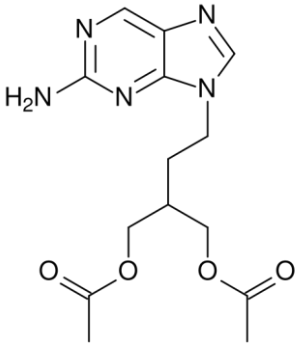
APO-FAMCICLOVIR TABLETS

NAME OF THE MEDICINE

Famciclovir.

Chemical Name: 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine

Structural Formula:



Molecular Formula: $C_{14}H_{19}N_5O_4$

Molecular Weight: 321.332

CAS Registry Number: 104227-87-4

DESCRIPTION

Famciclovir is a synthetic guanine derivative. It is a white to pale yellow crystalline solid with a melting point of 103°C.

Each tablet contains 125 mg, 250 mg or 500 mg famciclovir. In addition, each tablet also contains poloxamer, stearic acid, hypromellose, titanium dioxide and macrogol 8000.

PHARMACOLOGY

Pharmacodynamics

Virology

Famciclovir is the oral form of the antiviral compound penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has demonstrable *in vitro* activity against herpes simplex viruses (HSV types 1 and 2) and varicella zoster virus (VZV). The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir.

Penciclovir targets virus-infected cells where it is rapidly converted into penciclovir-triphosphate (mediated via virus-induced thymidine kinase). The triphosphate inhibits viral DNA polymerase by competition with deoxyguanosine triphosphate and is incorporated into the extending DNA chain, preventing significant chain elongation. Consequently, viral DNA synthesis and, therefore, viral replication are inhibited.

This triphosphate persists in infected cells in excess of 12 hours. The long intracellular half-life of penciclovir triphosphate ensures prolonged antiviral activity, as demonstrated in cell cultures with HSV-1 and HSV-2 and in animal studies.

Penciclovir is only readily phosphorylated in virus-infected cells. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Accordingly, uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

The most common form of resistance encountered with aciclovir among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would be expected to be cross-resistant to both penciclovir and aciclovir. However, penciclovir has been shown to be active against a clinically isolated aciclovir-resistant herpes simplex type 1 strain with an altered DNA polymerase.

The results from penciclovir and famciclovir patient studies, including studies of up to four months of treatment with famciclovir, showed that no resistance occurred as a result of treatment with either famciclovir or penciclovir. Penciclovir-resistant isolates were found at the start of treatment or in the placebo groups in 0.25% of the 1976 total isolates from HSV and VZV (5/1976) and in 0.19% of the 533 virus isolates from immunocompromised patients (1/533).

Pharmacokinetics

Famciclovir is the oral prodrug of penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to the antivirally active compound penciclovir. The bioavailability of penciclovir after oral famciclovir administration is 77%. Mean peak plasma concentrations (C_{max}) of penciclovir occurred at a median time of 45 minutes following administration of single oral doses of famciclovir (as shown in **Table 1**). No data is available on the pharmacokinetics of 1500mg famciclovir as a single dose.

Table 1: Mean peak plasma concentrations (C_{max}) of penciclovir after administration of single oral doses of famciclovir

Famciclovir single oral dose (mg)	C_{max} (µg/mL)
125	0.8
250	1.6
500	3.3
750	5.1
1000	6.6

Plasma concentration-time curves of penciclovir are similar following single and repeat (b.i.d. and t.i.d.) dosing and there is no accumulation of penciclovir on repeated dosing. Penciclovir and its 6-deoxy precursor are poorly (< 20%) bound to plasma proteins. Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted in urine. No unchanged famciclovir has been detected in urine. Tubular secretion and glomerular filtration contribute to renal elimination of the compound. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir is approximately 2.0 hours. There is no accumulation of penciclovir on repeated dosing with famciclovir.

Effect of food

Penciclovir C_{max} was decreased by approximately 50% and T_{max} was delayed by 1.5 hours when a capsule formulation of famciclovir was administered 30 minutes after food. When famciclovir tablets were administered 30 minutes after food, penciclovir C_{max} was reduced by approximately 20% and T_{max} was delayed by 0.75 hour. The systemic availability (AUC) of penciclovir following either preparation was unaffected. The clinical consequences of these effects on plasma concentration are unknown.

Characteristics in special populations

Patients with Herpes Zoster

Uncomplicated Herpes virus does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration of famciclovir.

Renal impairment

Plasma clearance, renal clearance and plasma elimination rate constant decreased linearly with reductions in renal function. A dosage interval adjustment is recommended for patients with renal insufficiency (see **DOSAGE AND ADMINISTRATION**).

