidovudine, didanosine, stavudine) and nucleotide

analogues (e.g. tenofovir, adefovir), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and anti-infective agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these drugs should only be considered for concomitant use with valganciclovir if the potential benefits outweigh the potential risks (see section 4.4).

4.6 Fertility, pregnancy and lactation

Contraception in males and females
As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir unless it is certain that the female partner is not at risk of pregnancy (see sections 4.4 and 5.3).

Pregnancy
The safety of Valcyte for use in pregnant women has not been established. 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 section 5.3) there is a theoretical risk of teratogenicity in humans.

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

Breast-feeding
It is unknown if ganciclovir is excreted in human breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Animal data indicate that ganciclovir is excreted in the milk of lactating rats Therefore, breast-feeding must be discontinued during treatment with valganciclovir (see sections 4.3 and 5.3).

Fertility
A small clinical study with renal transplant patients receiving Valcyte for CMV prophylaxis for up to 200 days demonstrated an impact of valganciclovir on spermatogenesis, with decreased sperm density and motility measured after treatment completion. This effect appears to be reversible and approximately six months after Valcyte discontinuation, mean sperm density and motility recovered to levels comparable to those observed in the untreated controls.

In animal studies, ganciclovir impaired fertility in male and female mice and has shown to inhibit spermatogenesis and induce testicular atrophy in mice, rats and dogs at doses considered clinically relevant.

Based on clinical and nonclinical studies, it is considered likely that ganciclovir (and valganciclovir) may cause temporary or permanent inhibition of human spermatogenesis (see sections 4.4 and 5.3).

4.7 Effects on ability to drive and use machines

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

Adverse reactions such as seizures, dizziness and confusion have been reported with the use of Valcyte and/or ganciclovir. If they occur, such effects may affect the patient's ability to drive and operate machinery.

4.8 Undesirable effects

a Summary of the safety profile

Valganciclovir is a prodrug of ganciclovir, which is rapidly and extensively metabolised to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir use can be expected to occur with valganciclovir. All of the adverse drug reactions observed in valganciclovir clinical studies have been previously observed with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (formulation no longer available) or with valganciclovir are included in the table of adverse drug reactions below.

In patients treated with valganciclovir/ganciclovir the most serious and frequent adverse drug reactions are haematological reactions and include neutropenia, anaemia and thrombocytopenia – see section 4.4.

The frequencies presented in the table of adverse reactions are derived from a pooled population of patients (n=1704) receiving maintenance therapy with ganciclovir or valganciclovir. Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia, the frequencies of which are derived from post-marketing experience. Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC <500/ µL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

b Tabulated list of adverse drug reactions

ADR (MedDRA) System Organ Class	**Frequency Category**
Infections and infestations:	
Candida infections including oral candidiasis.	Very common
Upper respiratory tract infection	
Sepsis	Common
Influenza	
Urinary tract infection	
Cellulitis	
Blood and lymphatic disorders:	
Neutropenia	Very common
Anaemia	
Thrombocytopenia	Common
Leukopenia	
Pancytopenia	
Bone marrow failure	Uncommon
Aplastic anaemia	Rare
Agranulocytosis*	
Granulocytopenia*	
Immune system disorders:	
Hypersensitivity	Common
Anaphylactic reaction*	Rare
Metabolic and nutrition disorders:	
Decreased appetite	Very common
Weight decreased	Common
Psychiatric disorders:	
Depression	Common
Confusional state	
Anxiety	
Agitation	Uncommon
Psychotic disorder	
Thinking abnormal	
Hallucinations	
Nervous system disorders:	
Headache	Very common
Insomnia	Common
Neuropathy peripheral	
Dizziness	

