AUSTRALIAN PRODUCT INFORMATION

VACLOVIR®

(valaciclovir (as hydrochloride)) tablets

1 NAME OF THE MEDICINE

Valaciclovir (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VACLOVIR tablets contain 250, 500 or 1000 mg of valaciclovir (as hydrochloride) as the active ingredient.

For the full list of excipients see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

250 mg tablets: white coloured, oval shaped, biconvex film coated tablet.

500 mg tablets: white coloured, oval shaped, biconvex film coated tablet with break line on one side and plain on the other side.

1000 mg tablets: white coloured, oval shaped, biconvex film coated tablet with a break line on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of herpes zoster (shingles) in adult patients who commence therapy within 72 hours of the onset of rash.

For the treatment of ophthalmic zoster.

For the treatment of recurrent herpes labialis (cold sores).

For the treatment of clinical episodes of genital herpes simplex infections.

For the prevention of recurrent genital herpes.

Reduction of transmission of genital herpes in patients suffering from recurrent genital herpes. In addition to therapy with VACLOVIR, it is recommended that patients use safer sex practices (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Prophylaxis of cytomegalovirus (CMV) infection and disease following solid organ transplantation in patients at risk of CMV disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage in Adults

For the Treatment of Herpes Zoster (Shingles)

For the treatment of herpes zoster: 1000 mg of VACLOVIR three times a day for 7 days.

For the Treatment of Herpes Labialis (Cold Sores)

The recommended dosage of VACLOVIR for the treatment of cold sores is 2000 mg twice daily for 1 day, with the second dose taken about 12 hours (no sooner than 6 hours) after the first dose. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).

Genital Herpes

For the Treatment of Genital Herpes

For the treatment of first clinical presentation of genital herpes: 500 mg of VACLOVIR twice a day for 5 to 10 days.

For recurrent episodes of genital herpes: 500 mg twice a day for 5 days.

Dosing should begin as early as possible. For recurrent episodes of genital herpes, this should ideally be during the prodromal period or immediately following the appearance of the first signs or symptoms.

For the Prevention of Genital Herpes

For the prevention of genital herpes in patients with a history of fewer than 10 recurrences each year: 500 mg of valaciclovir once daily, either as a single dose or a divided dose (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

For the prevention of genital herpes in patients with a history of 10 or more recurrences each year when not taking suppressive therapy: 1000 mg of valaciclovir once daily.

For immunocompromised patients: 500 mg twice daily

Reduction of Transmission of Genital Herpes

In immunocompetent heterosexual adults with less than 10 recurrences per year and with the susceptible partner discordant for HSV-2 antibodies: 500 mg of VACLOVIR to be taken once daily by the infected partner.

There are no data on the reduction of transmission in other patient populations.

For the Prophylaxis of Cytomegalovirus Infection (CMV) and Disease

Dosage in Adults and Adolescents (from 12 years of age)

The dosage of VACLOVIR is 2 g four times a day for 90 days, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Dosage in Renal Impairment).

Dosage in Renal Impairment

Caution is advised when administering VACLOVIR to patients with impaired renal function. Adequate hydration should be maintained (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dose Reduction in the treatment of herpes zoster and genital herpes simplex:

The dose of VACLOVIR should be modified as follows in patients with significantly impaired renal function:

Table 1:

Creatinine Clearance	VACLOVIR Dose				
	Herpes Zoster	Genital Herpes Simplex			
		Treatment	Prevention		Reduction of Transmission of Genital Herpes
			Immuno-competent	Immuno-compromised	
15 – 30 mL/min	1000 mg twice a day	No modification required	No modification required	No modification required	No modification required
< 15 mL/min	1000 mg once a day	500 mg once daily	250 mg once daily	500 mg once daily	250 mg once daily

Dose reduction in the treatment of herpes labialis:

The dose of VACLOVIR should be modified as follows in patients with significantly impaired renal function:

Table 2:

Creatinine Clearance	VACLOVIR Dose
≥ 50 mL/min	2000 mg twice a day
31 – 49 mL/min	1000 mg twice a day
15 – 30 mL/min	500 mg twice a day
< 15 mL/min	500 mg single dose

In patients on haemodialysis, the VACLOVIR dose recommended for patients with a creatinine clearance of less than 15 mL/min should be used, but the dose should be administered after the haemodialysis has been performed.

CMV prophylaxis:

The dosage of VACLOVIR should be adjusted in patients with impaired renal function as shown in the table below:

Table 3:

Creatinine Clearance mL/min	VACLOVIR Dosage
75 or greater	2 g four times daily
50 to less than 75	1.5 g four times a day
25 to less than 50	1.5 g three times a day
10 to less than 25	1.5 g twice a day
Less than 10 or dialysis [o]	1.5 g once a day

[o] In patients on haemodialysis, the VACLOVIR dosage should be administered after the haemodialysis has been performed.

The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly (e.g. immediately after transplantation or engraftment). The VACLOVIR dosage should be adjusted accordingly.

Dosage in Hepatic Impairment

Studies with a 1 g unit dose of VACLOVIR show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment; however clinical experience is limited.

For higher doses recommended for CMV prophylaxis see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Dosage in Children

No data are available.

Dosage in the Elderly

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Dosage in Renal Impairment).

Adequate hydration should be maintained.

4.3 CONTRAINDICATIONS

VACLOVIR is contraindicated in patients known to be hypersensitive to valaciclovir, aciclovir or any component of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome (TPP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease who were treated with valaciclovir for prolonged periods and also in allogenic bone marrow transplant and renal transplant recipients who were treated with valaciclovir while participating in clinical trials at doses of 8 g per day. Treatment with valaciclovir should be stopped immediately if clinical signs, symptoms and laboratory abnormalities consistent with TTP/HUS occur.

Similar signs have been observed in patients with the same underlying or concurrent conditions who were not treated with valaciclovir.

Use of valaciclovir at doses of 1000 mg/day in immunocompromised patients with $CD4^+$ counts > 100 x 10^6 L has not been associated with occurrences of thrombotic microangiopathy (TMA). However, use in severely immunocompromised patients ($CD4^+$ counts < 100 x 10^6 L) has not been examined at this low dosage.

Severe Cutaneous Adverse Reactions (SCARs)

SCARs, including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) have been reported in patients receiving valaciclovir and/or aciclovir (the principal metabolite of valaciclovir).

SCARs can be life-threatening or fatal. At the time of prescribing patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCAR appear, valaciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed SCAR with the use of valaciclovir, treatment with valaciclovir must not be restarted in this patient at any time.

Use of High Dose Valaciclovir in Hepatic Impairment and Liver Transplantation

There are no data available on the use of higher doses of valaciclovir (4000 mg or more per day) in patients with liver disease. Specific studies of valaciclovir have not been conducted in liver transplantation, and hence caution should be exercised when administering daily doses greater than 4000 mg to these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Hepatic Impairment).

Use for Zoster Treatment

Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Hydration Status

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Patients without adequate hydration

Precipitation of aciclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

Use in Cold Sores (Herpes Labialis)

Patients should be advised to initiate treatment at the earliest symptom of a cold sore (e.g. tingling, itching or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (e.g. papule, vesicle or ulcer). Patients should be instructed that treatment for cold sores should not exceed 1 day (2 doses) and that their doses should be taken 12 hours apart. Patients should be informed that valaciclovir is not a cure for cold sores (*herpes labialis)*.

