VALCYTE®

Valganciclovir

Prescription drug

Antiviral

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Antiviral
ATC code: J05AB14

1.2 Type of Dosage Form

Film-coated tablet

1.3 Route of Administration

Oral

1.4 Sterile/Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: valganciclovir (as valganciclovir hydrochloride).
Excipients: Povidone, crospovidone, microcrystalline cellulose, stearic acid, opadry pink.
Film-coated tablets: 450 mg.

1.6 Product Description

Pink, convex oval film-coated tablets, with "VGC" embossed on one side and "450" on the other side.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

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

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

2.2 Dosage and Administration

Caution – strict adherence to dosage recommendations is essential to avoid overdose.

Standard dosage
Valcyte is administered orally, and should be taken with food (see sections *3.2.5 Pharmacokinetics in Special Populations* and *3.2.1 Absorption*). Valcyte is rapidly and extensively converted into ganciclovir. The bioavailability of ganciclovir from Valcyte is 10-fold higher than from ganciclovir capsules, therefore the dosage and administration of Valcyte tablets as described below should be closely followed (see sections *2.4 Warnings and Precautions* and *2.7 Overdose*).

Treatment of CMV Retinitis in AIDS
Induction treatment
For patients with active CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) twice a day for 21 days, whenever possible, taken with food. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section *2.4 Warnings and Precautions*).

Maintenance treatment

For immunocompromised patients at risk of relapse of CMV retinitis the recommended dosage is 900 mg (two 450 mg tablets) once daily with food. Patients whose retinitis worsens may repeat induction treatment (see *Induction Treatment*).

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

Prevention of CMV Disease in Solid Organ Transplantation
For patients who have received a transplant, the recommended dose is 900 mg (two 450 mg tablets) once daily, starting within 10 days of transplantation until continuing 100 days post-transplantation. Whenever possible, the tablets should be taken with food.

2.2.1 Special dosage instructions
Patients with renal impairment
Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in the table below (see sections *3.2.5 Pharmacokinetics in Special Populations* and 2.4 *Warnings and Precautions*).

Table 1 Dose Modifications for AIDS Patients with Impaired Renal Function

CrCl (mL/min)	Induction dose	Maintenance dose
≥ 60	900 mg b.i.d	900 mg o.d.
40 – 59	450 mg b.i.d.	450 mg o.d.
25 – 39	450 mg o.d.	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly

Table 2 Dose Modification for Transplant Patients with Impaired Renal Function

CrCl* (mL/min)	Prevention Dose
≥ 60	900 mg o.d
40 – 59	450 mg o.d
25 – 39	450 mg every 2 days
10 – 24	450 mg twice weekly

An estimated creatinine clearance can be related to serum creatinine by the following formulae:

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

For females = 0.85 x male value

Patients undergoing haemodialysis
For patients on haemodialysis (CrCl < 10 mL/min), it is recommended that intravenous ganciclovir is used in accordance with the dose-reduction algorithm cited in the *Dosage and Administration* section of the approved intravenous ganciclovir Prescribing Information, rather than Valcyte tablets (see sections *3.2.5 Pharmacokinetics in Special Populations* and *2.4 Warnings and Precautions*).

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia & pancytopenia
Severe leukopenia, 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 hemoglobin is less than 8 g/dL (see sections *2.4 Warnings and Precautions* and *2.6 Undesirable Effects*).

Dose Reduction
Dosage reductions in renally impaired patients are required for Valcyte tablets (see section *3.2.5 Pharmacokinetics in Special Populations, Patients with Renal Impairment*). Dosage reductions should also be considered for those with neutropenia, anaemia and/or thrombocytopenia (see section *2.6 Undesirable*

Effects). Valcyte tablets should not be administered in patients with severe neutropenia (ANC less than 500/µL), severe thrombocytopenia (platelets less than 25000/µL), or severe anaemia (haemoglobin less than 8 g/100 mL).