Paraesthesia	
Hypoaesthesia	
Seizure	
Dysgeusia (taste disturbance)	
Tremor	Uncommon
Eye disorders:	
Visual impairment	Common
Retinal detachment**	
Vitreous floaters	
Eye pain	
Conjunctivitis	
Macular oedema	
Ear and labyrinth disorders:	
Ear pain	Common
Deafness	Uncommon
Cardiac disorders*:*	
Arrhythmias	Uncommon
Vascular disorders*:*	
Hypotension	Common
Respiratory, thoracic and mediastinal disorders:	
Cough	Very common
Dyspnoea	
Gastrointestinal disorders:	
Diarrhoea	Very common
Nausea	
Vomiting	
Abdominal pain	
Dyspepsia	Common
Flatulence	
Abdominal pain upper	
Constipation	
Mouth ulceration	
Dysphagia	
Abdominal distention	
Pancreatitis	
Hepato-biliary disorders:	
Blood alkaline phosphatase increased	Common
Hepatic function abnormal	
Aspartate aminotransferase increased	
Alanine aminotransferase increased	
Skin and subcutaneous tissues disorders:	
Dermatitis	Very common
Night sweats	Common
Pruritus	
Rash	
Alopecia	
Dry skin	Uncommon
Urticaria	
Musculo-skeletal and connective tissue disorders:	
Back pain	Common
Myalgia	
Arthralgia	
Muscle spasms	
Renal and urinary disorders:	
Renal impairment	Common

Creatinine clearance renal decreased	
Blood creatinine increased	
Renal failure	Uncommon
Haematuria	
Reproductive system and breast disorders:	
Infertility male	Uncommon
General disorders and administration site conditions:	
Pyrexia	Very common
Fatigue	
Pain	Common
Chills	
Malaise	
Asthenia	
Chest pain	Uncommon

**The frequencies of these adverse reactions are derived from post-marketing experience*
***Retinal detachment has only been reported in HIV patients treated for CMV retinitis*

Description of selected adverse reactions
Neutropenia
The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalises within 2 to 5 days after discontinuation of the drug or dose reduction (see section 4.4).

Thrombocytopenia
Patients with low baseline platelet counts (< 100,000 /µL) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with AIDS (see section 4.4). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Influence of treatment duration or indication on adverse reactions
Severe neutropenia (ANC <500/µL) is seen more frequently in CMV retinitis patients (14%) undergoing treatment with valganciclovir, intravenous or oral ganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia was 10%.

There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both valganciclovir and oral ganciclovir when compared to CMV retinitis patients. However, impaired renal function is a feature common in solid organ transplantation patients.

The overall safety profile of Valcyte did not change with the extension of prophylaxis up to 200 days in high risk kidney transplant patients. Leukopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia were similar in both arms.

c Paediatric population

Valcyte has been studied in 179 paediatric solid organ transplant patients who were at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days.

The most frequently reported adverse reactions on treatment in paediatric clinical trials were diarrhoea, nausea, neutropenia, leukopenia and anaemia.
In solid organ transplant patients, the overall safety profile was similar in paediatric patients as compared to adults. Neutropenia was reported with slightly higher incidence in the two studies conducted in paediatric solid organ transplant patients as compared to adults, but there was no correlation between neutropenia and infectious adverse events in the paediatric population. A higher risk of cytopenias in neonates and infants warrants careful monitoring of blood counts in these age groups (see section 4.4).

In kidney transplant paediatric patients, prolongation of valganciclovir exposure up to 200 days was not associated with an overall increase in the incidence of adverse events. The incidence of severe neutropenia (ANC < 500/µL) was higher in paediatric kidney patients treated until Day 200 as compared to paediatric patients treated until Day 100 and as compared to adult kidney transplant patients treated until Day 100 or Day 200 (see section 4.4).

Only limited data are available in neonates or infants with symptomatic congenital CMV infection treated with Valcyte, however the safety appears to be consistent with the known safety profile of valganciclovir/ganciclovir.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose experience with valganciclovir and intravenous ganciclovir
It is expected that an overdose of valganciclovir could possibly result in increased renal toxicity (see section 4.2 and section 4.4).

Reports of overdoses with intravenous ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

Haematological toxicity: myelosuppression includingpancytopenia,bone marrow failure, leukopenia, neutropenia, granulocytopenia.

– *Hepatotoxicity*: hepatitis, liver function disorder
– *Renal toxicity*: worsening of haematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine
– *Gastrointestinal toxicity*: abdominal pain, diarrhoea, vomiting
– *Neurotoxicity:* generalised tremor, seizure

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05A B14

Mechanism of action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and inhibits replication of herpes viruses *in vitro* and *in vivo*. 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 (HBV).

In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. Triphosphate metabolism has been shown to occur in HSV- and HCMV- infected cells with half-lives of 18 and between 6 and 24 hours respectively, after the 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: (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, further viral DNA elongation.