Use in Genital Herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. Continuous therapy with valaciclovir in patients with recurrent genital herpes reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still possible. Therefore, in addition to therapy with valaciclovir, it is recommended that patients use safer sex practices. As genital herpes is a sexually transmitted infection, patients should, in order to further reduce the risk of infecting partners, avoid contact with lesions, damaged skin/mucosa, and avoid intercourse when lesions and/or symptoms are present. Genital herpes is frequently transmitted in the absence of symptoms through asymptomatic viral shedding; therefore patients should be counselled to use safer sex practices. The effect of valaciclovir on transmission of sexually transmitted infections other than herpes (including HIV, gonorrhoea, syphilis and chlamydia) is unknown.

The efficacy of valaciclovir for reducing transmission of genital herpes has not been established in individuals with multiple partners, non-heterosexual couples and couples not counselled to use safer sex practises.

Use in Ocular HSV Infections

Clinical response should be closely monitored in these patients. Considerations should be given to intravenous antiviral therapy when response to oral therapy is unlikely to be sufficient.

Use in CMV Infections

Data on the efficacy of valaciclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMV positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy), indicate that valaciclovir should only be used in these patients when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Central Nervous System Effects

Reversible neurological reactions including agitation, dizziness, confusion, hallucinations, rarely decreased consciousness and very rarely tremor, ataxia, dysarthria, convulsions, encephalopathy and coma have been reported. These events are usually seen in patients with renal impairment or with other predisposing factors. In organ transplant patients receiving high doses (8 g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses. Valaciclovir should be discontinued if central nervous system adverse reactions occur.

Use in Hepatic Impairment

For further information see Section 5.2 PHARMACOKINETIC PROPERTIES – Special Populations – Hepatic Impairment.

Use in Renal Impairment

Renal insufficiency or acute renal failure has been observed in patients taking valaciclovir at the recommended dosage and/or with no previous renal conditions and may be associated with renal pain.

The dose of valaciclovir must be reduced in patients with renal impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Valaciclovir is converted to aciclovir which is eliminated by renal clearance (see Section 5.2 PHARMACOKINETIC PROPERTIES). Patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Cases of acute renal failure have been reported in patients without adequate hydration. Precipitation of aciclovir in renal tubules may occur when the solubility is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

Caution should be exercised when administering valaciclovir to patients with significant renal impairment or those receiving potentially nephrotoxic agents, since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system such as those that occur infrequently in patients treated with intravenous aciclovir.

Use in the Elderly

Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Elderly patients are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Paediatric Use

Safety and effectiveness in children have not been established.

Effects of Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs (including e.g. tenofovir) administered concurrently that compete with this mechanism or inhibit active tubular secretion may increase aciclovir plasma concentrations by this mechanism following valaciclovir administration. Similarly, valaciclovir administration may increase plasma concentrations of the concurrently administered substance.

Following 1 g valaciclovir, cimetidine and probenecid increase the AUC of aciclovir by this mechanism by about 45%, and reduce aciclovir renal clearance by about 25%, by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC by about 65%. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of aciclovir.

In patients receiving high-dose valaciclovir (8 g/day) (e.g. at doses for zoster treatment or CMV prophylaxis) caution is required during concurrent administration with drugs which inhibit active renal tubular secretion, compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of

mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered. No changes in peak concentrations or AUCs are observed with co-administration of valaciclovir and mycophenolate mofetil in healthy volunteers. There is limited experience with the use of the combination of valaciclovir and mycophenolate mofetil.

Care is also required (with monitoring for changes in renal function) if administering high-dose valaciclovir with drugs which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Valaciclovir did not impair fertility or reproduction in rats dosed by the oral route at 200 mg/kg per day, corresponding to plasma levels 2.8 (HZV) and 0.3 (CMV) times human plasma concentrations (AUC). However, high parenteral doses of aciclovir caused testicular atrophy and aspermogenesis in rats (80 mg/kg/day) and dogs (100 mg/kg/day).

No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 aciclovir recipients, with culture confirmed genital HSV-2 and with normal baseline sperm counts after 6 months of daily treatment with 400 mg to 1 g of aciclovir.

Use in Pregnancy

Pregnancy Category: B3

Valaciclovir was not teratogenic in rats or rabbits given oral doses of 400 mg/kg (which results in exposures of 1.1 and 2.0 times (HZV) and 0.4 and 0.7 times (CMV) human exposure, respectively, based on body surface area) during the period of major organogenesis. Aciclovir was not teratogenic in the mouse (450 mg/kg PO), rabbit (50 mg/kg SC and IV) or rat (50 mg/kg SC) when dosed throughout the period of organogenesis. Plasma concentrations of aciclovir in the rat were 3.5 (HZV) and 0.8 (CMV) times human concentrations. In additional studies in which rats were given three SC doses of 100 mg/kg aciclovir on gestation day 10, fetal abnormalities, such as head and tail anomalies, were reported. Plasma concentrations of aciclovir in the rat were 19 (HZV) and 4.3 (CMV) times human concentrations.

There are no adequate and well-controlled studies of valaciclovir or aciclovir in pregnant women. A prospective epidemiologic registry of aciclovir use during pregnancy has been ongoing since June 1984. Pregnancy registries have documented the pregnancy outcomes in women exposed to valaciclovir or to any formulation (oral or intravenous) of aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered and post marketing experience indicate no malformative or feto/neonatal toxicity. Registry findings do not indicate an increased risk of major birth defects after aciclovir exposure in comparison with the general population. The accumulated case histories represent an insufficient sample for reaching reliable and definitive conclusions regarding the risk associated with aciclovir exposure during pregnancy. The daily aciclovir AUCs (area under plasma concentration-time curve) following valaciclovir 1000 mg and 8000 mg daily would be approximately 2 and 9 times greater than that expected with oral aciclovir 1000 mg daily, respectively. Animal studies do not show reproductive toxicity for valaciclovir (see Section 5.3 PRECLINICAL SAFETY DATA).

There are limited data on the use of valaciclovir in pregnancy. Valaciclovir should only be used in pregnancy if the potential benefit outweighs the potential risk.

Use in Lactation

Lactating rats given a 25 mg/kg PO dose of ^{14}C-valaciclovir showed peak milk radioactivity levels of 26 micrograms/eq/g, 2 hours post dose. The milk radioactivity levels declined slower than in plasma and were undetectable at 12 hours. Suckling pups had radioactivity in the stomach and intestinal contents up to 7 hours post dose, but not in tissues.

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. In a study conducted on 5 women, following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal aciclovir serum concentrations. The aciclovir AUC was 2.2 times (range 1.4 to 2.6) higher in breast milk compared to maternal serum.

In other studies, conducted with oral aciclovir administration, aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding aciclovir plasma concentration.

Caution is therefore advised if valaciclovir is to be administered to a breast-feeding mother. Valaciclovir should only be administered to breast-feeding mothers if the benefits to the mother outweigh the potential risks to the baby.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No special precautions necessary.

A detrimental effect on driving or the ability to operate machinery cannot be predicted from the pharmacological properties of valaciclovir or the active substance aciclovir. No studies to investigate the effect of valaciclovir on such activities have been conducted. However, the clinical status of the patient and the adverse event profile of valaciclovir should be borne in mind when considering a patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Valaciclovir was well tolerated when used for the treatment of herpes zoster and genital herpes in clinical trials. The most commonly reported adverse experiences were headache and nausea and these were reported in a similar proportion of patients on valaciclovir, aciclovir and placebo.

More serious adverse reactions such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure, neurological disorders and DRESS (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) are discussed in greater detail in other sections of the Product Information.

Herpes Zoster Infections

The following table lists all adverse events reported during a six-month observation period in immunocompetent patients receiving short-term treatment (7 or 14 days) with valaciclovir and reference products in controlled clinical trials.

Table 4:

	% Incidence of Adverse Events			
Patient Age Group	**≥ 50 Years**		**18 to 50 Years**	
	Valaciclovir 1 g 3x daily (n = 765) 14 days: n = 381 7 days: n = 384	**Aciclovir 800 mg 5x daily 7 days (n = 376)**	**Valaciclovir 1 g 3x daily 7 days (n = 202)**	**Placebo 7 days (n = 197)**
Nausea	16.5	19.1	9.9	7.6
Headache	12.9	12.8	16.8	11.7
Vomiting	6.8	7.7	4.5	2.5
Diarrhoea	5.5	7.4	4.5	6.1
Constipation	5.1	5.3	1.5	2.5
Asthenia	4.4	5.3	3.0	3.6
Dizziness	3.7	5.9	2.0	2.0

	% Incidence of Adverse Events			
Patient Age Group	**≥ 50 Years**		**18 to 50 Years**	
	Valaciclovir 1 g 3x daily (n = 765) 14 days: n = 381 7 days: n = 384	**Aciclovir 800 mg 5x daily 7 days (n = 376)**	**Valaciclovir 1 g 3x daily 7 days (n = 202)**	**Placebo 7 days (n = 197)**
Abdominal Pain	3.3	2.7	2.5	1.5
Anorexia	3.0	2.7	0.5	2.0
Dyspepsia	2.5	1.9	-	-
Dry Mouth	1.8	0.5	-	-
Flatulence	1.8	1.6	-	-
Fever	1.4	2.4	-	-
Insomnia	1.6	0.5	-	-
Rhinitis	1.3	1.6	1.5	1.5
Chills	1.0	1.6	-	-
Back Pain	1.0	0.5	-	-
Nervousness	1.0	0.0	-	-
Somnolence	0.9	2.1	-	-
Pain	0.8	1.6	-	-
Rash	0.7	1.9	-	-
Myalgia	-	-	0.5	2.5
Infection	-	-	2.0	1.0

HSV Infections

Initial and recurrent genital herpes (short-term treatment)

The adverse events reported by greater than 2% of a given treatment group in the initial and recurrent genital herpes clinical trials with valaciclovir and reference products used in the trials are listed in the following table:

Table 5:

Patient Age Group	**% Incidence of Adverse Events 17 – 79 Years**		
	Valaciclovir 1 g 2x daily (n = 1203) 10 days: n = 323 5 days: n = 880 500 mg 2x daily 5 days (n = 738)	**Aciclovir 200 mg 5x daily 5 days (n = 1187)**	**Placebo (n = 441)**
Headache	16	11	14
Nausea	6	7	7
Diarrhoea	4	3	6
Dizziness	3	2	2

Patient Age Group	% Incidence of Adverse Events 17 – 79 Years		
	Valaciclovir 1 g 2x daily (n = 1203) 10 days: n = 323 5 days: n = 880 500 mg 2x daily 5 days (n = 738)	**Aciclovir 200 mg 5x daily 5 days (n = 1187)**	**Placebo (n = 441)**
Abdominal Pain	2	3	2
Asthenia	2	2	4
Rhinitis	2	2	2
Pharyngitis	1	2	1
Pain	1	1	2
Dyspepsia	1	1	2
Vomiting	1	2	0
Back Pain	1	1	2

Prevention of Genital Herpes (long-term preventative therapy)

The adverse events reported at an incidence of 5% or greater in a given treatment group, in clinical trials for the preventative treatment of genital herpes with valaciclovir and reference products, are listed in the following table:

Table 6:

	% Incidence of adverse events					
	Immunocompetent				Immunocompromised	
	V 500mg 1 x daily 52 weeks n=266	V 250mg 2 x daily 52 weeks n=274	A 400mg 2 x daily 52 weeks n=267	PBO 52 weeks n=134	V 500mg 2 x daily 48 weeks n = 355	A 400mg 2 x daily 48 weeks n = 349
Headache	38	35	37	34	18	17
Rhinitis	23	26	25	18	13	14
Infection	18	15	21	16	16	13
Flu syndrome	12	20	18	13	7	7
Pharyngitis	12	8	11	14	11	13
Nausea	11	9	12	8	16	12
Back Pain	8	12	13	6	6	7
Diarrhoea	9	8	12	14	19	19
Abdominal Pain	9	9	7	6	12	7
Pain	11	6	8	4	6	6
Sinusitis	8	7	12	5	7	7
Accidental Injury	7	7	10	3	3	5
Dysmenorrhoea	5	8	8	4	-	-
Dyspepsia	3	6	7	8	3	4
Rash	5	5	6	7	14	14
Arthralgia	5	5	7	4	3	3
Depression	5	5	4	5	9	7
Allergic Reaction	6	6	4	4	-	-
Urinary Tract Infection	5	2	7	2	-	-
Bronchitis	5	4	5	2	3	7
Myalgia	5	4	8	2	3	5
Asthenia	4	5	3	5	8	9
Tooth Disorder	5	3	4	3	1	3
Unevaluable Reaction	5	3	5	2	3	4
Migraine	4	4	5	2	-	-
Acne	3	4	3	3	5	3
Dizziness	2	5	3	1	2	3
Insomnia	5	3	1	2	3	4
Vomiting	3	3	5	2	7	5
Pruritus	2	3	2	1	5	3
Increased Coughing	3	4	1	2	6	10
Fever	3	1	1	1	11	11
Rectal Disorder	-	-	-	-	4	5

V = Valaciclovir
A = Acidovir
PBO = Placebo

Prophylaxis of Cytomegalovirus (CMV) Infection and Disease, Following Organ Transplantation

Valaciclovir was well tolerated in the clinical studies of renal and heart transplant patients. The nature and frequency of adverse events were similar between placebo, aciclovir and valaciclovir treated patients, with the exception of adverse events relating to the CNS (hallucinations, confusion and thinking abnormality). These were reported more frequently in valaciclovir than placebo in renal transplant patients. The most common adverse events reported in renal transplant patients were anaemia, hypertension and headache. Headache and myalgia were the most common adverse events reported in heart transplant patients. All the clinical adverse events occurring at an incidence of ≥ 5% or ≥ 20% in a given treatment group, in clinical trials for CMV prophylaxis following renal and heart transplants respectively are listed in the following tables:

Table 7:

Summary of all adverse events reported at an incidence ≥ 5% by renal transplant recipients in clinical trials for CMV prophylaxis

	Renal Transplant Recipients	
Adverse Event	**Valaciclovir* (n=306)**	**Placebo (n=310)**
Anaemia	12%	12%
Hypertension	11%	8%
Headache	9%	11%
Diarrhoea	9%	12%
Abdominal Pain	8%	11%
Leukopenia	8%	8%
Hallucination	8%	1%
Fever	8%	11%
Nausea	8%	7%
Vomiting	8%	7%
Peripheral Oedema	8%	9%
Confusion	7%	2%
Dyspnoea	7%	5%
Pain	7%	7%
Constipation	7%	5%
Insomnia	6%	3%
ALT** increase	5%	6%
Thrombocytopenia	5%	5%
Pruritus	5%	2%
Arthralgia	5%	6%
Tremor	4%	6%

Table 8:

Summary of all adverse events reported at an incidence ≥ 20% by heart transplant recipients in clinical trials for CMV prophylaxis

	Heart Transplant Recipients	
Adverse Event	**Valaciclovir* (n=14)**	**Aciclovir (n=13)**
Headache	57%	62%
Myalgia	57%	46%
Cough increase	57%	46%
Peripheral Oedema	50%	62%
Asthenia	43%	15%
Effus Pericard	43%	46%
Pain	43%	31%
Dyspnoea	36%	38%
Back Pain	29%	15%
Nausea	21%	23%
Insomnia	21%	15%
General Oedema	21%	54%
Hypertension	21%	38%
Somnolence	21%	23%
Constipation	21%	15%
Depression	21%	15%
Sleep Disorder	21%	15%
Chest Pain	21%	-
Dizziness	7%	31%
Diarrhoea	7%	23%
Mouth Ulcer	-	23%

Oedema	4%	5%
AST*** Increase	4%	6%

* The dosage adjustment of valaciclovir (and aciclovir) in renal and heart transplant clinical studies differed
** ALT = alanine aminotransferase
*** AST = aspartate aminotransferase

Herpes Labialis (Cold Sores)

In clinical studies for the treatment of cold sores, the adverse events reported by patients receiving valaciclovir (n = 609) or placebo (n = 609) included headache (valaciclovir 14%, placebo 10%) and dizziness (valaciclovir 2%, placebo 1%). The frequencies of abnormal ALT (> 2x ULN) were 1.8% for patients receiving valaciclovir compared with 0.8% for placebo. Other laboratory abnormalities (haemoglobin, white blood cells, alkaline phosphatase and serum creatinine) occurred with similar frequencies in the 2 groups.

Post-Marketing Experience

The following adverse events have been observed during post-approval use of valaciclovir:

Blood and lymphatic system disorders:

Thrombocytopenia, leukopenia*, thrombotic microangiopathy (TMA) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

* Leukopenia is mainly reported in immunocompromised patients

Aplastic anaemia, leukocytoclastic vasculitis, thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS).

Immune system disorders:

Anaphylaxis

Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnoea, pruritis, rash and urticaria.

Psychiatric and nervous system disorders:

Headache, decreased consciousness, dizziness, confusion and hallucinations, coma, agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, aggressive behaviour, delirium.

Neurological disorders, sometimes severe, may be linked with encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In organ transplant patients receiving high doses (8000 mg daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders:

Dyspnoea

Gastrointestinal tract:

Abdominal discomfort, vomiting, diarrhoea, nausea

Hepato-biliary disorders:

Reversible increases in liver function tests, (e.g. bilirubin, liver enzymes), occasionally described as hepatitis

Skin and subcutaneous tissue disorders:

Rashes including photosensitivity, pruritus, urticaria, angioedema, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS) and erythema multiform (EM). (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal and urinary disorders:

Renal pain, haematuria (often associated with other renal events), renal impairment, acute renal failure (especially in elderly patients or in patients with renal impairment receiving higher than the recommended doses), tubulointerstitial nephritis.

Renal pain may be associated with renal failure.

Intratubular precipitation of aciclovir crystals in the kidney has also been reported. Adequate fluid intake should be ensured during treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Elevated blood creatin and blood urea nitrogen (BUN).

General:

Facial oedema, hypertension, tachycardia.

Ophthalmologic:

Visual abnormalities.

Other:

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced HIV disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

Reporting Suspected Adverse Reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and Signs

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Management

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Valaciclovir is rapidly and almost completely converted in man to aciclovir probably by the enzyme valaciclovir hydrolase. Aciclovir is a specific inhibitor of the herpes viruses with *in vitro* activity against herpes simplex viruses (HSV) type 1 and type 2 (IC_{50} 0.1 – 3.0 micromoles), varicella-zoster virus (VZV) (IC_{50} 1.6 – 5.1 micromoles) and human cytomegalovirus (HCMV) (IC_{50} 10 - > 200 micromoles). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form. The first stage of phosphorylation requires the activity of a virus-specific enzyme: thymidine kinase in HSV and VZV infected cells or protein kinase in HCMV infected cells. This requirement for activation of aciclovir by a virus specific enzyme largely explains its unique selectivity. The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic Effects

Pharmacodynamics/Resistance Development

Resistance to aciclovir is normally due to a thymidine kinase deficient phenotype. In animal models, the viral fitness and pathogenicity of this phenotype appears to be reduced. Infrequently, reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants in animal models resembles that of the wild-type virus.

Resistance of HSV and VZV to aciclovir occurs by the same mechanisms. While most of the aciclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to valaciclovir (and therefore, to aciclovir) should be considered in patients who show poor clinical response during therapy.

Clinical Trials

Herpes Zoster Infections

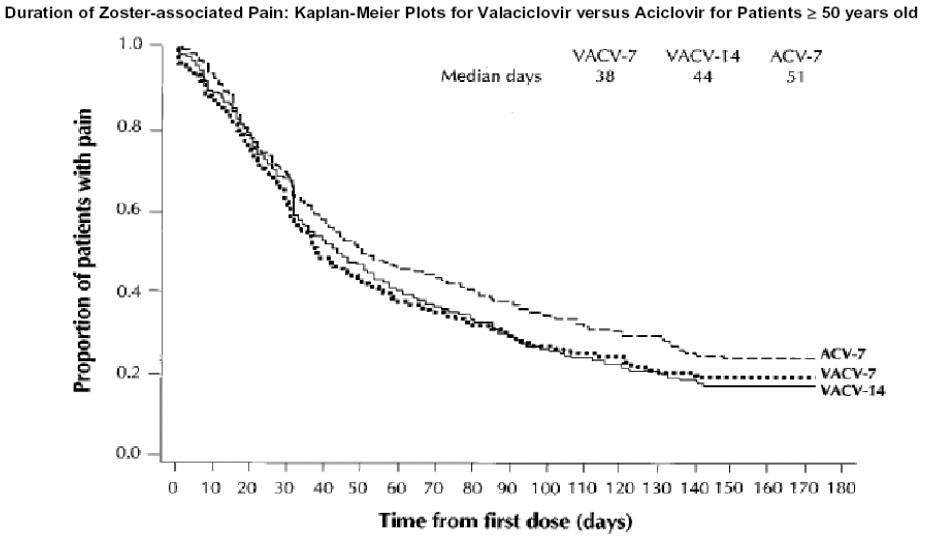
Two doses of valaciclovir were compared to aciclovir in a double-blind, randomised trial in immunocompetent patients aged 50 years and over with herpes zoster (n = 1141). All patients were treated within 72 hours of the appearance of the rash. Valaciclovir 1 g three times daily for seven days achieved statistically significant reductions in the duration of zoster-associated pain (which is the sum of acute pain and post-herpetic neuralgia) and in the duration of post-herpetic neuralgia when compared with aciclovir. There was no statistically significant difference between the three treatments for the resolution of rash.

