Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valcyte 450mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 496.3 mg of valganciclovir hydrochloride equivalent to 450 mg of valganciclovir (as free base).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets

Product imported from Italy:
Pink, convex, oval film-coated tablets with “VGC” embossed on one side and “450” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Valcyte is indicated for the prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from CMV-positive donor.

4.2 Posology and method of administration

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 b.i.d. is therapeutically equivalent to intravenous ganciclovir 5 mg/kg b.i.d.

Standard dosage in adults

Induction treatment of CMV retinitis:
For patients with active CMV retinitis, the recommended dose is 900 mg valganciclovir (two Valcyte 450 mg tablets) twice a day for 21 days and, whenever possible, taken with food. 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 900mg valganciclovir (two Valcyte 450 mg tablets) once daily and, whenever possible, taken with food. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

Prevention of CMV disease in solid organ transplantation:

For kidney transplant patients, the recommended dose is 900 mg (two Valcyte 450 mg tablets) once daily, starting within 10 days of 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 (two Valcyte 450 mg tablets) once daily, starting within 10 days of transplantation and continuing until 100 days post−transplantation.

Whenever possible, the tablets should be taken with food.

Special dosage instructions

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

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

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

For females = 0.85 × male value

CrCl (mL/min)	Induction dose of valganciclovir	Maintenance/Prevention dose of valganciclovir
≥ 60	900 mg (2 tablets) twice daily	900 mg (2 tablets) once daily
40 – 59	450 mg (1 tablet) twice daily	450 mg (1 tablet) once daily
25 – 39	450 mg (1 tablet) once daily	450 mg (1 tablet) every 2 days
10 – 24	450 mg (1 tablet) every 2 days	450 mg (1 tablet) twice weekly
< 10	not recommended	not recommended

Patients undergoing haemodialysis:
For patients on haemodialysis (CrCl < 10 mL/min) a dose recommendation cannot be given. Thus Valcyte should not be used in these patients (see sections 4.4 and 5.2).

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

Paediatric patients:
The safety and efficacy of Valcyte in pediatric patients have not been established in adequate and well-controlled clinical studies. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly patients:
Safety and efficacy have not been established in this patient population.

Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia;
See section 4.4 before 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 sections 4.4 and 4.8).

Method of administration

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

The tablets should not be broken or crushed. Since Valcyte is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see section 4.4). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.

4.3 Contraindications

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

Due to the similarity of the chemical structure of Valcyte and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible. Therefore, Valcyte is contraindicated in patients with hypersensitivity to aciclovir and valaciclovir.
Valcyte is contraindicated during lactation, refer to section 4.6**.**

4.4 Special warnings and precautions for use

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, aspermatogenic and carcinogenic, and a suppressor of female 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). 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 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.

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression 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 8 g/dL (see sections 4.2 and 4.8).

When extending prophylaxis beyond 100 days the possible risk of developing leucopenia 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 be monitored during therapy. Increased haematological monitoring may be warranted in patients with renal impairment. In patients developing severe leucopenia, 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).

The bioavailability of ganciclovir after a single dose of 900 mg valganciclovir is approximately 60%, compared with approximately 6% after administration of 1000 mg oral ganciclovir (as capsules). Excessive exposure to ganciclovir may be associated with life-threatening adverse reactions. Therefore, careful adherence to the dose recommendations is advised when instituting therapy, when switching from induction to maintenance therapy, and in patients who may switch from oral ganciclovir to valganciclovir as Valcyte cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valcyte tablets (see sections 4.2 and 4.9).

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

Valcyte should not be used in patients on haemodialysis (see sections 4.2 and 5.2).

Convulsions 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.

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.

Effects of other medicinal products on ganciclovir
Imipenem-cilastatin
Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

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 Valcyte should be closely monitored for ganciclovir toxicity.

Effects of ganciclovir on other medicinal products
Zidovudine
When zidovudine was given in the presence of oral ganciclovir there was a small (17%), but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage (see section 4.4).

Didanosine
Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6 g/day, an increase in the AUC of didanosine ranging from 84 to 124% has been observed, and likewise 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. There was no clinically significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (see section 4.4).

Mycophenolate Mofetil
Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co-administration of these agents (which have the potential to compete for renal tubular secretion) will result in increases in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid (MPA) pharmacokinetics is anticipated and MMF dose adjustment is not required.

In patients with renal impairment to whom MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed and the patients monitored carefully. Since both MMF and ganciclovir have the potential to cause neutropenia and leucopenia, patients should be monitored for additive toxicity.

Zalcitabine
No clinically significant pharmacokinetic changes were observed after concomitant administration of ganciclovir and zalcitabine. Both valganciclovir and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events.

Stavudine
No clinically significant interactions were observed when stavudine and oral ganciclovir were given in combination.

Trimethoprim
No clinically significant pharmacokinetic interaction was observed when trimethoprim and oral ganciclovir were given in combination. However, there is a potential for toxicity to be enhanced since both drugs are known to be myelosuppressive and therefore both drugs should be used concomitantly only if the potential benefits outweigh the risks.

Other antiretrovirals
At clinically relevant concentrations, there is unlikely to be either a synergistic or antagonistic effect on the inhibition of either HIV in the presence of ganciclovir or CMV in the presence of a variety of antiretroviral drugs. Metabolic interactions with, for example, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are unlikely due to the lack of P450 involvement in the metabolism of either valganciclovir or ganciclovir.

Other potential drug interactions
Toxicity may be enhanced when valganciclovir is co-administered with, or is given immediately before or after, other drugs that inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, testes and germinal layers of the skin and gastrointestinal mucosa. Examples of these types of drugs are dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulpha combinations, nucleoside analogues and hydroxyurea.

Since ganciclovir is excreted through the kidney (section *5.2*), toxicity may also be enhanced during co-administration of valganciclovir with drugs that might reduce the renal clearance of ganciclovir and hence increase its exposure. 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.

Therefore, all of these drugs should be considered for concomitant use with valganciclovir only if the potential benefits outweigh the potential risks (see section 4.4).

4.6 Fertility, pregnancy and lactation

There are no data from 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 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 child.

Women of child-bearing potential must be advised to use effective contraception during treatment. Male patients must be advised to practise barrier 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 section 5.3).

It is unknown if ganciclovir is excreted in 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. Therefore, breast-feeding must be discontinued.

4.7 Effects on ability to drive and use machines

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

Convulsions, sedation, dizziness, ataxia, and/or confusion have been reported with the use of Valcyte and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness, including the patient's ability to drive and operate machinery.

4.8 Undesirable effects

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 undesirable effects observed with valganciclovir clinical studies have been previously observed with ganciclovir.

The most commonly reported adverse drug reactions following administration of valganciclovir are neutropenia, anaemia and diarrhoea**.**

Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. In addition, valganciclovir is associated with a higher risk of neutropenia and leucopenia compared to oral ganciclovir.

Severe neutropenia (< 500 ANC/μL) is seen more frequently in CMV retinitis patients undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir.

The frequency of adverse reactions reported in clinical trials with either valganciclovir, oral ganciclovir, or intravenous ganciclovir is presented in the table below. The adverse reactions listed were reported in clinical trials in patients with AIDS for the induction or maintenance treatment of CMV retinitis, or in liver, kidney or heart transplant patients for the prophylaxis of CMV disease . The term (severe) in parenthesis in the table indicates that the adverse reaction has been reported in patients at both mild/moderate intensity and severe/life-threatening intensity at that specific frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body System	**Very Common (≥1/10)**	**Common (≥1/100 <1/10)**	**Uncommon (≥1/1000 < 1/100)**	**Rare (≥1/10,000, < 1/1000)**
Infections and infestations		Oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection		
Blood and lymphatic system disorders	(severe) neutropenia, anaemia	Severe anaemia, (severe) thrombocytopenia, (severe) leucopenia, (severe) pancytopenia	Bone marrow failure	Aplastic anaemia
Immune system disorders			Anaphylactic reaction	
Metabolic and nutrition disorders		decreased appetite, anorexia		
Psychiatric disorders		Depression, anxiety, confusion, abnormal thinking	Agitation, psychotic disorder, hallucination	
Nervous system disorders		Headache, insomnia, dysgeusia, (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness, convulsion	tremor	
Eye disorders		Macular oedema, retinal detachment, vitreous floaters, eye pain	Visual disturbance, conjunctivitis	
Ear and labyrinth disorders		Ear pain	Deafness	
Cardiac disorders			Arrhythmia	
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Cough		
Gastrointestinal disorders	Diarrhoea	Nausea, vomiting, abdominal pain, abdominal pain upper, dyspepsia, constipation, flatulence, dysphagia	Abdominal distension, mouth ulceration, pancreatitis	
Hepato-biliary disorders		(severe) hepatic function abnormal, blood alkaline phosphatase increased, aspartate	Alanine aminotransferase increased	