2.3 Contraindications

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

Valcyte tablets should not be administered if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25000/µL, or the hemoglobin is less than 8 g/dL.

2.4 Warnings and Precautions

2.4.1 General

Clinical toxicities of Valcyte, which is metabolized to ganciclovir, include leukopenia and thrombocytopenia.

The diagnosis of CMV retinitis should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis include candidiasis, toxoplasmosis, histoplasmosis, retinal scars and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason it is essential that the diagnosis of CMV be established by an ophthalmologist familiar with the presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV in the urine, blood, throat, or other sites, but a negative culture does not rule out CMV retinitis.

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).

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception

In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic and to impair fertility. Valcyte should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers.

Prior to initiation of valganciclovir treatment, patients should be advised of the potential risks to the fetus and to use contraceptive measures. Based on clinical and nonclinical studies, Valcyte may cause temporary or permanent inhibition of spermatogenesis (see sections *2.5.1 Females and Males Reproductive Potential, 2.5.2 Pregnancy, 2.5.3 Lactation, 2.6 Undesirable Effects, 3.3 Nonclinical Safety* and *4.2 Special Instructions for Use, Handling and Disposal*).

Myelosuppression

Valcyte should be used with caution in patients with pre-existing hematological cytopenia or who have received or are receiving myelosuppressive drugs or a history of drug-related hematological cytopenia and in patients receiving radiotherapy.

Cytopenia may occur at any time during treatment and may increase with continued dosing. Cell counts usually begin to recover within 3 to 7 days of discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil counts in patients receiving ganciclovir for treatment of CMV retinitis.

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 hemoglobin is less than 8 g/dL (see sections *2.2.1 Special Dosage Instructions*, *2.4 Warnings and Precautions* and *2.6 Undesirable Effects*).

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment (see section *2.2.4 Laboratory Tests*), and in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µL at the beginning of treatment.

In patients with severe leukopenia, neutropenia, anaemia and/or thrombocytopenia treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see section *2.6 Undesirable Effects*).

Renal impairment
In patients with impaired renal function, dosage adjustments based on creatinine clearance are required.

For patients on haemodialysis (CrCl < 10 mL/min) it is recommended that intravenous ganciclovir be used (in accordance with the dose-reduction algorithm cited in the approved ganciclovir product information on section *2.2 Dosage and Administration: Renal Impairment*) rather than Valcyte tablets (see sections *3.2.5 Pharmacokinetics Special Populations*, *2.4 Warnings and Precautions* and *2.2 Dosage and Administration*).

Increased serum creatinine levels have been observed in trials evaluating Valcyte tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see section *2.2 Dosage and Administration*).

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 *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

Zidovudine and Valcyte each have the potential to cause neutropenia and anaemia. Some patients may not tolerate concomitant therapy at full dosage (see sections *2.8 Interactions with Other Medicinal Products and Other Forms of Interactions*).

Didanosine plasma concentrations may increase during concomitant use with Valcyte; therefore patients should be closely monitored for didanosine toxicity (see sections *2.8 Interactions with Other Medicinal Products and Other Forms of Interactions*).

Concomitant use of other drugs that are known to be myelosuppressive or associated with renal impairment with Valcyte may result in added toxicity (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interactions*).

The bioavailability of ganciclovir from Valcyte tablets is 10-fold higher than from ganciclovir capsules. Valcyte tablets 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 *2.2 Dosage and Administration* and *2.7 Overdose*).