Hepatic impairment

Well-compensated chronic liver disease (chronic hepatitis [n=6], chronic ethanol abuse [n=8] or biliary cirrhosis [n=1]) has no effect on the extent of availability (AUC) of penciclovir following a single dose of 500 mg famciclovir. No dose adjustment is recommended for patients with well-compensated hepatic impairment (see **DOSAGE AND ADMINISTRATION - Hepatic Impairment and PRECAUTIONS**). However, there was a 43% decrease in penciclovir mean maximum plasma concentration and the time to maximum plasma concentration was increased by a median of 0.75 hour in patients with hepatic insufficiency compared to normal volunteers. The pharmacokinetics have not been evaluated in patients with severe uncompensated hepatic impairment.

Elderly patients

Based on cross-study comparisons of single dose studies, the mean penciclovir AUC was approximately 30% higher, half-life 23% longer and penciclovir body weight adjusted renal clearance reduced by 19% in healthy elderly male volunteers (n=18, aged 65 to 79 years) compared to younger volunteers. Some of

this difference may be due to differences in renal function between the two groups. No dose adjustment based on age is recommended unless renal function is impaired (see **DOSAGE AND ADMINISTRATION**).

HIV patients
Extrapolated data from a study (n=8) where famciclovir was given as a single dose resulted in a mean AUC of 24 µg.h/mL, which is similar to that obtained in healthy subjects.

Race
A retrospective evaluation was performed to compare the pharmacokinetic parameters obtained in Black and Caucasian subjects after single and repeat once-daily, twice-daily or three times-daily administration of famciclovir 500 mg. Data from a study in healthy volunteers (single dose), a study in subjects with varying degrees of renal impairment (single and repeat dose) and a study in subjects with hepatic impairment (single dose) did not indicate any relevant differences in the pharmacokinetics of penciclovir between Black and Caucasian subjects.

Transplant patients
In a study of allogeneic bone marrow transplant or peripheral blood stem cell transplant or allogeneic renal transplant patients (n=21), intravenous penciclovir for one month was followed by oral use of famciclovir. The doses of penciclovir and famciclovir were adjusted according to creatinine clearance. During repeat dosing with famciclovir, the AUC of penciclovir was found to be 66 µg.h/mL in subjects with creatinine clearance greater than 50 mL/min. No safety concerns were identified despite the higher than normal AUCs reported - additional dosage adjustment in renal transplant patients is not recommended.

CLINICAL TRIALS

Herpes Zoster

Placebo-controlled trial

Famciclovir was studied in a placebo-controlled, double-blind trial of 419 otherwise healthy patients with uncomplicated herpes zoster who were treated with famciclovir 500 mg t.i.d. (n=138), famciclovir 750 mg t.i.d. (n=135) or placebo (n=146). Treatment was begun within 72 hours of initial lesion appearance and therapy was continued for 7 days.

Dermatology and virology: The times to full crusting, loss of vesicles, loss of ulcers and loss of crusts were shorter for famciclovir 500 mg-treated patients than for placebo-treated patients in the overall study population. The median time to full crusting in famciclovir 500 mg-treated patients was 5 days compared to 7 days in placebo-treated patients. No additional efficacy was demonstrated with the higher dose of famciclovir (750 mg t.i.d.) when compared to famciclovir 500 mg t.i.d. In the total population, 65.2% of patients had a positive viral culture at some time during their acute infection. Patients treated with famciclovir 500 mg had a shorter median duration of viral shedding (time to last positive viral culture) than did placebo-treated patients (1 day and 2 days, respectively).

Acute pain and post-herpetic neuralgia: There were no overall differences in the duration of acute pain (*i.e.* pain before rash healing) between famciclovir and placebo-treated groups. In addition, there was no difference in the incidence of post-herpetic neuralgia (*i.e.* pain after rash healing) between the treatment groups. In the 186 patients (44.4% of total study population) who did develop post-herpetic neuralgia, the median duration of post-herpetic neuralgia was shorter in patients treated with famciclovir 500 mg than in those treated with placebo (63 days and 119 days, respectively).

Active-control trial

A second double-blind controlled trial in 545 otherwise healthy patients with uncomplicated herpes zoster treated within 72 hours of initial lesion appearance compared famciclovir 250 mg t.i.d. (n=134), famciclovir 500 mg t.i.d. (n=134), famciclovir 750 mg t.i.d. (n=138) and aciclovir 800 mg 5 times *per* day (n=139) for 7 days. In this study, patients treated with famciclovir at each dose and aciclovir had comparable times to full lesion crusting and times to loss of acute pain. There were no statistically significant differences in the time to loss of post-herpetic neuralgia between famciclovir and aciclovir-treated groups.

