AUSTRALIAN PRODUCT INFORMATION
VALACICLOVIR APOTEX
(VALACICLOVIR HYDROCHLORIDE)

1 NAME OF THE MEDICINE

Valaciclovir Hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VALACICLOVIR APOTEX film-coated tablets contains 500 mg valaciclovir (as hydrochloride).

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

3 PHARMACEUTICAL FORM

Tablet.

Blue coloured, capsule shaped, biconvex, film coated tablets, debossed with **'V'** and **'5'** on either side of the breakline on one side, notched on either side along with the breakline and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VALACICLOVIR APOTEX are indicated:

- 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 clinical episodes of genital herpes simplex infections.
- For the prevention of recurrent genital herpes in immunocompromised patients with creatinine clearance of >15 mL/min.
- For reduction of transmission of genital herpes in patients suffering from recurrent genital herpes. In addition to therapy with valaciclovir, it is recommended that patients use safer sex practices. (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).**

- For 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 treatment of herpes zoster, 1000 mg of valaciclovir (2 tablets of VALACICLOVIR APOTEX) three times a day for seven days.

For treatment of first clinical presentation of genital herpes, 500 mg of valaciclovir (1 tablet of VALACICLOVIR APOTEX) twice a day for 5 to 10 days.

For recurrent episodes of genital herpes, 500 mg of valaciclovir (1 tablet of VALACICLOVIR APOTEX) twice daily 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 in immunocompromised patients, 500 mg of valaciclovir (1 tablet of VALACICLOVIR APOTEX) 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 valaciclovir (1 tablet of VALACICLOVIR APOTEX) 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 (CMV) infection and disease:

Dosage in adults and adolescents (from 12 years of age)

The dosage of valaciclovir is 2 g (4 tablets of VALACICLOVIR APOTEX) 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 valaciclovir to patients with impaired renal function. Adequate hydration should be maintained.

Herpes zoster treatment and herpes simplex treatment, suppression and reduction of transmission of genital herpes: The dose of valaciclovir should be modified as follows in patients with significantly impaired renal function, see Table 1:

Table 1

Creatinine Clearance	Valaciclovir Dose		
	Herpes Zoster	Herpes Simplex	
		Treatment	Reduction of Transmission of genital herpes
15-30 mL/min	1000 mg twice a day	No modification required	No modification required
< 15 mL/min	1000 mg once a day	500 mg once daily	250 mg once daily

For the prevention of herpes simplex in immunocompromised patients with creatinine clearance of >15 mL/min, no dose modification is required.

In patients on haemodialysis the valaciclovir 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 valaciclovir should be adjusted in patients with impaired renal function as shown in the Table 2 below:

Table 2

Creatinine clearance mL/min	Valaciclovir 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 ◊	1.5 g once a day

◊ In patients on haemodialysis, the valaciclovir 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 valaciclovir dosage should be adjusted accordingly.

Dosage in hepatic impairment

Studies with a 1 g unit dose of valaciclovir 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

Dosage in special patient groups

No dosage recommendations.

Monitoring advice

No special monitoring necessary.

Instructions for use

No special instructions for use.

4.3 CONTRAINDICATIONS

VALACICLOVIR APOTEX 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, 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 grams per day.

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 > $100x10^6L$ has not been associated with occurrences of thrombotic microangiopathy (TMA). However

use in severely immunocompromised patients ($CD4^+$ counts < $100x10^6L$) has not been examined at this low dosage.

Hydration Status

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

Information for Patients

Patients should be informed that valaciclovir (or any other antiviral) is not a cure for genital herpes. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding.

Use in Genital Herpes

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. In addition to therapy with valaciclovir, it is recommended that patients use safer sex practices.

Use of high dose valaciclovir in hepatic impairment and liver transplantation

There are no data available on the use of high doses of valaciclovir (8 g/day) in patients with liver disease. Caution should therefore be exercised when administering high doses of valaciclovir to these patients. Specific studies of valaciclovir have not been conducted in liver transplantation; however high dose aciclovir has been studied in this population.