2.4.2 Drug Abuse and Dependence
No information is available for drug abuse and dependence with Valcyte.

2.4.3 Ability to Drive and Use Machines
Adverse reactions such as seizures, dizziness, and confusion have been reported with the use of Valcyte and/or ganciclovir (see section *2.6 Undesirable Effects*). If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential

Fertility
In animal studies ganciclovir was found to impair fertility (see section *3.3.3 Impairment of Fertility*). In a clinical study, renal transplant patients receiving Valcyte for CMV prophylaxis for up to 200 days were compared to an untreated control group. Spermatogenesis was inhibited during treatment with Valcyte. At follow-up, approximately six months after treatment discontinuation, the mean sperm density in treated patients was comparable to that observed in the untreated control group. In Valcyte treated patients, all patients with normal sperm density (n=7) and 8/13 patients with low sperm density at baseline, had normal density after treatment cessation. In the control group, all patients with normal sperm density (n=6) and 2/4 patients with low sperm density at baseline, had normal density at the end of follow-up.

Contraception
Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment. Sexually active men are recommended use condoms during and for at least 90 days after cessation of treatment with Valcyte, unless it is certain that the female partner is not at risk of becoming pregnant (see sections *2.4 Warnings and Precautions* and *3.3.4 Reproductive Toxicity).*

2.5.2 Pregnancy
The safety of Valcyte for use in pregnant human has not been established. However, ganciclovir readily diffuses across the human placenta. The use of Valcyte should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. In animal studies ganciclovir was associated with reproductive toxicity and teratogenicity (see sections *3.3.3 Impairment of Fertility* and *3.3.4 Teratogenicity*).

The safe use of Valcyte during labor and delivery has not been established.

Valganciclovir is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (1.8x the mean drug exposure to ganciclovir in humans following the maximum recommended dose of valganciclovir, 900 mg twice daily, based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were fetal toxicity and embryolethality.

Daily intravenous doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach. The drug exposure in mice as estimated by the AUC was approximately 1.6x the human AUC.

Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women.

2.5.3 Lactation
Peri and postnatal development has not been studied with valganciclovir or with ganciclovir but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats.

However, many drugs are excreted in human milk and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir.

Therefore, a decision should be made to discontinue the drug or discontinue nursing taking into consideration the potential benefit of Valcyte to the nursing mother. The minimum time interval before breastfeeding can safely be resumed after the last dose of Valcyte tablets is unknown.

2.5.4 Pediatric Use
Safety and efficacy have not been established in this patient population. The use of Valcyte in children is not recommended because the pharmacokinetic characteristics of Valcyte have not been established in this patient population.

2.5.5 Geriatric Use
Safety and efficacy have not been established in this patient population (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

The pharmacokinetic profiles of Valcyte in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of Valcyte.

Clinical studies of Valcyte did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Valcyte is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see sections *2.4 Warnings and Precautions* and *2.2 Dosage and Administration*).

2.5.6 Renal Impairment
In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

2.5.7 Hepatic Impairment
Safety and efficacy have not been established in this patient population (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

2.6 Undesirable Effects
2.6.1 Clinical Trials
Experience with Valcyte
Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir usage can therefore be expected to occur with Valcyte. All of the adverse drug reactions observed in Valcyte clinical studies have been previously observed with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see *Table 3*).

In patients treated with valganciclovir/ganciclovir the most serious and frequent adverse drug reactions are hematological reactions and include neutropenia, anaemia and thrombocytopenia.

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 leukopenia compared to oral ganciclovir.

The frequencies presented in the table of adverse reactions are derived from a pooled population of patients (n=1704) receiving maintenance therapy with ganciclovir (GAN 1697, GAN 1653, GAN 2304, GAN 1774,

GAN 2226, AVI 034, GAN 041) or valganciclovir (WV15376, WV15705). Exception is made for anaphylactic reaction, agranulocytosis and granulocytopenia the frequencies of which are derived from postmarketing experience. Frequencies are presented as percentages and as CIOMS frequency categories defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).
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.