Higher doses of famciclovir (500 mg t.i.d.; 750 mg t.i.d.) have not been shown to confer greater benefit. The minimum effective dose of famciclovir in the treatment of herpes zoster has not been established.

Immunocompromised

A double-blind, controlled clinical trial was conducted in 148 oncology and transplant patients with herpes zoster infections who received famciclovir 500 mg t.i.d. (n=71) or aciclovir 800 mg 5 times *per* day (n=77) for 10 days. Patients started study medication within 72 hours of rash onset. Overall, famciclovir and

aciclovir showed comparable efficacy. The median times to full crusting and complete healing were 8 and 20 days for the famciclovir group and 9 and 21 days for the aciclovir group. The median times to loss of all pain were 14 and 17 days for the famciclovir and aciclovir groups, respectively. Withdrawal due to dissemination of zoster and continued new lesion formation beyond 10 days of onset was reported in 7% of the famciclovir group and 9% of the aciclovir group.

Genital Herpes

Placebo-controlled trials (episodic therapy)

5-Day Treatment

In two double-blind, placebo-controlled trials, 626 otherwise healthy patients with a recurrence of genital herpes were treated with famciclovir 125 mg b.i.d. (n=160), famciclovir 250 mg b.i.d. (n=169), famciclovir 500 mg b.i.d. (n=154) or placebo (n=143) for 5 days. Treatment was initiated within 6 hours of either symptom onset or lesion appearance. In the two studies combined, the median time to healing in famciclovir 125 mg-treated patients was 4 days compared to 5 days in placebo-treated patients. The median time to cessation of viral shedding was 1.8 *versus* 3.4 days in famciclovir 125 mg and placebo recipients, respectively. The median time to loss of all symptoms was 3.2 days in famciclovir 125 mg-treated patients *versus* 3.8 days in placebo-treated patients. When used to treat acute recurrent genital herpes, no additional efficacy was demonstrated with higher doses of famciclovir (250 mg b.i.d. or 500 mg b.i.d.) when compared to famciclovir 125 mg b.i.d. over 5 days.

1-Day Treatment

In one double-blind, placebo-controlled trial, 329 immunocompetent patients with a recurrence of genital herpes were treated with famciclovir 1 g b.i.d. (n=163) or placebo (n=166) for 1 day. Treatment was initiated within 6 hours of either symptom onset or lesion appearance. Among patients with non-aborted lesions, the median time to healing in famciclovir 1 g-treated patients (n=125) was 4.3 days compared to 6.1 days in placebo-treated patients (n=145). The median difference in time to healing between the placebo- and famciclovir-treated groups was 1.2 days (95% CI: 0.5–2.0). 23% of famciclovir-treated patients had aborted lesions (no development beyond erythema) compared to 13% in placebo-treated patients. The median time to loss of all symptoms (e.g. burning, itching, pain, tenderness, tingling) was 3.3 days in famciclovir-treated patients versus 5.4 days in placebo-treated patients.

In one randomized (2:1), double-blind, placebo-controlled study to assess the safety and efficacy of patient-initiated single-day treatment, 304 black immunocompetent patients with recurrent genital herpes were treated with famciclovir 1 g b.i.d. (n= 206) or placebo (n=98) 1 g b.i.d. The study was conducted in 43 centres in the USA and South Africa, in patients with a history of at least four recurrences of genital herpes in the past 12 months and laboratory confirmation of HSV-2 infection. The median time to healing among patients with non-aborted lesions was 5.4 days in famciclovir-treated patients (n=152) as compared to 4.8 days in placebo-treated patients (n=78). The median difference in time to healing between the placebo and famciclovir-treated groups was -0.26 days (95% CI: -0.98–0.40). There were no unexpected or new safety findings in this trial.

Active-control trial (episodic therapy)

2-Day Treatment

In a randomized, double-blind, non-inferiority, multi-centre study (59 sites in Australia and 7 in Canada), famciclovir 500 mg statim then 250 mg b.i.d. for 2 days (short-course) was compared to the standard regimen of 125 mg b.i.d. for 5 days in the treatment of adult patients with recurrent genital herpes. HIV-infected patients were eligible if CD4 ≥ 500 cells/μL and/or CD4% ≥ 25%.

The study was designed to treat and follow each eligible patient for two complete and consecutive recurrences. A total of 1038 recurrences occurred in 616 patients that were randomized and treated. Treatment was initiated by patients within 12 hours of development of a lesion or onset of symptoms.

Patients attended for assessment within 24 hours and then 5.5 days following initiation of treatment. A daily diary was used to record treatment compliance, progression of lesions and symptoms, functional impact and side effects from the treatment.