Table 9:

	Median duration (days)		
	Valaciclovir		**Aciclovir**
	1 g three times daily		**800 mg five times daily**
	For 7 days (n = 384)	**For 14 days (n = 381)**	**For 7 days (n = 376)**
All Zoster associated Pain (Z-aP)	38	44	51
Post Herpetic Neuralgia (PHN)	30	35	39

There was no significant difference to the duration of zoster-associated pain when treatment was started within 48 or 72 hours. Patients treated within 48 hours of rash onset were found to have faster healing rates as measured by the duration of new lesion formation and time to crusting or healing of 50% or more of lesions. Thus, greater benefit is gained if the drug is started within 48 hours. See Figure 1.

Figure 1:



NOTE: ACV-7 – acyclovir at 800mg five times daily for 7 days; VACV-7 – valaciclovir at 1000mg three times daily for 7 days; VACV-14 – valaciclovir at 1000mg three times daily for 14 days

In a second, placebo-controlled trial in patients under 50 years of age (n = 399), demonstration of efficacy was restricted to a small decrease in mean time to cessation of new lesion formation. No significant effects were demonstrated for other outcomes of herpes zoster in this age group. Nevertheless, the occasional younger patients with severe herpes zoster may benefit from therapy with valaciclovir. Herpes zoster is usually a milder condition in younger patients.

In ophthalmic zoster, oral aciclovir has been shown to reduce the incidence of stromal keratitis and both the incidence and severity of anterior uveitis but not other ocular complications or acute pain. The recommended dose of valaciclovir produces higher plasma concentrations of aciclovir than those associated with these beneficial effects.

Herpes Labialis Infections (cold sores)

Two double-blind, placebo-controlled clinical trials were conducted in 1856 healthy immunocompetent adults and adolescents (≥ 12 years old) with a history of recurrent cold sores. Patients self-initiated therapy at the earliest symptoms and prior to any signs of a cold sore. The majority of patients initiated treatment within 2 hours of onset of symptoms.

The two trials investigated the clinician based duration of episode and prevention/blockage of cold sore lesion development as diametrically opposed primary and secondary endpoints.

Patients were randomised into 3 groups: valaciclovir 2 g twice daily for one day or valaciclovir 2 g twice daily for one day, followed by 1 g twice daily on day 2, or placebo on both days.

An integrated analysis of both trials showed a statistically significant prevention/blockage of onset of lesions in 44% of patients on one day therapy compared to 37% receiving placebo. The mean duration of cold sores in the integrated analysis showed a significant reduction in duration of approximately 1 day when compared to placebo. The ITT population showed the mean duration of episodes was 6.2 days in the placebo group and 5.2 days in the 1 day group giving a treatment difference of -1.0 day (CI: -1.4, -0.6).

The single study results showed the mean duration of cold sore episodes was approximately 1 day shorter in treated subjects when compared to placebo. For the ITT population, when tested as the primary endpoint, the

mean duration of episodes was 6.1 days in the placebo group and 5.0 days in the 1 day group, giving a treatment difference of -1.1 days (CI: -1.6, -0.6). When tested as the secondary endpoint, for the ITT population, the mean duration of episodes was 6.3 days in the placebo group and 5.3 days in the 1 day group, giving a treatment difference of -1.0 days (CI: -1.5, -0.5).

The onset of lesions was prevented in the 43 to 44% of patients on one day valaciclovir therapy compared with 35 to 38% placebo treated patients. No significant difference was observed between subjects receiving valaciclovir or placebo in the prevention of progression of cold sore lesions beyond the papular stage when tested as the primary or secondary endpoint.

There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore, i.e. papule, vesicle or ulcer. The 2-day regimen did not offer additional benefit over the 1-day regimen.

The data are based on treatment of a single episode of herpes labialis.

Acute Treatment of Initial and Recurrent Herpes Simplex Virus (HSV) Infections

Four large, multicentre, randomised, double-blind trials were conducted in adults with herpes simplex infections. These studies included a total of 3569 treated patients of whom 1941 received valaciclovir.

Initial Genital Herpes Simplex Infections

One study compared valaciclovir (1000 mg twice daily) with aciclovir (200 mg five times daily) administered for 10 days in immunocompetent patients with initial (primary or first episode) genital herpes. Patients reported to the clinic for treatment within 72 hours of the first signs or symptoms of genital herpes.

Patients were randomised to receive valaciclovir (n = 323) or aciclovir (n = 320) for 10 days. The median time to lesion healing was 9 days in each treatment group. The median time to the cessation of viral shedding was 3 days in each treatment group. Median time to cessation of pain was 5 days in each treatment group.

Recurrent Genital Herpes Simplex Infections

The other three studies enrolled immunocompetent patients with a history of recurrent genital herpes infections. These studies compared valaciclovir (1000 mg and/or 500 mg twice daily) with aciclovir (200 mg five times daily) and/or placebo, administered for 5 days. Patients self-initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

The primary efficacy end-points in each study were:

- lesions healing time and pain/discomfort
- proportions of patients in whom lesions were prevented (aborted lesions)
- viral shedding

In one study, patients were randomised to receive five days of treatment with either valaciclovir 500 mg bid (n = 360) or placebo (n = 259).

Duration of lesions: the median time to lesion healing was four days in the group receiving valaciclovir 500 mg versus six days in the placebo group.

Cessation of viral shedding: the median time to cessation of viral shedding in patients with at least one positive culture (42% of the overall study population) was two days in the group receiving valaciclovir 500 mg versus four days in the placebo group.

Cessation of pain: the median time to cessation of pain was three days in the group receiving valaciclovir 500 mg versus four days in the placebo group. Results supporting efficacy were replicated in the other two studies.

Prevention of lesion development (aborted episodes): pooled analysis of the three studies also showed that the use of valaciclovir in patients who self-initiated treatment in the prodrome, increased the chances of preventing lesion development (aborting episodes) by 31% to 44% compared with placebo.

Prevention of Recurrent Genital Herpes Simplex Virus (HSV) Infections

Three large, multicentre, double-blind, randomised trials were conducted to investigate the efficacy of valaciclovir for the prevention of recurrent genital HSV infection. Two studies evaluated the disease in immunocompetent individuals, while the third evaluated an immunocompromised (HIV-infected) population.

Immunocompetent Patients

The two trials conducted in immunocompetent patients included a total of 1861 patients, of which 1366 received valaciclovir for up to 52 weeks. The primary endpoint in both trials was defined as the first clinical recurrence of HSV infection, and the proportion recurrence free at the end of 12 months was another endpoint. In Study BQRT/95/0026, 500 mg once daily treatment with valaciclovir was compared with placebo in patients with a history of at least 8 recurrences per year. Clinical recurrence was defined as lesions reaching the papule/vesicle stage, and valaciclovir delayed or prevented 85% of the recurrences compared with placebo.