Table 3 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704)

ADR (MedDRA) System Organ Class	**Percentage**	**Frequency Category**
Infections and infestations:		
Candida infections including oral candidiasis	22.42%	Very common
Upper respiratory tract infection	16.26%	
Sepsis	6.92%	Common
Influenza	3.23%	
Urinary tract infection	2.35%	
Cellulitis	1.47%	
Blood and lymphatic disorders:		
Neutropenia	26.12%	Very common
Anaemia	19.89%	
Thrombocytopenia	7.34%	Common
Leukopenia	3.93%	
Pancytopenia	1.06%	
Bone marrow failure	0.29%	Uncommon
Aplastic anaemia	0.06%	Rare
Agranulocytosis*	0.02%	
Granulocytopenia*	0.02%	
Immune system disorders:		
Hypersensitivity	1.12%	Common
Anaphylactic reaction*	0.02%	Rare
Metabolic and nutrition disorders:		
Decreased appetite	12.09%	Very common
Weight decreased	6.46%	Common
Psychiatric disorders:		
Depression	6.69%	Common
Confusional state	2.99%	
Anxiety	2.64%	
Agitation	0.59%	Uncommon
Psychotic disorder	0.23%	
Thinking abnormal	0.18%	
Hallucinations	0.18%	

Nervous system disorders:		
Headache	17.37%	Very common
Insomnia	7.22%	Common
Neuropathy peripheral	6.16%	
Dizziness	5.52%	
Paraesthesia	3.58%	
Hypoaesthesia	2.58%	
Seizures	2.29%	
Dysgeusia (taste disturbance)	1.35%	
Tremor	0.88%	Uncommon
Eye disorders:		
Visual impairment	7.10%	Common
Retinal detachment**	5.93%	
Vitreous floaters	3.99%	
Eye pain	2.99%	
Conjunctivitis	1.58%	
Macular edema	1.06%	
Ear and labyrinth disorders:		
Ear pain	1.17%	Common
Deafness	0.65%	Uncommon
Cardiac disorders*:*		
Arrhythmia	0.47%	Uncommon
Vascular disorders*:*		
Hypotension	2.05%	Common
Respiratory, thoracic and mediastinal disorders:		
Cough	18.31%	Very common
Dyspnea	11.80%	
Gastrointestinal disorders:		
Diarrhoea	34.27%	Very common
Nausea	26.35%	
Vomiting	14.85%	
Abdominal pain	10.97%	
Dyspepsia	4.81%	Common
Flatulence	4.58%	
Abdominal pain upper	4.58%	
Constipation	3.70%	
Mouth ulceration	3.17%	
Dysphagia	2.93%	
Abdominal distention	2.41%	
Pancreatitis	1.64%	
Hepatobiliary disorders:		
Blood alkaline phosphatase increased	3.58%	Common
Hepatic function abnormal	3.23%	
Aspartate aminotransferase increased	1.88%	
Alanine aminotransferase increased	1.23%	
Skin and subcutaneous tissues disorders:		
Dermatitis	11.80%	Very common
Night sweats	7.92%	Common
Pruritus	4.58%	
Rash	2.52%	
Alopecia	1.29%	

Dry skin	0.94%	Uncommon
Urticaria	0.70%	
Musculoskeletal and connective tissue disorders:		
Back pain	4.46%	Common
Myalgia	3.52%	
Arthralgia	3.35%	
Muscle spasms	2.99%	
Renal and urinary disorders:		
Renal impairment	2.52%	Common
Creatinine clearance renal decreased	2.35%	
Blood creatinine increased	1.88%	
Renal failure	0.76%	Uncommon
Hematuria	0.70%	
Reproductive system and breast disorders:		
Infertility male	0.23%	Uncommon
General disorders and administration site conditions:		
Pyrexia	33.51%	Very common
Fatigue	18.96%	
Pain	5.81%	Common
Chills	5.40%	
Malaise	2.11%	
Asthenia	2.00%	
Chest pain	0.88%	Uncommon

** The frequencies of these adverse reactions are derived from postmarketing 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 normalizes within 2 to 5 days after discontinuation of the drug or dose reduction (see section *2.4 Warnings and Precautions*).