The primary endpoint was the estimated probability of being not lesion-free at 5.5 elapsed days (132 hours) after patient self-initiation of therapy. The estimated probability was 24.4% for recurrences treated with the 2-day regimen and was 27.6 % for recurrences treated with the 5-day regimen. The upper one-sided 97.5% confidence limit of the treatment difference was 1.7%, which was within the pre-defined margin for claiming non-inferiority. Non-inferiority was maintained in five sensitivity analyses, confirming a robust result.

Over the course of treatment, there were no differences between the mean symptom and functional impact scores for either the famciclovir short-course or the standard-course treatment groups.

The study concluded that the 2-day famciclovir regimen was equivalent to the 5-day regimen in the treatment of adult patients with recurrent genital herpes.

Placebo-controlled trials (suppressive therapy)

In two placebo controlled suppression studies, immunocompetent patients (n=934) with at least six recurrences of genital herpes per year received 125 mg t.i.d. (n=233), 250 mg b.i.d. (n=236), 250 mg t.i.d. (n=232) or placebo (n=233) for 52 weeks. Treatment was initiated during an asymptomatic period. Among those who received famciclovir 250 mg b.i.d., the proportion of patients who remained free from virologically confirmed recurrence at the 12-month end point was 68% in one trial and 72% in the second trial compared with approximately 21% in the placebo groups. Median days to first clinically confirmed recurrence for the famciclovir 250 mg b.i.d. treatment groups were > 365 days for the famciclovir 250 mg b.i.d. treatment groups compared to 67 days for the placebo treated group in one of the studies and 336 days for the famciclovir groups compared to 47 days for the placebo group in the second study.

Immunocompromised

A randomized, double-blind controlled trial in 293 HIV-infected patients with a recurrence of genital herpes compared famciclovir 500 mg b.i.d. (n=150) and aciclovir 400 mg 5 times per day (n=143) for 7 days. Treatment was initiated within 48 hours of lesion onset. Famciclovir and aciclovir were equally effective in prevention of new lesion formation while patients were receiving treatment. Efficacy in the three main time-to-event parameters were also comparable. The median times to complete healing of lesions, cessation of viral shedding and loss of lesion pain were 7 days, 2 days and 3 days for both the famciclovir and aciclovir treatment groups, respectively.

A further double-blind, placebo-controlled crossover study was conducted in 48 patients with HIV to assess famciclovir (500 mg b.i.d.) in the suppression of HSV recurrence for 8 weeks. Famciclovir showed statistically significant superiority over placebo in the efficacy parameters measured. There was an approximate 10-fold reduction in the percentage of days with HSV shedding (p=0.0003) and a 6.7-fold reduction in the proportion of patients with HSV shedding from anogenital sites (p=0.0065) in the famciclovir treated group. There was also an 8.7-fold reduction in the proportion of patients with HSV shedding from any site. Overall in the famciclovir group, the proportion of days of asymptomatic, symptomatic, subclinical or lesional HSV shedding from any site was significantly reduced compared to placebo (p=0.0012).

In the famciclovir treatment group there was a 2.6-fold reduction in the percentage of days with lesions (p=0.0101) and a 3.6-fold reduction in the percentage of days with lesions/symptoms (p=0.0089) over the placebo group.

Herpes Labialis (Cold Sores)

Placebo-controlled trial

In one large placebo-controlled trial, 701 immunocompetent adults with recurrent herpes labialis were treated with famciclovir 1500 mg once (n=227), famciclovir 750 mg b.i.d. (n=220) or placebo (n=254) for 1 day. As well, patients also had to be in good general health, aged at least 18 years, have normal renal and hepatic function, had prior pregnancy tests if they were females of reproductive age and have experienced 3 or more episodes of cold sores in the preceding 12 months. Patients were required to have a history of prodromal symptoms preceding at least 50% of the recurrent episodes and at least 50% of these episodes had to have progressed to the vesicular lesion stage. Women of childbearing potential had to agree to use reliable birth control measures during the study. Pregnant or breast-feeding women were excluded. Patients were excluded if they had received an investigational drug in the 4 weeks prior to the study, had been previously vaccinated against herpes or were using a topical immunosuppressive agent on or near the face or a systemic immunosuppressive agent within 1 month of screening. Patients were also excluded if they were immunosuppressed due to underlying disease or concomitant treatment, had a recent history of drug or alcohol abuse, were suffering from inflammatory skin diseases (e.g. eczema or dermatitis) that would interfere with the assessment of lesions or were allergic or hypersensitive to products containing aciclovir, penciclovir, famciclovir or other nucleoside analogues.