		aminotransferase increased		
Skin and subcutaneous disorders		Dermatitis, night sweats, pruritis	Alopecia, urticaria, dry skin	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia, arthralgia, muscle spasms		
Renal and urinary disorder		Creatinine clearance renal decreased, renal impairment	Haematuria, renal failure	
Reproductive system and breast disorders			Male infertility	
General disorders and administration site conditions		Fatigue, pyrexia, chills, pain, chest pain, malaise, asthenia		
Investigations		Weight decreased, blood creatinine increased		

Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Paediatrics
There are very limited paediatric data on the exposure to valganciclovir (see also sections 5.1 and 5.2). The following is a summary of all adverse events which occurred in more than 10% (very common) of the total paediatric population on treatment:

Body System	**Very Common Adverse Events Reported in Clinical Trials**
Blood and lymphatic system disorders	Anemia, neutropenia
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, constipation
General disorders and administration site conditions	Pyrexia, transplant rejection

4.9 Overdose

Overdose experience with Valganciclovir
One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).

It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see sections 4.2 and 4.4).

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

Overdose experience with intravenous ganciclovir
Reports of overdoses with intravenous ganciclovir 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:* pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia.
- *Hepatotoxicity*: hepatitis, liver function disorder.
- *Renal toxicity*: worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine.
- *Gastrointestinal toxicity*: abdominal pain, diarrhoea, vomiting.
- *Neurotoxicity*: generalised tremor, convulsion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J05A B14 (anti-infectives for systemic use, antivirals for systemic use, direct acting antivirals).

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, HHV8), 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 μM (0.02 μg/mL) to 14 μM (3.5 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:
Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either Valcyte 900mg b.i.d or intravenous ganciclovir 5 mg/kg b.i.d. 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 900mg 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 od) or oral ganciclovir (1000 mg tid) 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). 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.

Paediatrics

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 a dosing algorithm 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 4.8). These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients.

The pharmacokinetics and safety of single dose valganciclovir (dose range 14-16-20 mg/kg/dose) was studied in 24 neonates (aged 8-34 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 the most time of the study period. This treatment indication is not recommended presently for valganciclovir. The design of the study and obtained results 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.

Absorption
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 absolute bioavailability of ganciclovir from 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). For comparison, the bioavailability of ganciclovir after administration of 1000mg oral ganciclovir (as capsules) is 6-8 %.

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

Parameter	Ganciclovir (5 mg/kg, i.v.) n = 18	Valganciclovir (900 mg, p.o.) n = 25	
		Ganciclovir	Valganciclovir
AUC (0-12 h) (μg.h/ml)	28.6 ± 9.0	32.8 ± 10.1	0.37 ± 0.22
Cmax (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 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 (1000mg tid) n = 82	Valganciclovir (900 mg, od) n = 161
		Ganciclovir
AUC (0-24 h) (μg.h/ml)	28.0 ± 10.9	46.3 ± 15.2
Cmax (μg/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.

Food effect:
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. 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 Cmax 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. Plasma protein binding of ganciclovir was 1-2 % over 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 (n=114).

Metabolism
Valganciclovir is rapidly and extensively metabolised 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 faeces or urine.