Thrombocytopenia
Patients with low baseline platelet counts (< 100000/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 HIV (see section *2.4 Warnings and Precautions*). 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 undergoing treatment with valganciclovir 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 more frequent 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.

Laboratory Abnormalities
Laboratory abnormalities reported in adult CMV retinitis patients and SOT patients receiving valganciclovir until Day 100 post-transplant are listed in Table 4. The incidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high risk kidney transplant patients.

Table 4 Laboratory Abnormalities in Adult Patients

Laboratory Abnormalities	**CMV Retinitis Patients**	**Solid Organ Transplant Patients (Dosing until Day 100 Post-Transplant)**	
	Valganciclovir (n=370)	**Valganciclovir (n=244)**	**Oral ganciclovir (n=126)**
	%	**%**	**%**
Neutropenia (ANC/µL)			
< 500	16	5	3
500 - < 750	17	3	2
750 - < 1000	17	5	2
Anaemia (hemoglobin g/dL)			
< 6.5	7	1	2
6.5 - < 8.0	10	5	7
8.0 - < 9.5	14	31	25
Thrombocytopenia (platelets/µL)			
< 25000	3	0	2
25000 - < 50000	5	1	3
50000 - < 100000	21	18	21
Serum creatinine (mg/dL)			
> 2.5	2	14	21
> 1.5 - 2.5	11	45	47

2.6.2 Postmarketing Experience
Safety reports from the postmarketing setting are consistent with safety data from clinical trials with ganciclovir and valganciclovir (see section *2.6.1 Undesirable Effects - Table 3*). Healthcare professionals are asked to report any suspected adverse reactions to the national reporting system BPOM at e-meso.pom.go.id and pv-center@pom.go.id.

2.7 Overdose
Overdose experience with valganciclovir and intravenous ganciclovir
It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see sections *2.4 Warnings and Precautions* and *2.2 Dosage and Administration*).

Reports of overdoses with intravenous ganciclovir, some with fatal outcomes, have been received from clinical trials and during postmarketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:
- Hematological toxicity: myelosuppression including pancytopenia, bone marrow depression, leukopenia, neutropenia, granulocytopenia
- Hepatotoxicity: hepatitis, liver function disorder
- Renal toxicity: worsening of hematuria in a patient with preexisting renal impairment, acute kidney injury, elevated creatinine
- Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting
- Neurotoxicity: generalized tremor, convulsion

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section *3.2.5 Pharmacokinetics in Special Populations*).

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

Drug interactions with Valcyte

Valcyte is the prodrug of ganciclovir; therefore interactions associated with ganciclovir are expected.

Imipenem-cilastatin

Seizures 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 *2.4 Warnings and Precautions*).

Potential drug interactions

Toxicity may be enhanced when ganciclovir/valganciclovir is coadministered with other drugs known to be myelosuppressive or associated with renal impairment. This includes nucleoside analogues (e.g. zidovudine, didanosine, stavudine), 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 *2.4 Warnings and Precautions*).

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 *2.4 Warnings and Precautions*).

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. If didanosine is given two hours prior to ganciclovir a 23% decrease in the AUC of ganciclovir occurs. There is no effect on the AUC of ganciclovir if the two drugs are given at the same time. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see section *2.4 Warnings and Precautions*).

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 excretion. Therefore patients taking probenecid and valganciclovir should be closely monitored for ganciclovir toxicity.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which 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 herpesvirus 6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus.

In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir

triphosphate, which is then slowly metabolized intracellularly. This has been shown to occur in CMV-infected cells (half-life 18 hours) and HSV-infected cells (half-life between 6 and 24 hours) after 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. Typical antiviral IC_{50} against CMV *in vitro* is in the range 0.08 μM (0.02 μg/mL) to 14 μM (3.5 μg/mL).

Valcyte tablets allow systemic exposure of ganciclovir comparable to that achieved with recommended doses of intravenous ganciclovir, which has been shown to be efficacious in the treatment of CMV.

