SUMMARY OF PRODUCT CHARACTERISTICS

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VALCYTE®

1. NAME OF THE MEDICINAL PRODUCT

Valcyte 450mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see section *6.1*.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, convex oval film-coated tablet, 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 a CMV-positive donor.

4.2 Posology and method of administration

Caution – Strict adherence to dosage recommendations is essential to avoid overdose; see section *4.4 Special warnings and precautions for use* and section *4.9 Overdose*.

Valganciclovir is rapidly and extensively metabolised to ganciclovir after oral dosing. Oral valganciclovir 900mg b.i.d. is therapeutically equivalent to intravenous ganciclovir 5mg/kg b.i.d.

Standard dosage in adults

Induction treatment of CMV retinitis:
For patients with active CMV retinitis, the recommended dose is 900mg valganciclovir (two Valcyte 450mg 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 Special warnings and precautions for use*).

Maintenance treatment of CMV retinitis:
Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900mg valganciclovir (two Valcyte 450mg 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 patients who have received a transplant, the recommended dose is 900mg (two Valcyte 450mg 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 section *4.4 Special warnings and precautions for use* and section *5.2 Pharmacokinetic properties*).

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

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

$$\text{For females} = 0.85 \times \text{male value}$$

CrCl (mL/min)	Induction dose of valganciclovir	Maintenance/Prevention dose of valganciclovir
≥ 60	900mg (2 tablets) twice daily	900mg (2 tablets) once daily
40 – 59	450mg (1 tablet) twice daily	450mg (1 tablet) once daily
25 – 39	450mg (1 tablet) once daily	450mg (1 tablet) every 2 days
10 – 24	450mg (1 tablet) every 2 days	450mg (1 tablet) twice weekly

Patients undergoing haemodialysis*:*
For patients on haemodialysis (CrCl < 10mL/min) a dose recommendation cannot be given. Thus Valcyte should not be used in these patients (see section *4.4 Special warnings and precautions for use* and section *5.2 Pharmacokinetic properties*).

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

Paediatric patients:
Safety and efficacy have not been established in this patient population (see section *4.4 Special warnings and precautions for use* and section *5.3 Preclinical safety data*).

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 Special warnings and precautions for use* 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 section *4.4 Special warnings and precautions for use* and section *4.8 Undesirable effects*).

Method of administration
Valcyte is administered orally, and whenever possible, should be taken with food (see section *5.2 Pharmacokinetic properties, Absorption*).

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 Special warnings and precautions for use*). 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 contra-indicated 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 contra-indicated in patients with hypersensitivity to aciclovir and valaciclovir.

Valcyte is contra-indicated during lactation, refer to section *4.6 Pregnancy and lactation***.**

4.4 Special warnings and special 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 Preclinical safety data*). 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 section *4.6 Pregnancy and lactation*, section *4.8 Undesirable effects* and section *5.3 Preclinical safety data*).

The use of Valcyte in children and adolescents is not recommended because the pharmacokinetic characteristics of Valcyte have not been established in these patient populations (see section *4.2 Posology and method of administration*). Furthermore, 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 8g/dL (see section *4.2 Posology and method of administration* and section *4.8 Undesirable effects*).

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 section *4.2*

Posology and method of administration, Special dosage instructions and section *4.8 Undesirable effects*).

The bioavailability of ganciclovir after a single dose of 900mg valganciclovir is approximately 60%, compared with approximately 6% after administration of 1000mg 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 section *4.2 Posology and method of administration* and section *4.9 Overdose*).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see section *4.2 Posology and method of administration, Special dosage instructions* and section *5.2 Pharmacokinetic properties, Pharmacokinetics in special populations*).

Valcyte should not be used in patients on haemodialysis (see section 4.2 *Posology and method of administration, Special dosage instructions* and section 5.2 *Pharmacokinetic properties, Pharmacokinetics in special populations*).

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 Interaction with other medicinal products and other forms of interaction*).

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 Interaction with other medicinal products and other forms of interaction*).

The controlled clinical study using valganciclovir for the prophylactic treatment of CMV disease in transplantation, as detailed in section 5.1 *Pharmacodynamic properties, Clinical efficacy*, 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.

Drug interactions with 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 Special warnings and precautions for use*).

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.

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 Special warnings and precautions for use*).

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 6g/day, an increase in the AUC of didanosine ranging from 84 to 124% has been observed, and likewise at intravenous doses of 5 and 10mg/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 Special warnings and precautions for use*).

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 Special warnings and precautions for use*).

4.6 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 Preclinical safety data*) 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 Preclinical safety data*).

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 usage can be expected to occur with valganciclovir. All of the undesirable effects observed in 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**.**

The oral formulations, valganciclovir and ganciclovir, are 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 or oral ganciclovir.

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.