Patients were instructed to take the first dose of study medication within 1 hour of symptom onset. However, some patients commenced treatment after 1 hour of onset of symptoms. Both famciclovir regimens significantly reduced time to healing of primary vesicular herpes labialis lesions (the primary efficacy variable) in the modified ITT population compared with placebo. The median time to healing in famciclovir 1500 mg single-dose treated patients was 4.4 days compared to 4.0 days in famciclovir 750 mg bid and 6.2 days in placebo-treated patients. This translates to treatment effects of 1.8 (CI 95% 0.9, 2.7) and 2.2 (CI95% 1.3, 3.1) days, respectively. A single 1500 mg dose of famciclovir reduced the time to resolution of pain and tenderness (median time 1.7 days versus 2.9 days) compared with placebo and was marginally more effective than famciclovir 750 mg b.i.d. (median time 2.1 days).

INDICATIONS

Famciclovir is indicated for:

- treatment of herpes zoster infection in adult patients who commence therapy within 72 hours of the onset of rash. Greatest benefit occurs if the drug is started within 48 hours. Efficacy has not been demonstrated in patients less than 50 years of age, although the occasional younger patient with severe herpes zoster may benefit from therapy with famciclovir. Herpes zoster infection is generally a milder condition in younger patients.
- treatment of recurrent episodes of genital herpes in adults and adolescents 12 years of age and older.
- suppression of recurrent genital herpes.
- treatment of recurrent herpes labialis (cold sores) in immunocompetent adult patients.

Famciclovir is also indicated in immunocompromised patients for:

- treatment of uncomplicated herpes zoster
- treatment of recurrent herpes simplex
- suppression of recurrent herpes simplex.

CONTRAINDICATIONS

Famciclovir is contraindicated in patients with known hypersensitivity to famciclovir or to any of the ingredients in this medicine.

It is also contraindicated in those patients who have shown hypersensitivity to penciclovir, the active metabolite of famciclovir.

PRECAUTIONS

Efficacy has not been studied in ophthalmic zoster, chicken pox or zoster encephalomyelitis patients.

Special attention should be paid to patients with impaired renal function and dosage adjustment may be necessary. Appropriate dosage adjustments for renally-impaired patients are provided (see **DOSAGE AND ADMINISTRATION**). No special precautions are required for elderly patients with normal renal function and patients with mild or moderate hepatic impairment. Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir (see **PHARMACOLOGY**).

Genital herpes is a sexually transmitted disease. The risk of transmission is increased during acute episodes. Patients should be advised to use condoms between episodes to reduce the risk of transmission and to avoid sexual intercourse when symptoms are present, even if treatment with an antiviral has been initiated. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. Therefore, in addition to therapy with famciclovir, it is recommended that patients use “safer sex” practices.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Data presented below include reference to area under the plasma concentration curve (24-hour AUC) for penciclovir in humans following the lowest and highest recommended doses for famciclovir (*i.e.* penciclovir AUC of 4.5 µg.h/mL at 125 mg b.i.d. for acute recurrent genital herpes, and a penciclovir AUC of 27 µg.h/mL at 500 mg t.i.d. for herpes infections in immunocompromised patients). This is based on the assumption that the pharmacokinetics in immunocompetent subjects is similar to the pharmacokinetics in immunocompromised subjects, as shown in the study on HIV patients (see **PHARMACOLOGY, Pharmacokinetics**). If the higher values of AUC obtained in the renal transplant patients were used as a basis for comparison, the multiples specified here would be decreased. Exposures in animal studies are expressed as multiples of human exposures at the highest and lowest dosing schedules based on penciclovir AUC or body surface area.

Carcinogenesis

The carcinogenic potential of famciclovir was evaluated in 2-year dietary studies in rats and mice. A significant increase in the incidence of mammary adenocarcinoma was seen in female rats receiving 600

mg/kg/day. No increases in tumour incidences were reported for male rats treated at doses of up to 240 mg/kg/day or in mice of either sex at doses of up to 600 mg/kg/day. At the no effect levels of 240 and 200 mg/kg/day in male and female rats, the daily exposures to penciclovir based on AUC were about 40 and 29 µg.h/mL respectively, or approximately 1–8 times the human systemic exposures at 500 mg t.i.d or 125 mg b.i.d. Systemic exposures at the no effect dose in male and female mice were 65 and 46 µg.h/mL respectively, or approximately 2–12 times the human systemic exposure (AUC).

Genotoxicity

Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a series of *in vitro* and *in vivo* assays. Famciclovir showed no genotoxic potential in a series of assays for gene mutations, chromosomal damage and DNA damage. