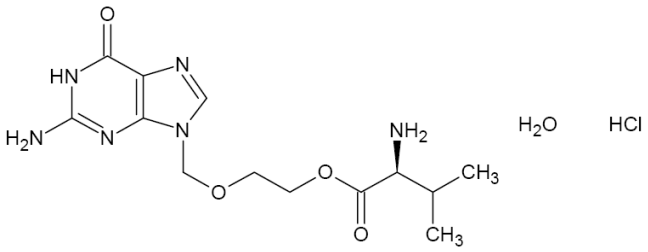
**APO-VALACICLOVIR TABLETS**

## NAME OF THE MEDICINE

Valaciclovir Hydrochloride Monohydrate

Chemical Name: (1) L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethylester, monohydrochloride(2) L-Valine, ester with 9-[(2-hydroxyethoxy) methyl] guanine, monohydrochloride

Structural Formula:




Molecular Formula: $C_{13}H_{20}N_6O_4HCl.H_2O$

Molecular Weight: 378.8

CAS Registry Number: 124832-27-5

## DESCRIPTION

Valaciclovir is the L-valine ester of aciclovir. Aciclovir is a purine nucleoside analogue. The maximum solubility of valaciclovir hydrochloride monohydrate in water is 174 mg/mL at 25°C.

## PHARMACOLOGY

### Pharmacological Actions

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.

## 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 a 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.

## Pharmacokinetics

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 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.

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 gram 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 gram 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 CSF/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 Pharmacokinetics: Metabolism and Pharmacokinetics: Special Patient 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.

Elimination

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.

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.

**Special Populations**

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 Pharmacokinetics: 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 Precautions).

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 gram 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 DOSAGE AND ADMINISTRATION).

End-Stage Renal Disease (ESRD): Following administration of Valaciclovir to volunteers with ESRD, the average acyclovir half-life is approximately 14 hours. During haemodialysis, the acyclovir half-life is approximately 4 hours. Approximately one third of acyclovir in the body is removed by dialysis during a 4-hour haemodialysis session. Apparent plasma clearance of acyclovir in dialysis patients was 86.3 ± 21.3 mL/min/1.73 m2, compared to 679.16 ± 162.76 mL/min/1.73 m2 in healthy volunteers. Reduction in dosage is recommended in patients with renal impairment.

## CLINICAL TRIALS

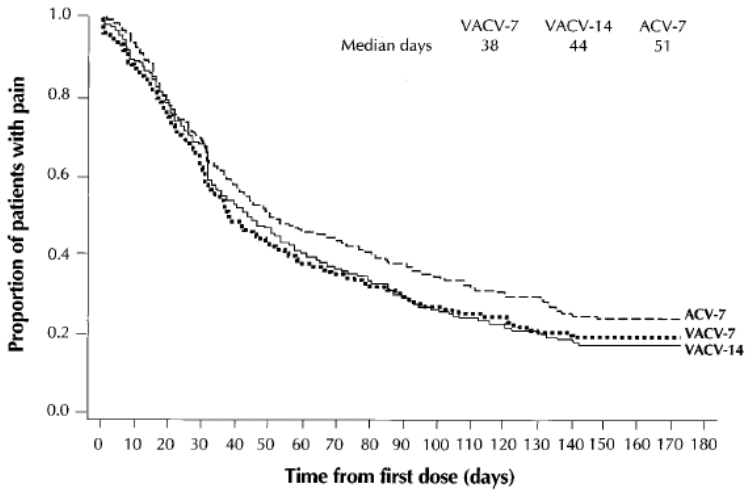
### Herpes Zoster Infections

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.

| | **Median duration (days)** | | |
|---|---|---|---|
| | **Valaciclovir 1 g three times daily** | | **Aciclovir 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.

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




NOTE: ACV-7 – aciclovir 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.

**Cold Sores (Herpes Labialis)**

Two double-blind, placebo-controlled clinical trials were conducted in 1,856 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 grams twice daily for one day OR valaciclovir 2 grams twice daily for one day, followed by 1 gram 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 - 44% of patients on one day valaciclovir therapy compared with 35 - 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.

<u>Initial genital herpes simplex infections</u>

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 Zovirax (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
Immunocompromised patients

A study examined a total of 1062 immunocompromised patients (HIV-infected, $CD_4^+$ counts of ≥ 100/$mm^3$ at enrolment) of whom 713 received valaciclovir (1000 mg once daily, 500mg 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.

**Prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation**

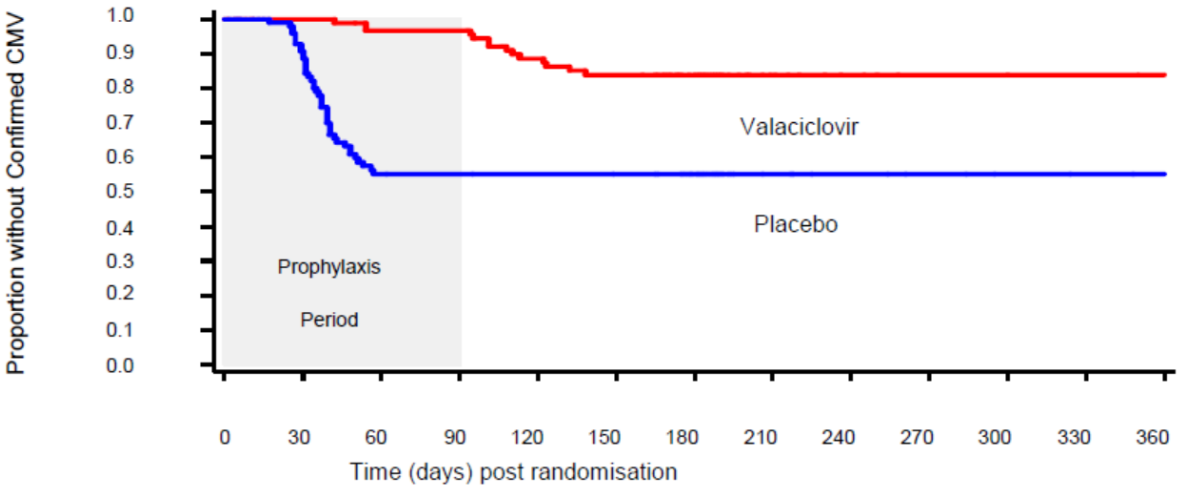
Three double-blind, randomised clinical studies were conducted to investigate the efficacy and safety of valaciclovir in the prophylaxis of CMV infection and disease following renal or heart transplantation. These studies included a total of 643 patients, of whom 320 received valaciclovir, 13 received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

**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).

**Results for the primary and secondary endpoints in the pivotal trials**

| **End points** | **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**<br>- **biopsy proven**<br>- **clinical** | 0.43<br><br>0.55 | 0.27, 0.70<br><br>0.37, 0.83 | 0.001<br><br>0.004 | 0.86<br><br>0.75 | 0.60, 1.22<br><br>0.55, 1.03 | 0.40<br><br>0.073 | 0.51<br><br>n/d | 0.22, 1.19<br><br>n/d | 0.09<br><br>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.

## 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 in immunocompromised patients.

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

## CONTRAINDICATIONS

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

## PRECAUTIONS

Thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome (TTP/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 grams 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 1000mg/day in immunocompromised patients with $CD4^+$ counts > $100x10^6$L has not been associated with occurrences of thrombotic microangiopathy (TMA). However use in severely immunocompromised patients ($CD4^+$ counts < $100x10^6$L) has not been examined at this low dosage.

**Use in patients with renal impairment**

The dose of valaciclovir must be reduced in patients with renal impairment (see **Dosage and Administration**). Valaciclovir is converted to aciclovir which is eliminated by renal clearance (see **Pharmacology**). 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 **Adverse Effects**).

**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.

**Effects on Fertility**

Valaciclovir did not impair fertility or reproduction in rats at 200mg/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 (80mg/kg/day) and dogs (100mg/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 aciclovir.

**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. Pregnancy registries have documented the pregnancy outcomes in women exposed to valaciclovir or to any formulation of aciclovir (the active metabolite of valaciclovir); 111 and 1,246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered. 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 area under plasma concentration time curve (AUC) following valaciclovir 1,000 and 8,000 mg daily would be approximately two and nine times greater than that expected with oral aciclovir 1,000 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. 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 had 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.

### Paediatric use

Safety and effectiveness in children have not been established.

### 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 **Adverse Effects**).

### 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.

**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.

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

### Driving

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.

### Central Nervous System 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. Valaciclovir should be discontinued if central nervous system adverse reactions occur.

## INTERACTIONS WITH OTHER MEDICINES

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 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 co-administered.

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. cyclosporin, tacrolimus).