Infections and infestations:	
Common (≥ 1/100, < 1/10):	oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection.
Blood and lymphatic system disorders:	
Very common (≥ 1/10):	(severe) neutropenia, anaemia.
Common (≥ 1/100, < 1/10):	severe anaemia, (severe) thrombocytopenia, (severe) leucopenia, (severe) pancytopenia.
Uncommon (≥ 1/1000, < 1/100):	bone marrow depression.
Immune system disorders:	
Uncommon (≥ 1/1000, < 1/100):	anaphylactic reaction.
Metabolic and nutrition disorders:	
Common (≥ 1/100, < 1/10):	appetite decreased, anorexia.
Psychiatric disorders:	
Common (≥ 1/100, < 1/10):	depression, anxiety, confusion, abnormal thinking.
Uncommon (≥ 1/1000, < 1/100):	agitation, psychotic disorder.
Nervous system disorders:	
Common (≥ 1/100, < 1/10):	headache, insomnia, dysgeusia (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness (excluding vertigo), convulsions.
Uncommon (≥ 1/1000, < 1/100):	tremor.
Eye disorders:	
Common (≥ 1/100, < 1/10):	macular oedema, retinal detachment, vitreous floaters, eye pain.
Uncommon (≥ 1/1000, < 1/100):	vision abnormal, conjunctivitis.
Ear and labyrinth disorders:	
Common (≥ 1/100, < 1/10):	ear pain.
Uncommon (≥ 1/1000, < 1/100):	deafness.
Cardiac disorders:	
Uncommon (≥ 1/1000, < 1/100):	arrhythmias.
Vascular disorders:	
Uncommon (≥ 1/1000, < 1/100):	hypotension.
Respiratory, thoracic and mediastinal disorders:	
Very common (≥ 1/10):	dyspnoea.
Common (≥ 1/100, < 1/10):	cough.
Gastrointestinal disorders:	
Very common (≥ 1/10):	diarrhoea.
Common (≥ 1/100, < 1/10):	nausea, vomiting, abdominal pain, abdominal pain upper, dyspepsia, constipation, flatulence, dysphagia.
Uncommon (≥ 1/1000, < 1/100):	abdominal distention, mouth ulcerations, pancreatitis.

Hepato-biliary disorders:	
Common (≥ 1/100, < 1/10):	(severe) hepatic function abnormal, blood alkaline phosphatase increased, aspartate aminotransferase increased.
Uncommon (≥ 1/1000, < 1/100):	alanine aminotransferase increased.
Skin and subcutaneous disorders:	
Common (≥ 1/100, < 1/10):	dermatitis, night sweats, pruritus.
Uncommon (≥ 1/1000, < 1/100):	alopecia, urticaria, dry skin.
Musculoskeletal, connective tissue and bone disorders:	
Common (≥ 1/100, < 1/10):	back pain, myalgia, arthralgia, muscle cramps.
Renal and urinary disorders:	
Common (≥ 1/100, < 1/10):	creatinine clearance renal decreased, renal impairment.
Uncommon (≥ 1/1000, < 1/100):	haematuria, renal failure.
Reproductive system and breast disorders:	
Uncommon (≥ 1/1000, < 1/100):	male infertility.
General disorders and administration site conditions:	
Common (≥ 1/100, < 1/10):	fatigue, pyrexia, rigors, pain, chest pain, malaise, asthenia.
Investigations:	
Common (≥ 1/100, < 1/10):	weight decreased, blood creatinine increased.

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 section *4.2 Posology and method of administration* and section *4.4 Special warnings and precautions for use*).

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section *5.2 Pharmacokinetic properties, Patients undergoing haemodialysis*).

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 0.08μM (0.02μg/mL) to 14μM (3.5μg/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 5mg/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 (900mg od) or oral ganciclovir (1000mg 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.

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:
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%.

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 (5mg/kg, i.v.) n = 18	Valganciclovir (900mg, 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
C_{max} (μg/ml)	10.4 ± 4.9	6.7 ± 2.1	0.18 ± 0.06

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

Valganciclovir in 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 (900mg, od) n = 161
		Ganciclovir
AUC(0 - 24 h) (μg.h/ml)	28.0 ± 10.9	46.3 ± 15.2
C_{max} (μg/ml)	1.4 ± 0.5	5.3 ± 1.5

The systemic exposure of 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 2625mg was demonstrated only under fed conditions. When valganciclovir was given with food at the recommended dose of 900mg, 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 Posology and method of administration*).

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 51μg/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 (1000mg 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 section *4.2 Posology and method of administration* and section *4.4 Special warnings and precautions for use*).

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 450mg tablet strength. Thus, Valcyte should not be used in these patients (see section *4.2 Posology and method of administration* and section *4.4 Special warnings and precautions for use*).

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.

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

Tablet core	Tablet film-coat
Povidone K30	Opadry Pink YS-1-14519A containing:
Crospovidone	Hypromellose
Microcrystalline cellulose	Titanium dioxide (E171)
Stearic acid	Macrogol 400
	Red iron oxide (E172)
	Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle, with child-resistant polypropylene closure, and cotton pad enclosed.

60 tablets.

6.6 Instructions for use and handling, and disposal

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

7. MARKETING AUTHORISATION HOLDER

Roche Products Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, UK.

8. MARKETING AUTHORISATION NUMBER(S)

PL 00031/0599

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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