Use in renal impairment

The dose of valaciclovir must be reduced in patients with renal impairment (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). Aciclovir delivered by valaciclovir is eliminated by renal clearance (see **Section 5.2 PHARMACOLOGICAL 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**).

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. In the event of acute renal failure

and anuria, the patient may benefit from hemodialysis until renal function is restored (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

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**).

Reversible neurological reactions including 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 (8g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Paediatric Use

Safety and effectiveness in children have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations following valaciclovir administration.

Following 1g valaciclovir, cimetidine and probenecid increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of aciclovir.

In patients receiving high-dose valaciclovir (8g/day) for CMV prophylaxis, caution is required during concurrent administration with drugs which 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 coadministered.

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 (eg cyclosporin, tacrolimus).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effect on Fertility

Valaciclovir did not impair fertility or reproduction in rats at 200 mg/kg per day, corresponding to plasma levels 2.8 (HZV) and 0.3 (CMV) times human plasma concentrations (AUC).

Use in 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, foetal 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. As of July 1998, outcomes of live births have been documented in 574 women exposed to systemic aciclovir during the first trimester of pregnancy (most at oral doses up to 1000mg per day). Registry findings do not indicate an increased risk of major birth defects after aciclovir exposure, i.e. 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.

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 µg/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.

Limited data show that aciclovir does pass into human breast milk. Aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding aciclovir plasma concentrations. 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 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.

Herpes Zoster Infections:

The following Table 3 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 3

% Incidence of adverse events				
Patient age group	**≥ 50 years**		**18 to 50 years**	
	valaciclovir 1 g 3 x daily (n=765) 14 days (n=381) 7 days (n=384)	**aciclovir 800 mg 5 x daily 7 days (n=376)**	**valaciclovir 1 g 3 x 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
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 4:

Table 4

	% Incidence of adverse events (in patient age group of 17 - 79 years)		
	valaciclovir 1 g 2 x daily (n=1203) 10 days (n=323) 5 days (n=880) 500 mg 2 x daily 5 days (n=738)	**aciclovir 200 mg 5 x daily 5 days (n=1187)**	**placebo (n=441)**
Headache	16	11	14
Nausea	6	7	7
Diarrhoea	4	3	6
Dizziness	3	2	2
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 5:

Table 5

% Incidence of adverse events in immunocompromised patients		
	Valaciclovir 500mg 2 x daily 48 weeks (n = 355)	**Aciclovir 400mg 2 x daily 48 weeks (n = 349)**
Headache	18	17
Rhinitis	13	14
Infection	16	13
Flu syndrome	7	7
Pharyngitis	11	13
Nausea	16	12
Back Pain	6	7
Diarrhoea	19	19
Abdominal Pain	12	7
Pain	6	6
Sinusitis	7	7
Accidental Injury	3	5
Dysmenorrhoea	-	-
Dyspepsia	3	4

Rash	14	14
Arthralgia	3	3
Depression	9	7
Allergic Reaction	-	-
Urinary Tract Infection	-	-
Bronchitis	3	7
Myalgia	3	5
Asthenia	8	9
Tooth Disorder	1	3
Unevaluable Reaction	3	4
Migraine	-	-
Acne	5	3
Dizziness	2	3
Insomnia	3	4
Vomiting	7	5
Pruritus	5	3
Increased Coughing	6	10
Fever	11	11
Rectal Disorder	4	5

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 the renal transplant patients were anaemia, hypertension and headache. Headache and mylagia were the most common adverse events reported in the 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 6 and 7.

Table 6

Summary of all adverse events reported at an incidence ≥ 5% by renal transplant recipients in clinical trials for CMV prophylaxis.		
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%
Oedema	4%	5%
AST*** increase	4%	6%

Table 7

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

*The dosage adjustment of valaciclovir (and aciclovir) in the renal and heart transplant clinical studies differed.