Antiviral Activity

The *in-vitro* anti-viral activity, measured as IC_{50} of ganciclovir against CMV, is in the range of 0.08 micromoles (0.02 microgram/ml) to 14 micromoles (3.5 microgram/ml).

The clinical antiviral effect of Valcyte has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis. 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 and safety

Adult patients

Treatment of CMV retinitis:
Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either Valcyte 900 mg (twice daily) or intravenous ganciclovir 5 mg/kg (twice daily). The proportion of patients with photographic progression of CMV retinitis at week 4 was comparable in both treatment groups, 7/70 and 7/71 patients progressing in the intravenous ganciclovir and valganciclovir arms respectively.

Following induction treatment dosing, all patients in this study received maintenance treatment with Valcyte given at the dose of 900 mg once daily. The mean (median) time from randomisation to progression of CMV retinitis in the group receiving induction and maintenance treatment with Valcyte was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with Valcyte was 219 (125) days.

Prevention of CMV disease in transplantation
A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver and kidney transplant patients (lung and gastro-intestinal transplant patients were not included in the study) at high-risk of CMV disease (D+/R-) who received either Valcyte (900 mg once daily) or oral ganciclovir (1000 mg three times daily) starting within 10 days of transplantation 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). The large majority of cases occurred following cessation of prophylaxis (post-Day 100) with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm. 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, with the incidence of graft loss being equivalent, occurring in 0.8% of patients, in each arm.

A double-blind, placebo controlled study has been conducted in 326 kidney transplant patients at high risk of CMV disease (D+/R-) to assess the efficacy and safety of extending Valcyte CMV prophylaxis from 100 to 200 days post-transplant. Patients were randomized (1:1) to receive Valcyte tablets (900 mg od) within 10 days of transplantation either until Day 200 post-transplant or until Day 100 post-transplant followed by 100 days of placebo.

The proportion of patients who developed CMV disease during the first 12 months post-transplant is shown in the table below.

Percentage of Kidney Transplant Patients with CMV Disease[1], 12 Month ITT Population [A]

	Valganciclovir 900 mg od 100 Days N = 163	**Valganciclovir 900 mg od 200 Days N = 155**	**Between Treatment Group Difference**
Patients with confirmed or assumed CMV disease[2]	71 (43.6%) [35.8% ; 51.5%]	36 (23.2%) [16.8% ; 30.7%]	20.3% [9.9% ; 30.8%]
Patients with confirmed CMV disease	60 (36.8%) [29.4% ; 44.7%]	25 (16.1%) [10.7% ; 22.9%]	20.7% [10.9% ; 30.4%]

[1] CMV Disease is defined as either CMV syndrome or tissue invasive CMV. [2] Confirmed CMV is a clinically confirmed case of CMV disease. Patients were assumed to have CMV disease if there was no week 52 assessment and no confirmation of CMV disease before this time point.
[A] The results found up to 24 months were in line with the up to 12 month results: Confirmed or assumed CMV disease was 48.5% in the 100 days treatment arm versus 34.2% in the 200 days treatment arm; difference between the treatment groups was 14.3% [3.2 %; 25.3%].

Significantly less high risk kidney transplant patients developed CMV disease following CMV prophylaxis with Valcyte until Day 200 post-transplant compared to patients who received CMV prophylaxis with Valcyte until Day 100 post-transplant.

The graft survival rate as well as the incidence of biopsy proven acute rejection was similar in both treatment groups. The graft survival rate at 12 months post-transplant was 98.2% (160/163) for the 100 day dosing regimen and 98.1% (152/155) for the 200 day dosing regimen. Up to 24 month post-transplant, four additional cases of graft loss were reported, all in the 100 days dosing group. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100 day dosing regimen and 11.0% (17/155) for the 200 day dosing regimen. Up to 24 month post-transplant, one additional case has been reported in the 200 days dosing group.

Viral Resistance
Virus resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or the viral polymerase gene (UL54). In clinical isolates, seven canonical UL97 substitutions, M460V/I, H520Q, C592G, A594V, L595S, C603W are the most frequently reported ganciclovir resistance-associated substitutions. Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas viruses with mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target the viral polymerase.