## ADVERSE 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 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.

| | % 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 800mg 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:

| **Patient age group** | **% Incidence of adverse events17 – 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:

| | **Immunocompromised** | |
|---|---|---|
| | **V 500mg 2 x daily 48 weeks n=355** | **A 400 mg 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 |
| Athralgia | 3 | 3 |
| Depression | 9 | 7 |
| Allergic Reaction | - | - |
| Urinary Tract Infection | - | - |
| Bronchitis | 3 | 7 |
| Myalgia | 3 | 9 |
| Asthenia | 8 | 5 |
| 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 |

V= Valaciclovir; A= Aciclovir; 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 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.

**Summary of all adverse events reported at an incidence≥ 5% by <u>renal transplant recipients</u> 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% |
| Oedema | 4% | 5% |
| AST** increase | 4% | 6% |

**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% |

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

### Cold Sores (Herpes Labialis)

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 (>2 x 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) (refer to **PRECAUTIONS**).

*Leukopenia is mainly reported in immunocompromised patients

Immune system disorders:
Anaphylaxis

Psychiatric and nervous system disorders:
Decreased consciousness* dizziness*, confusion* and hallucinations*, coma*, agitation*, tremor*, ataxia*, dysarthia*, psychotic symptoms*, convulsions*, encephalopathy*

* The above events are generally reversible and usually in patients with renal impairment or with other predisposing factors (see **PRECAUTIONS**). In organ transplant patients receiving high doses (8 grams daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Respiratory, thoracic and mediastinal disorders:
Dyspnoea

Gastrointestinal tract:
Abdominal discomfort, vomiting and diarrhoea

Hepato-biliary disorders:
Reversible increases in liver function tests, occasionally described as hepatitis.

Skin and subcutaneous tissue disorders:
Rashes including photosensitivity, pruritus, urticaria, angioedema

Renal and urinary disorders:
Renal impairment, acute renal failure, renal pain, renal pain may be associated with renal failure.

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.

## DOSAGE AND ADMINISTRATION

### Dosage in Adults

For treatment of herpes zoster, 1000 mg of valaciclovir three times a day for seven days.

The recommended dosage of valaciclovir 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).

For treatment of first clinical presentation of genital herpes, 500 mg of valaciclovir twice a day for 5 to 10 days. For recurrent episodes of genital herpes, 500 mg 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 twice daily.

**For the prophylaxis of cytomegalovirus infection (CMV) and disease:**

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

The dosage of valaciclovir 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 ***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.

**Treatment of herpes zoster and genital herpes simplex:**

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

| Creatinine Clearance | Valaciclovir 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 | 500mg once daily | 250 mg daily |

**Treatment of herpes labialis:**

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

| Creatinine Clearance | Valaciclovir Dose |
|---|---|
| ≥ 50 mL/min | 2000 mg twice a day |
| 31-49L/min | 1000 mg twice a day |
| 15-30 mL/min | 500mg twice a day |
| <15 mL/min | 500 mg single dose |

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 below:

| 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 1g 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 **PRECAUTIONS.**

### 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 ***Dosage in renal impairment***). Adequate hydration should be maintained.

## OVERDOSAGE

#### 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. Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

#### PRESENTATION AND STORAGE CONDITIONS

**500 mg tablets**
Dark blue, capsule-shaped, biconvex film-coated tablets, engraved “APO” on one side, “VAL 500” on the other side.

Available in blisters of 2, 4, 6, 8, 10, 20, 30, 42, 60, 80, 90, 100, 240, 480 tablets (AUST R 158911) and bottles of 100, 240, 480, 50 tablets (AUST R 158910)*

**1000 mg tablets**
White, oval shaped, biconvex film coated-tablet, partially scored and engraved “APO” on one side, “VAL 1000” on the other side.

Available in blisters of 3, 4, 21 tablets (AUST R 158906) and bottles of 100, 250 tablets (AUST R 158907)*

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

Valaciclovir tablets are intended for oral administration. Each tablet contains either 500 mg or 1000 mg of valaciclovir.

In addition, each tablet contains the following inactive ingredients:
- Stearic Acid
- Colloidal Anhydrous Silica
- Hypromellose
- Macrogol 8000
- Titanium Dioxide
- Indigo Carmine Aluminium Lake (500 mg tablets only)

Store below 25°C

**NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park, NSW 2113
Australia

Apotex Pty Ltd is the licensee of the registered trademarks APO and APOTEX from the registered proprietor, Apotex Inc.

**POISON SCHEDULE OF THE MEDICINE**

S4: Prescription Only Medicine.

Date of TGA approval: 27 November 2009

Date of most recent amendment: 1 August 2014