** ALT = alanine aminotransferase.

*** AST = aspartate aminotransferase.

Other Adverse Reactions

The following adverse events have been observed in clinical practice with valaciclovir:

Gastrointestinal tract:

Common - nausea, abdominal discomfort, vomiting and diarrhea.

Haematological:

Rare – thrombocytopenia.

Very rare – leukopenia*, thrombotic microangiopathy (TMA) (refer to Section **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

*Leukopenia is mainly reported in immunocompromised patients.

Hypersensitivity, skin and subcutaneous tissue disorders:

Uncommon – rashes including photosensitivity, urticaria, pruritus

Rare – dyspnoea angioedema and anaphylaxis

Immune system disorders:

Very rare – anaphylaxis

Kidney:

Rare - renal impairment.

Very rare – reports of acute renal failure, renal pain

Renal pain associated with renal failure have been reported.

Liver:

Rare - reversible increases in liver function tests, occasionally described as hepatitis.

Neurological/psychiatry:

Common - headache.

Uncommon - dizziness*, confusion* and hallucinations* Rare - decreased consciousness*
Very rare - coma*, agitation*, tremor*, ataxia*, dysarthia*, psychotic symptoms*, convulsions*, encephalopathy*
*usually in patients with renal impairment or with other predisposing factors. In organ transplant patients receiving high doses of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Respiratory, thoracic and mediastinal disorders:
Uncommon – dyspnea
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 effects
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 http://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 Poison Information Centre on 131126 (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 – 3.0μM), varicella-zoster virus (VZV) (IC_{50} 1.6 – 5.1μM) and human cytomegalovirus (HCMV) (IC_{50} 10 - > 200μM). 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.

Drug Resistance

Resistance of HSV and VZV to aciclovir can result from qualitative and quantitative changes in the viral (thymidine kinase) TK and/or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to aciclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV and VZV to aciclovir occurs by the same mechanisms. While mast 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 valacyclovir (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

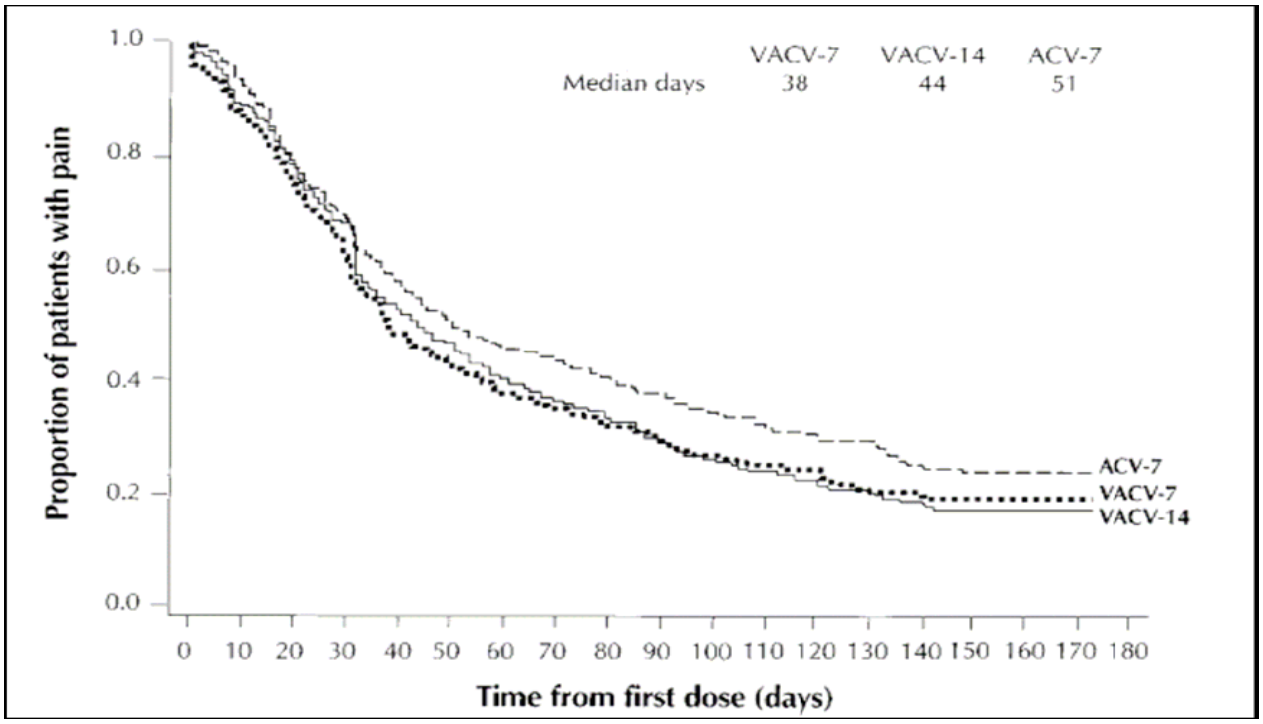
the sum of acute pain and post-herpetic neuralgia) and in the duration of post-herpetic neuralgia when compared with aciclovir, see Table 8. There was no statistically significant difference between the three treatments for the resolution of rash.