Study BQRT/96/0001 was a double-blind study comparing a variety of valaciclovir doses and aciclovir with placebo. Clinical recurrence was defined as lesions at the macule/papule stage. As HSV infection had been identified as a strong prognostic factor in previous genital herpes studies, subgroup analyses were conducted according to recurrence history. The results from the proportional hazard analyses (hazard ratios and 95% CI) for the active treatment comparisons with placebo obtained within each subgroup are presented as follows:

Table 10:

HSV Recurrence Frequency	Comparison	Hazard Ratio	95% Confidence Interval
< 10	VACV 250 mg bd vs PBO	0.122	(0.083, 0.181)
	VACV 1000 mg od vs PBO	0.160	(0.110, 0.231)
	VACV 500 mg od vs PBO	0.182	(0.128, 0.258)
	VACV 250 mg od vs PBO	0.319	(0.227, 0.448)
	ACV 400 mg bd vs PBO	0.160	(0.109, 0.234)
≥ 10	VACV 250 mg bd vs PBO	0.325	(0.226, 0.468)
	VACV 1000 mg od vs PBO	0.274	(0.188, 0.400)
	VACV 500 mg od vs PBO	0.451	(0.308, 0.659)
	VACV 250 mg od vs PBO	0.632	(0.446, 0.895)
	ACV 400 mg bd vs PBO	0.261	(0.181, 0.378)

PBO = placebo; VACV = valaciclovir; ACV = aciclovir; od = once daily; bd = twice daily

Results show that 250 mg twice daily offered the best clinical efficacy for suppression of genital herpes recurrences in this group of patients. However, the same total daily dose given as a single daily dose (i.e. 500 mg once daily) was also very effective, as confirmed with Study BQRT/95/0026.

Although 1000 mg daily was more effective than 500 mg once daily in the first study, the marginal difference between the two did not justify long-term exposure to double the daily dose. The hazard ratio comparing valaciclovir 1000 mg once daily and 500 mg once daily indicated an increase in efficacy of only approximately 12% (hazard ratio: 0.879; 95% CI: 0.637, 1.211).

Immunocompromised Patients

A third study examined a total of 1062 immunocompromised patients (HIV-infected, $CD4^+$ counts of ≥ $100/mm^3$ at enrolment) of whom 713 received valaciclovir (1000 mg once daily, 500 mg twice daily,

48 weeks) compared with 349 patients who received aciclovir (400 mg twice daily, 48 weeks). The primary endpoint was the time to first HSV recurrence (onset of macules/papules). The study demonstrated that valaciclovir 500 mg twice daily is as effective as aciclovir in preventing or delaying HSV infections in immunocompromised patients. Valaciclovir 500 mg twice daily was significantly more efficacious than valaciclovir 1000 mg once daily.

Reduction of Genital Herpes Simplex Virus Transmission

Study HS2AB3009 was a randomised, double-blind, placebo-controlled trial evaluating valaciclovir 500 mg once daily for eight months in the prevention of HSV-2 transmission in heterosexual monogamous couples. 1484 couples received treatment with 741 source partners receiving placebo and 743 source partners receiving valaciclovir. Source partners had to be seropositive for HSV-2 and have a history of recurrent genital herpes with less than 10 recurrences per year. Susceptible partners could not be seropositive for HSV-2, but could be seropositive for HSV-1. Couples were encouraged to practice safer sex (including use of condoms). The primary endpoint of the study was the proportion of couples that developed clinical evidence of a first episode of genital herpes HSV-2 in the susceptible partner. Clinical evidence of a first episode was defined as symptomatic genital herpes confirmed by laboratory analysis.

The results of this study established that the proportion of couples with clinical symptoms of genital herpes in the susceptible partner was higher in the placebo group than in the valaciclovir group (2.2% vs. 0.5% respectively). The risk of transmission of symptomatic genital herpes was reduced by 75% (95% CI: 26%, 92%, p = 0.011) in the valaciclovir group, a difference which is both clinically and statistically significant.

The results of the time to event analysis confirm those of the primary endpoint, with the time to clinical symptoms being significantly longer in the valaciclovir group compared with the placebo group (p = 0.008).

The proportion of couples with overall acquisition* of genital HSV-2 infection in the susceptible partner was 3.6% (27/741) in the placebo group and 1.9% (14/743) in the valaciclovir group (p = 0.054, approximate relative risk (95% CI): 0.52 (0.27, 0.97)). These analyses show that there was a 48% reduction in the risk of acquiring HSV-2 infection in the valaciclovir group compared with the placebo group. This difference approached statistical significance for overall acquisition.

(* Overall Acquisition: in which the susceptible partner acquired genital herpes HSV-2 infection, as documented by HSV-2 seroconversion only, or by seroconversion and/or detection of the virus by culture or PCR, and irrespective of the presence of clinical symptoms).

The result of the analysis of time to overall acquisition of HSV-2 (hazard ratio: 0.52; 95% CI: 0.27, 0.99), which explicitly allows for differential length of follow-up, is statistically significant (p = 0.039).

The proportion of couples with HSV-2 seroconversion in the susceptible partner was 3.2% (24/741) in the placebo group and 1.6% (12/743) in the valaciclovir group (p = 0.060, approximate relative risk (95% CI): 0.50 (0.25, 0.99)).

The proportion of couples with asymptomatic seroconversion in the susceptible partner was 1.5% (11/741) in the placebo group and 1.3% (10/743) in the valaciclovir group (p = 0.996), approximate relative risk (95% CI): 0.91 (0.39, 2.12)).

Valaciclovir was effective in reducing the risk of genital HSV-2 recurrence in source partners (the proportion of source partners with a genital HSV-2 recurrence was: placebo: 573/724, 79%; valaciclovir: 288/715, 40%), with the time to first recurrence being significantly longer in the valaciclovir group compared with the placebo group (p < 0.001; hazard ratio: 0.30; 95% CI: 0.26, 0.35).

The incidence of the primary endpoint was higher in the female susceptible partners than in the male susceptible partners. The proportion of female susceptible partners in whom clinical evidence of first episode genital HSV-2 infection was reported was 4.1% (10/244) in the placebo group and 0.8% (2/244) in the valaciclovir group. The proportion of male susceptible partners in whom clinical evidence of first episode genital HSV-2 infection was reported was 1.2% (6/497) in the placebo group and 0.4% (2/499) in the valaciclovir group.

The safety profile of valaciclovir in this study was similar to that of placebo, and to that demonstrated previously for this dosing regimen in a similar population.

Prophylaxis of Cytomegalovirus (CMV) Infection and Disease, Following Organ Transplantation

Three double-blind, randomised, clinical studies were conducted to investigate the efficacy and safety of valaciclovir in the prophylaxis of CMV infection and disease following renal or heart transplantation. These studies included a total of 643 patients, of whom 320 received valaciclovir, 13 received aciclovir and 310 received placebo.