Treatment of CMV retinitis:
Genotypic analysis of CMV in polymorphonuclear leucocytes (PMNL) isolates from 148 patients with CMV retinitis enrolled in one clinical study has shown that 2.2%, 6.5%, 12.8%, and 15.3% contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment.

Prevention of CMV disease in transplantation:
Active comparator study
Resistance was studied by genotypic analysis of CMV in PMNL samples collected i) on Day 100 (end of study drug prophylaxis) and ii) 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 on the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which two resistance mutations were observed, giving an incidence of resistance of 6.9%.

Extending prophylaxis study from 100 to 200 days post-transplant
Genotypic analysis was performed on the UL54 and UL97 genes derived from virus extracted from 72 patients who met the resistance analysis criteria: patients who experienced a positive viral load (>600 copies/ml) at the end of prophylaxis and/or patients who had confirmed CMV disease up to 12 months (52 weeks) post-transplant. Three patients in each treatment group had a known ganciclovir resistance mutation.

Paediatric population

Treatment of CMV retinitis:
The European Medicines Agency has waived the obligation to perform studies with Valcytein all subsets of the paediatric population inthe treatment of infection due to CMV in immuno-compromised patients (see section 4.2 for information on paediatric use).

Prevention of CMV disease in transplantation

A phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) receiving valganciclovir once daily for up to 100 days according to the paediatric dosing algorithm (see section 4.2) produced exposures similar to that in adults (see section 5.2). Follow up after treatment was 12 weeks. CMV D/R serology status at baseline was D+/R- in 40%, D+/R+ in 38%, D-/R+ in 19% and D-/R- in 3% of the cases. Presence of CMV virus was reported in 7 patients. The observed adverse drug reactions were of similar nature as those in adults (see section 4.8).

A phase IV tolerability study in paediatric kidney transplant recipients (aged 1 to 16 years, n=57) receiving valganciclovir once daily for up to 200 days according to the dosing algorithm (see section 4.2) resulted in a low incidence of CMV. Follow up after treatment was 24 weeks. CMV D/R serology status at baseline was D+/R+ in 45%, D+/R- in 39%, D-/R+ in 7%, D-/R- in 7% and ND/R+ in 2% of the cases. CMV viremia was reported in 3 patients and a case of CMV syndrome was suspected in one patient but not confirmed by CMV PCR by the central laboratory. The observed adverse drug reactions were of similar nature to those in adults (see section 4.8).

These data support the extrapolation of efficacy data from adults to children and provide posology recommendations for paediatric patients.

A phase I pharmacokinetic and safety study in heart transplant patients (aged 3 weeks to 125 days, n=14) who received a single daily dose of valganciclovir according to the paediatric dosing algorithm (see section 4.2) on 2 consecutive days produced exposures similar to those in adults (see section 5.2). Follow up after treatment was 7 days. The safety profile was consistent with other paediatric and adult studies, although patient numbers and valganciclovir exposure were limited in this study.

Congenital CMV
The efficacy and safety of ganciclovir and/or valganciclovir was studied in neonates and infants with congenital symptomatic CMV infection in two studies.

In the first study, the pharmacokinetics and safety of a single dose of valganciclovir (dose range 14-16-20 mg/kg/dose) was studied in 24 neonates (aged 8to 34 days) with symptomatic congenital CMV disease (see section 5.2). The neonates received 6 weeks of antiviral treatment, whereas 19 of the 24 patients received up to 4 weeks of treatment with oral valganciclovir, in the remaining 2 weeks they received i.v. ganciclovir. The 5 remaining patients received i.v. ganciclovir for most of the study period. In the second study the efficacy and safety of six weeks versus six months of valganciclovir treatment was studied in 109 infants aged 2- to 30 days with symptomatic congenital CMV disease. All infants received oral valganciclovir at a dose of 16 mg/kg b.i.d. for 6 weeks. After 6 weeks of treatment the infants were randomized 1:1 to continue treatment with valganciclovir at the same dose or receive a matched placebo to complete 6 months of treatment.

This treatment indication is not currently recommended for valganciclovir. The design of the studies and results obtained are too limited to allow appropriate efficacy and safety conclusions on valganciclovir.