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

3.1.2 Clinical/Efficacy Studies

Treatment of CMV retinitis
Clinical studies of Valcyte have been conducted in patients with AIDS and CMV retinitis. Valcyte has shown comparable efficacy for induction treatment of CMV retinitis to intravenous ganciclovir.

Patients with newly diagnosed CMV retinitis were randomized in one study to induction therapy with either Valcyte or intravenous ganciclovir. The proportion of patients with progression of CMV retinitis at week 4 was the same in both treatment groups.

Following induction treatment dosing, patients in this study received maintenance treatment with Valcyte given at the dose of 900 mg daily. The mean (median) time from randomization 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.

Valcyte allows systemic exposure of ganciclovir similar to that achieved with recommended doses of intravenous ganciclovir, which has been shown to be efficacious in the treatment of CMV retinitis. Ganciclovir AUC has been shown to correlate with time to progression of CMV retinitis.

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 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), as adjudicated by an independent Endpoint Committee, 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 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 randomized to valganciclovir compared with 36.0% in the oral ganciclovir 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.

Extending CMV prophylactic therapy with Valcyte until Day 200 post-transplant demonstrated superiority in preventing CMV disease within the first 12 months post-transplant in high risk kidney transplant patients compared to the 100 days dosing regimen.

The proportion of patients who developed CMV disease during the first 12 months post-transplant is shown in Table 5.

Table 5 Percentage of Kidney Transplant Patients with CMV Disease[1], 12 Month ITT Population

	Valganciclovir 900 mg od 100 Days	**Valganciclovir 900 mg od 200 Days**	**Cochran-Mantel-Haenszel p-value**
Patients with confirmed or assumed CMV disease[2]	71/163 (43.6%)	36/155 (23.2%)	0.0001
Patients with confirmed CMV disease	60/163 (36.8%)	25/155 (16.1%)	< 0.0001

[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 either no week 52 assessment or no confirmation of CMV disease before this time point.

The graft survival rate at 12 months post-transplant was 98.2% (160/163) for the 100 days dosing regimen and 98.1% (152/155) for the 200 days dosing regimen. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100 days dosing regimen and 11.0% (17/155) for the 200 days dosing regimen.

Viral resistance
Viruses resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in either the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation or the viral polymerase gene (UL54). UL97 mutations arise earlier and more frequently than mutations in UL54. Virus containing mutations in the UL97 gene is resistant to ganciclovir alone, with M460V/I, H520Q, C592G, A594V, L595S, C603W being the most frequently reported ganciclovir resistance-associated substitutions. Mutations in the UL54 gene may show cross-resistance to other antivirals targeting the viral polymerase, and vice versa. Amino acid substitutions in UL54 conferring cross-resistance to ganciclovir and cidofovir are generally located within the exonuclease domains and region V, however amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codon 696-742) and III (codon 805-845).

Treatment of CMV retinitis
A genotypic analysis of CMV in polymorphonuclear leukocytes (PMNL) isolates from 148 patients enrolled in one clinical study has shown that 2.2% (3/137), 6.5% (8/123), 12.8% (13/101) and 15.3% (13/85) contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment (using the number of patients still on treatment at the assessment time as the denominator). Phenotypic resistance was not identified, but very few CMV culture isolates were available for analysis.

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 randomized 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 randomized to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 125 patients on the ganciclovir

comparator arm, samples from 29 patients with suspected CMV disease were tested, from which 2 resistance mutations were observed, giving an incidence of resistance of 6.9%.