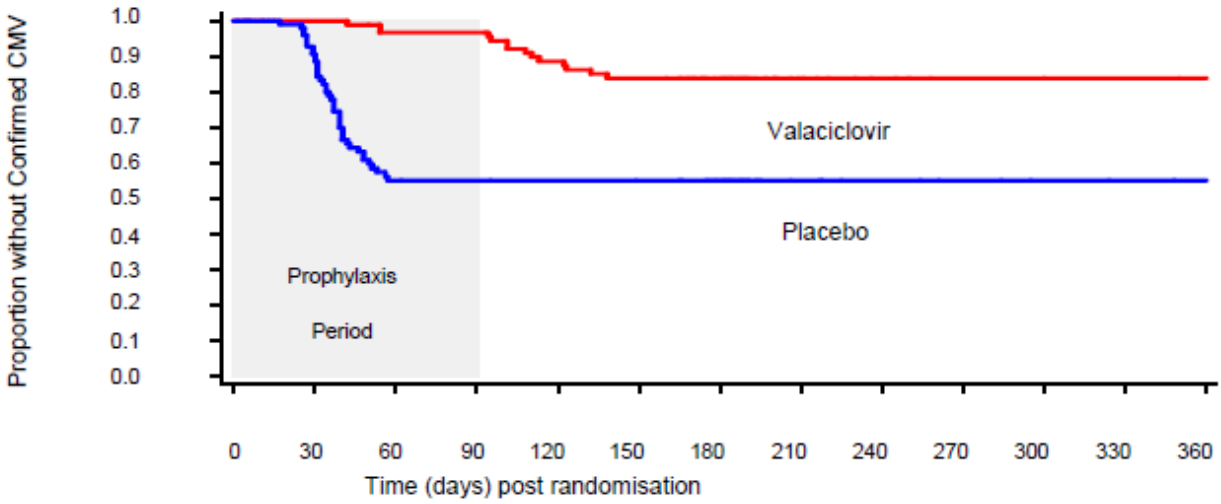
The primary efficacy endpoint in renal transplant studies was the development of CMV disease and the primary endpoint in the heart transplant study was the development of CMV antigenaemia. Secondary endpoints for the studies included CMV disease (heart transplant study), CMV infection, reduced acute graft rejection, fewer opportunistic bacterial or fungal infections and reduced herpes virus disease (HSV, VZV).

Renal Transplant Studies

The two renal transplant studies involved a total of 616 renal transplant recipients, of which 306 received a daily dose of 2 g valaciclovir four times daily (adjusted according to creatinine clearance for renal function) and 310 received placebo for 90 days. The patients were stratified by donor and recipient CMV-serostatus (seropositive recipients [R+] versus seronegative recipients of a graft from a seropositive donor [D+R-]). Patients commenced study drug within 72 hours post-transplant and continued treatment for 90 days (treatment period) receiving, following adjustment for renal function, a daily average dose of 4.7 g ([R+] subjects) and 5.3 g ([D+R-] subjects) valaciclovir. Patients were evaluated for efficacy and safety for six months post-transplant (study period).

In renal transplant recipients, valaciclovir was significantly better than placebo in preventing or delaying CMV disease by 78% and 82% in the [D+R-] and [R+] strata respectively during the six month study period.

Figure 2: Proportions of patients [D+R-] without confirmed CMV disease: Kaplan-Meier plots for valaciclovir versus placebo



Valaciclovir was also significantly better than placebo in preventing or delaying the development of viraemia, viruria and clinical HSV disease during the study period. No valaciclovir recipient developed VZV disease, whereas 2% and 4% of placebo patients did, R+ and D+R- strata respectively. Additionally, in D+R- patients, valaciclovir was shown to significantly reduce acute graft rejections (biopsy proven and clinical acute rejection by 57% and 45% respectively) and opportunistic infections (48% primarily bacterial and fungal infections). There were no significant differences in rates of chronic graft rejection. Allograft function and survival, including the proportion of patients with a functional graft at their last assessment were similar between treatment groups. Administration of valaciclovir was associated with significantly fewer hospital admissions and reduced use of ganciclovir and aciclovir for the treatment of CMV disease or other herpes virus infections, respectively.

Heart Transplant Study

The third study enrolled 27 heart transplant recipients. This study compared valaciclovir (n = 14, 2 g four times daily, adjusted according to creatinine clearance for renal function) with aciclovir (n = 13, 200 mg four times daily). Treatment was commenced within 3 days post-transplant and continued for 90 days. Patients were followed up until the end of the sixth month.

During the 90 day treatment period, 29% of patients on valaciclovir developed CMV antigenaemia (primary endpoint) compared to 92% of patients who received aciclovir. The time difference to CMV antigenaemia was statistically significant, with median time to CMV antigenaemia of 19 vs. 119 days in favour of valaciclovir (HR = 0.422; 95% CI: 0.179, 0.992; p = 0.049). At the end of the study period (3 months following the treatment period) the proportion of patients with CMV antigenaemia was similar in both treatment arms.

Notable but not statistically significant reductions in the rates of CMV infection (valaciclovir 43%, aciclovir 92%), symptomatic CMV infection (valaciclovir 0%, aciclovir 38%), CMV disease (valaciclovir 0%, aciclovir 23%) and HSV disease (valaciclovir 29%, aciclovir 54%) were observed during the 90 day treatment period. The incidence of other infections (bacterial, fungal, non-herpes virus) was also lower in the valaciclovir group throughout the entire study period (valaciclovir 36%, aciclovir 62%). There were no significant differences in graft rejection and survival rates between the valaciclovir and aciclovir patients at the end of the study (3 months following treatment period).

Table 11:

Results for the primary and secondary endpoints in the pivotal trials

Endpoints	Renal [D+ R-]			Renal [R+]			Heart		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
CMV disease	0.22	0.12, 0.40	< 0.0001	0.18	0.04, 0.83	<0.027	0.19	0.02, 1.70	0.09
CMV antigenaemia	n/d	n/d	n/d	n/d	n/d	n/d	0.42	0.18, 0.99	0.049
CMV infection	n/d	n/d	n/d	n/d	n/d	n/d	0.46	0.20, 1.06	0.075
CMV viraemia	0.25	0.14, 0.44	<0.0001	0.28	0.18, 0.45	<0.0001	n/d	n/d	n/d
CMV viruria	0.49	0.32, 0.76	0.001	0.32	0.24, 0.44	<0.0001	n/d	n/d	n/d
Acute graft rejection									
- biopsy proven	0.43	0.27,	0.001	0.86	0.60,	0.40	0.51	0.22,	0.09
- clinical	0.55	0.70	0.004	0.75	1.22	0.073	n/d	1.19	n/d
		0.37, 0.83			0.55, 1.03			n/d	
Opportunistic infections	0.52	0.36, 0.76	0.001	0.90	0.70, 1.16	0.41	(0.42)*	NP	NP
HSV disease	0.33	0.15, 0.74	0.007	0.16	0.09, 0.30	<0.0001	n/d	n/d	n/d
VZV disease	Did not develop			Did not develop			Did not develop		

Results based on entire study period (3 months treatment followed by 3 months follow up)

* odds ratio in brackets n/d = not done
NP = not protocolled

Bone Marrow Transplant Studies

Two additional clinical studies have been conducted to assess the safety and efficacy of valaciclovir tablets in the prophylaxis of CMV infection in bone marrow transplant recipients. The adverse event data from these trials is consistent with the current safety profile of valaciclovir.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After oral administration, valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by valaciclovir hydrolase, an enzyme isolated from

human liver. Mean peak aciclovir concentrations are 10 – 37 micromoles (2.2 – 8.3 micrograms/mL) following single doses 250 – 2000 mg valaciclovir to healthy subjects with normal renal function and occur at a median time of 1.00 – 2.00 hours post dose. The time to peak (T_{max}) is 1.6 hours for 2x 500 mg tablets and 1.9 hours for a 1000 mg tablet. The bioavailability of aciclovir following a dose of 1000 mg of valaciclovir is 54% and is unaffected by food. Peak plasma concentrations of valaciclovir are only 4% of aciclovir levels, occur 30 - 100 minutes post dose and are at or below the limit of quantification 3 hours after dosing.