5.2 Pharmacokinetic properties

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

Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir in the dose range 450 to 2625 mg was demonstrated only under fed conditions.

<u>Absorption</u>
Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolised in the intestinal wall and liver to ganciclovir. Systemic exposure to valganciclovir is transient and low. The bioavailability of ganciclovir from oral dosing of valganciclovir is approximately 60% across all the patient populations studied and the resultant exposure to ganciclovir is similar to that after its intravenous administration (please see below).

Valganciclovir in HIV positive, CMV positive patients:
Systemic exposure of HIV positive, CMV positive patients after twice daily administration of ganciclovir and valganciclovir for one week is:

Parameter	Ganciclovir (5 mg/kg, IV)	Valganciclovir (900 mg, p.o.) n = 25	

	n = 18		
		Ganciclovir	Valganciclovir
$AUC_{(0 - 12 h)}$ (microgram.h/ml)	28.6 ± 9.0	32.8 ± 10.1	0.37 ± 0.22
C_{max} (microgram/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 solid organ transplant patients:
Steady state systemic exposure of solid organ transplant patients to ganciclovir after daily oral administration of ganciclovir and valganciclovir is:

Parameter	Ganciclovir (1000 mg three times daily) n = 82	Valganciclovir (900 mg, once daily) n = 161
		Ganciclovir
$AUC_{(0 - 24 h)}$ (microgram.h/ml)	28.0 ± 10.9	46.3 ± 15.2
C_{max} (microgram/ml)	1.4 ± 0.5	5.3 ± 1.5

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

Following the administration of valganciclovir as an oral solution, equivalent systemic ganciclovir exposures were obtained compared to the tablet formulation.

Food effect:
When valganciclovir was given with food at the recommended dose of 900 mg, higher values were seen in both mean ganciclovir AUC (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%) than in the fasting state. Also, the inter-individual variation in exposure of ganciclovir decreases when taking Valcyte with food. Valcyte has only been administered with food in clinical studies. Therefore, it is recommended that Valcyte be administered with food (see section 4.2).

Distribution:
Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. The steady state volume of distribution (V_d) of ganciclovir after intravenous administration was 0.680 ± 0.161 l/kg (n=114). For IV ganciclovir, the volume of distribution is correlated with body weight with values for the steady state volume of distribution ranging from 0.54-0.87 L/kg. Ganciclovir penetrates the cerebrospinal fluid. Binding to plasma proteins was 1%-2% over ganciclovir concentrations of 0.5 and 51 microgram/mL.

Biotransformation
Valganciclovir is rapidly and extensively metabolised to ganciclovir; no other metabolites have been detected. Ganciclovir itself is not metabolised to a significant extent.

Elimination
Following dosing with oral valganciclovir, the drug is rapidly hydrolysed to ganciclovir. Ganciclovir is eliminated from the systemic circulation by glomerular filtration and active tubular secretion.In patients with normal renal function greater than 90% of IV administered ganciclovir was recovered un-metabolized in the urine within 24 hours. In patients with normal renal function the post-peak plasma concentrations of ganciclovir after administration of valganciclovir decline with a half-life ranging from 0.4 h to 2.0 h.

Pharmacokinetics in special clinical situations

Paediatric population
In a phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) valganciclovir was given once daily for up to 100 days. Pharmacokinetic parameters were similar across organ type and age range and comparable with adults. Population pharmacokinetic modeling suggested that bioavailability was approximately 60%. Clearance was positively influenced by both body surface area and renal function.

In a phase I pharmacokinetic and safety study in paediatric heart transplant recipients (aged 3 weeks to 125 days, n = 14), valganciclovir was given once daily for two study days. Population pharmacokinetics estimated that mean bioavailability was 64%.

A comparison of the results from these two studies and the pharmacokinetic results from the adult population shows that ranges of AUC $_{0\text{-}24h}$ were very similar across all age groups, including adults. Mean values for $AUC_{0\text{-}24h}$ and C_{max} were also similar across the paediatric age groups < 12 years old, although there was a trend of decreasing mean values for $AUC_{0\text{-}24h}$ and C_{max} across the entire pediatric age range, which appeared to correlate with increasing age. This trend was more apparent for mean values of clearance and half-life ($t_{1/2}$); however this is to be expected as clearance is influenced by changes in weight, height and renal function associated with patient growth, as indicated by population pharmacokinetic modelling.