Table 8

	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 hours 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.

Figure 1: Duration of Zoster-associated Pain: Kaplan-Meier Plots for Valaciclovir versus Aciclovir for Patients ≥ 50 years old.



NOTE: ACV-7 – aciclovir at 800 mg five times daily for 7 days; VACV-7 – valaciclovir at 1000 mg three times daily for 7 days; VACV-14 – valaciclovir at 1000 mg 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 required for these beneficial effects.

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 randomized 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 randomized 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 in Immunocompromised patients:

A 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:

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 was conducted. 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 seropostive 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 4.7g ([R+] subjects) and 5.3g ([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.

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), see Table 9.

Table 9 **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 - clinical	0.43 0.55	0.27, 0.70 0.37, 0.83	0.001 0.004	0.86 0.75	0.60, 1.22 0.55, 1.03	0.40 0.073	0.51 n/d	0.22, 1.19 n/d	0.09 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 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. This conversion is probably mediated by valaciclovir hydrolase, an enzyme isolated from human liver. Mean peak aciclovir concentrations are 10-37 μM (2.2 – 8.3 μg/mL) following single doses of 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 2 x 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. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing.

Distribution

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

Metabolism

No data available.

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. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 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.

Characteristics in patients

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

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 µg/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 & 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 gram valaciclovir given orally three times a day to treat herpes zoster (HZV) or with 2 gram 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 times (CMV) 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

Microcrystalline cellulose, magnesium stearate, crospovidone, povidone (K 30), povidone (K 90D), indigo carmine aluminium lake, and Opadry complete film coating system 02C50740 Blue (PI 12532).

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, the 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

Blister pack PVC/PVDC/Al (polyvinyl chloride/polyvinylidene chloride/aluminium)
Pack sizes: 10, 30, 42 or 100 tablets.

*Not all packs sizes and/or pack types may be available.

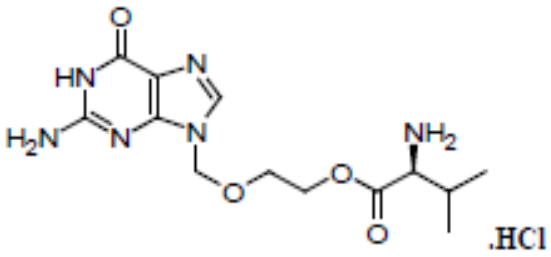
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure



Chemical 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 aciclovir which is a purine nucleoside analogue.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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Tel: (02) 8877 8333

Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

09 July 2009

10 DATE OF REVISION

28 November 2018

Summary table of changes

Section Changed	Summary of new information
8	Change in Sponsor address