Elimination
Following dosing with Valcyte, renal excretion, as ganciclovir, by glomerular filtration and active tubular secretion is the major route of elimination of valganciclovir. Renal clearance accounts for 81.5% ±22 % (n=70) of the systemic clearance of ganciclovir. The half-life of ganciclovir from valganciclovir is 4.1 ± 0.9 hours in HIV- and CMV-seropositive patients.

Pharmacokinetics in special clinical situations

Patients with renal impairment
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 4.2 and 4.4).

Patients undergoing haemodialysis
For patients receiving haemodialysis dose recommendations for Valcyte 450mg film-coated tablets cannot be given. This is because an individual dose of Valcyte required for these patients is less than the 450 mg tablet strength. Thus, Valcyte should not be used in these patients (see sections 4.2 and 4.4).

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

Pediatric patients:
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. Pharmacokinetics 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. The mean total clearance was 5.3 L/hr (88.3 mL/min) for a patient with creatinine clearance of 70.4 mL/min. The following table shows the mean Cmax, t ½ and AUC values including standard deviations for the relevant paediatric age groups compared to adult data:

PK Parameter	**Adults***	**Pediatrics**		
	≥ 18 years (n=160)	**≤ 2 years (n=17)**	**> 2 - < 12 years (n=21)**	**≥ 12 years (n=25)**
AUC_{0-24h} (μg.h/mL)	46.3 ± 15.2	64.3 ± 29.2	59.2 ± 15.1	50.3 ± 15.0
C_{max} (μg/mL)	5.3 ± 1.5	10.3 ± 3.3	9.4 ± 2.7	8.0 ± 2.4
Clearance (L/h)	12.7 ± 4.5	2.5 ± 2.4	4.5 ± 2.9	6.4 ± 2.9
$t_{1/2}$ (h)	6.5 ± 1.4	3.1 ±1.4	4.1 ± 1.3	5.5 ± 1.1

* Extracted from study report PV 16000

The once daily dose of Valcyte was based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and was calculated using the equation below:

Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using the modified Schwartz formula) where

Mosteller BSA (m^2) = √ (Height in cm x Weight in kg) / 3600)

$$\text{Schwartz Creatinine Clearance (ml / min / 1.73m}^2) = \frac{\text{k x Height (cm)}}{\text{Serum Creatinine (mg / dl)}}$$

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.

The dose should not exceed the adult 900 mg dose. In addition, if the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m2, then a maximum value of 150 mL/min/1.73m2 should be used in the equation. It should be noted that the paediatric dosage algorithm was developed based on pharmacokinetic data only and has not been verified in efficacy and safety studies (see 5.1).

Ganciclovir pharmacokinetics were also evaluated in 24 neonates aged 8 to 34 days with symptomatic congenital CMV disease. All patients 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. 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. The following table shows the mean AUC, Cmax, and t ½ values including standard deviations compared adult data:

PK Parameter	**Adults**	**Neonates**	
	5 mg/kg GAN Single dose (n=8)	**6 mg/kg GAN Twice daily (n=19)**	**16 mg/kg VAL Twice daily (n=19)**
$AUC_{0-\infty}$ (mg.h/L)	25.4 ± 4.32	--	--
AUC_{12h} (mg.h/L)	--	38.2 ± 42.7	30.1 ± 15.1
Cmax (μg/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

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

The pharmacokinetic modeling suggested that the typical value of clearance (L/hr), volume of distribution (L), and bioavailability of ganciclovir in neonates were 0.146 x Weight1.68, 1.15 x Weight, and 54%, respectively. These data are too limited to allow conclusions regarding efficacy or posology recommendations for pediatric patients with congenital CMV infection.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K30
Crospovidone
Microcrystalline cellulose
Stearic acid
Hypromellose
Titanium dioxide (E171)
Macrogol 400

Red iron oxide (E172)
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer packaging of the product on the market in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bottle of 60 tablets with a child resistant cap in a cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Clear Pharmacy
157-173 Roden Street
Belfast BT12 5QA
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1596/055/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First date of authorisation: 30th September 2011

10 DATE OF REVISION OF THE TEXT

June 2012