Aciclovir maximum concentration (C_{max}) and area under the aciclovir concentration-time curve (AUC) after single-dose administration of 100 mg, 250 mg, 500 mg, 750 mg and 1 g of valaciclovir to 8 healthy volunteers resulted in the mean C_{max} (± SD) of 0.83 (± 0.14), 2.15 (± 0.50), 3.28 (± 0.83), 4.17 (± 1.14) and 5.65 (± 2.37) mcg/mL, respectively; and a mean AUC (± SD) of 2.28 (± 0.40), 5.76 (± 0.60), 11.59 (± 1.79), 14.11 (± 3.54) and 19.52 (± 6.04) hr•mcg/mL, respectively.

Similarly, aciclovir C_{max} and AUC after the multiple-dose administration of 250 mg, 500 mg and 1 g of valaciclovir administered 4 times daily for 11 days in parallel groups of 8 healthy volunteers resulted in a mean C_{max} (± SD) of 2.11 (± 0.33), 3.69 (± 0.87) and 4.96 (± 0.64) mcg/mL, respectively; and a mean AUC (± SD) of 5.66 (± 1.09), 9.88 (± 2.01) and 15.70 (± 2.27) hr•mcg/mL, respectively.

Distribution

Binding of aciclovir to plasma proteins is very low (9 to 33%).

CSF penetration, determined by CFS/plasma AUC ratio, is about 25% for aciclovir and the metabolite 8-hydroxy-aciclovir (8-OH-ACV), and about 2.5% for the metabolite 9-(carboxymethoxy)methylguanine (CMMG), regardless of renal function (see Section 5.2 PHARMACOKINETICS PROPERTIES – Metabolism and Special Populations).

Metabolism

After oral administration, valaciclovir is converted to aciclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9-(carboxymethoxy)methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase. Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8-OH-ACV. Neither valaciclovir nor aciclovir is metabolised by cytochrome P450 enzymes.

Excretion

In patients with normal renal function, the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is eliminated principally as aciclovir (greater than 80% of the recovered dose) and the known aciclovir metabolite, 9-(carboxymethoxy)methylguanine (CMMG), in the urine.

Special Populations

The pharmacokinetics of valaciclovir and aciclovir are not altered significantly in patients with herpes zoster and herpes simplex infections after oral administration of valaciclovir.

Renal Impairment

The elimination of aciclovir is correlated to renal function and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function.

Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91 – 144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17 – 31 mL/min) receiving

1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5 – 6 times higher, respectively, in severe renal impairment compared with normal renal function. There was no difference in extent of CSF penetration (as determined by CSF/plasma AUC ratio) for aciclovir, CMMG or 8-OH-aciclovir between the two populations (see Section 5.2 PHARMACOKINETICS PROPERTIES - Distribution).

Hepatic Impairment

Administration of valaciclovir to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate but not the extent of conversion of valaciclovir to aciclovir is reduced, and the aciclovir half-life is not affected. Dosage modification is not recommended for patients with cirrhosis. For higher doses (4000 mg or more per day), see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use of High Dose Valaciclovir in Hepatic Impairment and Liver Transplantation.

HIV Infection

In patients with HIV infection, the disposition and pharmacokinetic characteristics of aciclovir after oral administration of multiple doses of 1000 mg valaciclovir are unaltered compared with healthy subjects.

Elderly

After single-dose administration of 1 g of valaciclovir in healthy geriatric volunteers, the half-life of aciclovir was 3.11 ± 0.51 hours, compared with 2.54 ± 0.33 hours in healthy younger adult volunteers. The pharmacokinetics of aciclovir following single- and multiple-dose oral administration of valaciclovir in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Valaciclovir was not mutagenic in bacterial cells nor did it demonstrate any clastogenic potential *in vitro* in human lymphocytes or *in vivo* in the rat bone marrow assay. The mouse micronucleus assay was negative at 250 mg/kg but weakly positive at 500 mg/kg. Valaciclovir, at concentrations ≥ 2000 micrograms/mL, in the presence of S9 metabolic activation was mutagenic in the mouse lymphoma assay. The active metabolite, aciclovir, was clastogenic in Chinese hamster cells *in vivo*, at exposure levels also causing nephrotoxicity (500 and 1000 mg/kg parenteral dose). There was also an increase, though not statistically significant, in chromosomal damage at maximum tolerated doses (100 mg/kg) of aciclovir in rats. No activity was found in a dominant lethal study in mice or in 4 microbial assays. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* (positive in human lymphocytes *in vitro* and one locus in mouse lymphoma cells, negative at 2 other loci in mouse lymphoma cells and 3 loci in a Chinese hamster ovary cell line).

The results of these mutagenicity tests *in vitro* and *in vivo* suggest that valaciclovir and aciclovir are unlikely to pose a genetic threat to man at therapeutic dose levels.

Carcinogenicity

The data presented below include references to the steady-state aciclovir AUC observed in humans treated with 1 g valaciclovir given orally three times a day to treat herpes zoster (HZV) or with 2 g valaciclovir given orally four times a day to treat cytomegalovirus (CMV). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to aciclovir.

Valaciclovir was noncarcinogenic in lifetime carcinogenicity bioassays at oral doses of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tumours between treated and control animals, nor did valaciclovir shorten the latency of tumours. Plasma concentrations (AUC) of aciclovir were equivalent to 1.1 (HZV) and 0.1 (CMV) times human levels in the mouse bioassay and 1.3 (HZV) and 0.1 (CMV) times human concentrations in the rat bioassay.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VACLOVIR tablets contain microcrystalline cellulose, magnesium stearate and Opadry complete film coating system OY-58900 white (ID 3446).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container types: Al/Al blister packs (250 mg, 500 mg, 1000 mg)

HDPE bottles with polypropylene caps (500 mg)

Pack sizes:	250 mg:	60 tablets (blister packs)
	500 mg:	2, 4, 6, 8, 10, 20, 30, 42, 60, 80, 90, 100, 240 and 480 tablets (blister packs)
		and 8, 10, 30, 42, 100, 240, 480 and 500 tablets (bottles)
	1000 mg:	3, 4, 21 (blister packs)

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 153822 – VACLOVIR 500 valaciclovir (as hydrochloride) 500 mg tablet blister pack

AUST R 153823 – VACLOVIR 500 valaciclovir (as hydrochloride) 500 mg tablet bottle pack

AUST R 153824 – VACLOVIR 250 valaciclovir (as hydrochloride) 250 mg tablet blister pack

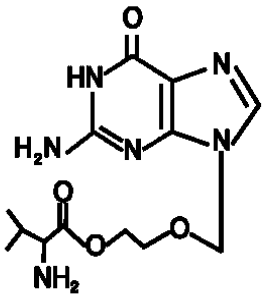
AUST R 153825 – VACLOVIR 1000 valaciclovir (as hydrochloride) 1000 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



Chemical name: 2-[(2-amino-6-oxo-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl *L*-valinate hydrochloride

Molecular formula: $C_{13}H_{20}N_6O_4$,HCl

Molecular weight: 360.8

CAS number: 124832-27-5

Valaciclovir is the L-valine ester of acyclovir. Aciclovir is a purine nucleoside analogue.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

4/11/2010

10 DATE OF REVISION

31/08/2026

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Expand drug reaction with eosinophilia and systemic symptoms (DRESS) precaution to include additional severe cutaneous adverse reactions (SCARs).
4.8	Minor editorial changes. Include additional adverse effects in 'Skin and subcutaneous tissue disorders'.

VACLOVIR® is a Viatris company trade mark

VACLOVIR_pi\Aug26/00