Resistance was evaluated in a study that extended valganciclovir CMV prophylaxis from 100 days to 200 days post-transplant in adult kidney transplant patients at high risk for CMV disease (D+/R-) (see section *3.1.2 Clinical/Efficacy Studies*). Five subjects from the 100 days group and four subjects from the 200 days group meeting the resistance analysis criteria had known ganciclovir resistance-associated amino acid substitutions detected. In six subjects, the following resistance associated amino acid substitutions were detected within pUL97: 100 days group: A440V, M460V, C592G; 200 days group: M460V, C603W. In three subjects, the following resistance-associated amino acid substitutions were detected within pUL54: 100 days group: E315D, 200 days group: E315D, P522S. Overall, the detection of known ganciclovir resistance-associated amino acid substitutions was observed more frequently in patients during prophylaxis therapy than after the completion of prophylaxis therapy (during therapy: 5/12 [42%] versus after therapy: 4/58 [7%]). The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

3.1.3 Immunogenicity
Not applicable.

3.2 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.

The parameters which control the exposure of ganciclovir from valganciclovir are bioavailability and renal function. The bioavailability of ganciclovir from valganciclovir is comparable across all the patient populations studied (adults and pediatrics). The systemic exposure of ganciclovir to heart, kidney, and liver transplant recipients was similar after oral administration of valganciclovir according to the adult renal function dosing algorithm and pediatric dosing algorithm (see section *2.2 Dosage and Administration*).

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.

3.2.1 Absorption
Valganciclovir is a prodrug of ganciclovir, which is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The bioavailability of ganciclovir from oral dosing of valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low, $AUC_{0\text{-}24h}$ and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

When valganciclovir is given with food mean ganciclovir $AUC_{0\text{-}24h}$ increased by 24% to 56% depending on the dose. When valganciclovir was given with food at a dose of 875 mg, increases were seen in both mean ganciclovir $AUC_{0\text{-}24h}$ (approximately 30%) and mean ganciclovir C_{max} values (approximately 14%). Therefore, it is recommended that Valcyte be administered with food (see section *2.2 Dosage and Administration*).

For ganciclovir, average $AUC_{0\text{-}24h}$ has been shown to correlate with time to progression of CMV retinitis.

3.2.2 Distribution
Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. The steady state volume of distribution of ganciclovir after intravenous administration was 0.680 ±0.161 L/kg. 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 µg/mL.

3.2.3 Metabolism
Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected.

Ganciclovir itself is not metabolized to a significant extent.

3.2.4 Elimination
Following dosing with oral valganciclovir, the drug is rapidly hydrolyzed 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 valganciclovir decline with a half-life ranging from 0.4 h to 2.0 h. In these patients ganciclovir concentrations decline with a half-life ranging from 3.5 to 4.5 hours similarly to that observed after direct IV administration of ganciclovir.

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of Valcyte tablets to either healthy or HIV-positive/CMV-positive subjects was 4.18 ± 0.80 hours (n=244), and that following administration of intravenous ganciclovir was 3.85 ± 0.74 hours (n=87).

3.2.5 Pharmacokinetics in Special Populations

Geriatric population
No investigations on valganciclovir or ganciclovir pharmacokinetics in adults older than 65 years of age have been undertaken. However as valganciclovir is a prodrug of ganciclovir and because ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in elderly (see section *2.2.1 Special Dosage Instructions)*.

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

Table 6 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	$AUC_{0-\infty}$ (µg·h/mL) Mean ± SD	Half-life (hours) Mean ± SD
51-70	6	249 ± 99	50.5 ± 23	4.9± 1.4
21-50	6	136 ± 64	100 ± 54	10.2 ± 4.4
11-20	6	45 ± 11	252 ± 64	21.8 ± 5.2
± 10	6	12.8 ± 8	407 ± 83	68.1 ± 35

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 *2.2.1 Special Dosage Instructions* and *2.4 Warnings and Precautions*).

Patients undergoing haemodialysis
For patients receiving haemodialysis (CrCl < 10 mL/min), it is recommended that intravenous ganciclovir (rather than valganciclovir) be used. This is because an individual dose of Valcyte tablets required for these patients is less than 450 mg (see sections *2.4 Warnings and Precautions* and *2.2 Dosage and Administration*).