The following table summarizes the model-estimated $AUC_{0\text{-}24h}$ ranges for ganciclovir from these two studies, as well as mean and standard deviation values for $AUC_{0\text{-}24h,}$ C_{max}, CL and t ½ for the relevant paediatric age groups compared to adult data:

PK Parameter	**Adults***	**Paediatrics**			
	≥ 18 years (n=160)	**< 4 months (n = 14)**	**4 months - ≤ 2 years (n=17)**	**> 2 - < 12 years (n=21)**	**≥ 12 years – 16 years (n=25)**
$AUC_{0\text{-}24h}$ (microgram·h/ml)	46.3 ± 15.2	68.1 ± 19.8	64.3 ± 29.2	59.2 ± 15.1	50.3 ± 15.0
Range of $AUC_{0\text{-}24h}$	15.4 – 116.1	34 - 124	34 - 152	36 - 108	22 - 93
C_{max} (microgram/ml)	5.3 ± 1.5	10.5 ± 3.36	10.3 ± 3.3	9.4 ± 2.7	8.0 ± 2.4
Clearance (l/h)	12.7 ± 4.5	1.25 ± 0.473	2.5 ± 2.4	4.5 ± 2.9	6.4 ± 2.9
$t_{1/2}$ (h)	6.5 ± 1.4	1.97 ± 0.185	3.1 ±1.4	4.1 ± 1.3	5.5 ± 1.1

* Extracted from study report PV 16000

The once daily dose of Valcyte in both of the studies described above was based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and was calculated using the dosing algorithm presented in section 4.2.

Ganciclovir pharmacokinetics following valganciclovir administration were also evaluated in two studies in neonates and infants with symptomatic congenital CMV disease. In the first study 24 neonates aged 8 to 34 days received 6 mg/kg intravenous ganciclovir twice daily. Patients were then treated with oral valganciclovir, where the dose of valganciclovir powder for oral solution ranged from 14 mg/kg to 20 mg/kg twice daily; total treatment duration was 6 weeks. A dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided comparable ganciclovir exposure as 6 mg/kg intravenous ganciclovir twice daily in neonates, and also achieved ganciclovir exposure similar to the effective adult 5 mg/kg intravenous dose.

In the second study, 109 neonates aged 2 to 30 days received 16 mg/kg valganciclovir powder for oral solution twice daily for 6 weeks and subsequently 96 out of 109 enrolled patients were randomized to continue receiving valganciclovir or placebo for 6 months. However, the mean $AUC_{0\text{-}12h}$ was lower compared to the mean $AUC_{0\text{-}12h}$ values from the first study. The following table shows the mean values of AUC, C_{max}, and $t_{½}$ including standard deviations compared with adult data:

PK Parameter	Adults	Paediatrics (neonates and infants)		
	5 mg/kg GAN Single dose (n=8)	**6 mg/kg GAN Twice daily (n=19)**	**16 mg/kg VAL Twice daily (n=19)**	**16 mg/kg VAL Twice daily (n = 100)**
$AUC_{0\text{-}\infty}$ (microgram·h/mL)	25.4 ± 4.32	**-**	-	-
$AUC_{0\text{-}12h}$ (microgram·h/mL)	-	38.2 ± 42.7	30.1 ± 15.1	20.85 ± 5.40
C_{max} (microgram/ml)	9.03 ± 1.26	12.9 ± 21.5	5.44 ± 4. 04	-
$t_{1/2}$ (h)	3.32 ± 0.47	2.52 ± 0. 55	2.98 ± 1. 26	2.98 ± 1.12

GAN = Ganciclovir, i.v. VAL = Valganciclovir, oral

These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients with congenital CMV infection.

Elderly

No investigations on valganciclovir or ganciclovir pharmacokinetics in adults older than 65 years of age have been undertaken (see section 4.2).

Patients with renal impairment
The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir was evaluated in 24 otherwise healthy individuals with renal impairment.

Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg Valcyte tablets in patients with various degrees of renal impairment:

Estimated Creatinine Clearance (mL/min)	**N**	**Apparent Clearance (mL/min) Mean ± SD**	**AUClast (microgram·h/mL) Mean ± SD**	**Half-life (hours) Mean ± SD**
51-70	6	249 ± 99	49.5 ± 22.4	4.85 ± 1.4
21-50	6	136 ± 64	91.9 ± 43.9	10.2 ± 4.4
11-20	6	45 ± 11	223 ± 46	21.8 ± 5.2
£10	6	12.8 ± 8	366 ± 66	67.5 ± 34

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see sections 4.2and 4.4).

Patients undergoing haemodialysis
For patients receiving haemodialysis Valcyte powder for oral solution is recommended to provide an individualised dose (see sections 4.2 and 4.4).

Stable liver transplant patients
The pharmacokinetics of ganciclovir from valganciclovir in stable liver transplant patients were investigated in one open label 4-part crossover study (N=28). The bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60%. Ganciclovir $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant patients.

Patients with hepatic impairment
The safety and efficacy of Valcyte have not been studied in patients with hepatic impairment. Hepatic impairment should not significantly affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made.

Patients with cystic fibrosis
In a phase I pharmacokinetic study in lung transplant recipients with or without cystic fibrosis (CF), 31 patients (16 CF/15 non-CF) received post-transplant prophylaxis with 900 mg/day Valcyte. The study indicated that cystic fibrosis had no statistically significant influence on the overall average systemic exposure to ganciclovir in lung transplant recipients. Ganciclovir exposure in lung transplant recipients was comparable to that shown to be efficacious in the prevention of CMV disease in other solid organ transplant recipients.

5.3 Preclinical safety data

Valganciclovir is a pro-drug of ganciclovir and therefore effects observed with ganciclovir apply equally to valganciclovir. Toxicity of valganciclovir in pre-clinical safety studies was the same as that seen with ganciclovir and was induced at ganciclovir exposure levels comparable to, or lower than, those in humans given the induction dose.

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

Ganciclovir was mutagenic in mouse lymphoma cells and clastogenic in mammalian cells. Such results are consistent with the positive mouse carcinogenicity study with ganciclovir. Ganciclovir is a potential carcinogen.

Further studies have shown ganciclovir to be teratogenic, embryotoxic, to inhibit spermatogenesis (i.e. impair male fertility) and to suppress female fertility.

Animal data indicate that ganciclovir is excreted in the milk of lactating rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Fumaric acid
Sodium Benzoate (E211)
Sodium Saccharin
Mannitol

Tutti-frutti flavour:
Maltodextrins (maize)
Propylene Glycol
Arabic gum E414 and natural flavouring substances mainly consisting of banana, pineapple and peach flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder for oral solution: 3 years.
Reconstituted solution: 49 days. Store in a refrigerator (2°C - 8°C)

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Carton containing a 100 ml amber glass bottle with a child-resistant polypropylene screw cap with a polyethylene liner, a low density polyethylene bottle adapter and a plastic bag containing 2 polypropylene/polyethylene (barrel/plunger) oral dispensers graduated to 10 ml (500 mg), with graduations of 0.5 ml (25 mg).

Each bottle contains 12 g of powder for oral solution. When reconstituted, the volume of the solution is 100 ml, providing a minimal usable volume of 88 ml.

Pack size: one bottle containing 12g powder.

6.6 Special precautions for disposal and other handling

Since Valcyte is considered a potential teratogen and carcinogen in humans, caution should be observed in handling the powder and the reconstituted solution (see section 4.4). Avoid inhalation and direct contact of the powder and solution with skin and mucous membranes. If such contact occurs, wash thoroughly with soap and water. If the powder or solution gets into the eyes, rinse eyes thoroughly with water.

It is recommended that Valcyte powder for oral solution be reconstituted by the pharmacist prior to dispensing to the patient.

<u>Preparation of oral solution</u>
1. Measure 91 ml of water in a graduated cylinder.
2. Remove the child resistant cap, add the water to the bottle, then close the bottle with the child resistant cap. Shake the closed bottle until the powder is dissolved forming a clear, colourless to brown solution.
3. Remove the child resistant cap and push the bottle adapter into the neck of the bottle.
4. Close the bottle with the child resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child resistant status of the cap.

5. Write the date of expiration of the reconstituted solution on the bottle label (see section 6.3).

Wearing of disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle / cap and the table after reconstitution.

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

7 MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

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