Ganciclovir is readily removable by haemodialysis. Data obtained during intermittent haemodialysis in patients dosed with valganciclovir showed estimated dialysis clearance as 138 mL/min ± 9.1% (n=3) and intra-dialysis half-life estimated to 3.47 h (n=6).

55% of ganciclovir was removed during a 3 hours dialysis session.

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 absolute bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60%, in agreement with estimates obtained in other patient populations. Ganciclovir AUC_{0-24h} was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant patients.

Hepatic impairment
No pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment undergoing valganciclovir therapy.

Patients with cystic fibrosis
In a phase I pharmacokinetic study, steady state systemic exposure to ganciclovir was assessed in lung transplant recipients with or without cystic fibrosis (n=31) who were receiving 900 mg/day of Valcyte as part of their post-transplant prophylaxis. 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.

3.3 Nonclinical Safety
In animal studies ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic. Valcyte should therefore be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. It is also considered likely that Valcyte causes temporary or permanent inhibition of spermatogenesis (see sections *2.4 Warning and Precautions*, *3.3.3 Impairment of Fertility* and *4.2 Special Instructions for Use, Handling and Disposal*).

No long-term carcinogenicity studies have been conducted with valganciclovir. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir

3.3.1 Carcinogenicity
In an 18-month study, ganciclovir was carcinogenic in the mouse after oral doses of 20 mg and 1000 mg/kg/day. All ganciclovir-induced tumours were of epithelial or vascular origin, except for histiocytic sarcoma of the liver. Epithelial tumours involved a wide variety of tissues. No carcinogenic effects occurred at 1 mg/kg/day. Based on data on plasma drug concentrations, exposure of humans to ganciclovir would be greater than exposure of mice in the above study at 20 mg/kg.

Valganciclovir and ganciclovir were 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.

3.3.2 Genotoxicity
Valganciclovir increased mutations in mouse lymphoma cells and was clastogenic in the mouse micronucleus assay. Valganciclovir was not mutagenic in the Ames Salmonella assay.

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes *in vitro*. Ganciclovir was clastogenic in the mouse micronucleus assay. Ganciclovir was not mutagenic in the Ames Salmonella assay.

3.3.3 Impairment of Fertility
Ganciclovir causes impaired fertility and teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both drugs (see section 2.*4 Warning and Precautions*).

Based upon animal studies where aspermia was induced at ganciclovir systemic exposures below therapeutic levels, it is considered likely that ganciclovir (and valganciclovir) could cause temporary or permanent inhibition of human spermatogenesis (see section *2.5.1 Females and Males of Reproductive Potential, Fertility*).

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 1.6x the mean drug exposure to ganciclovir in humans following the maximum recommended dose of valganciclovir, 900 mg twice daily, based on AUC comparisons).

Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1x the AUC of ganciclovir in humans following the maximum recommended dose of valganciclovir. Valganciclovir caused similar effects on spermatogenesis in mice, rats and dogs.

3.3.4 Reproductive Toxicity
Ganciclovir causes teratogenicity in animals.

Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. The same reprotoxicity warning is seen as applying to both drugs (see section *2.4 Warning and Precautions*).

3.3.5 Other
No additional information is available.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage
Do not store above 30°C.

4.2 Special Instructions for Use, Handling and Disposal

Incompatibilities
Not applicable.

Stability
Caution should be exercised in the handling of Valcyte tablets. Tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see section *3.3 Nonclinical Safety, Carcinogenicity, Mutagenicity, Teratogenicity*). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

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

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

Presentation
Box, 1 bottle @ 60 film-coated tablets Reg.No.: DKI2463300217A1

Medicine: keep out of reach of children
On medical prescription only
Harus dengan resep dokter

Manufactured by:
Patheon Inc., Mississauga, Canada
for CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany

Registered by:
PT. Tunggal Idaman Abdi,
Jl. Jend. Ahmad Yani No. 7
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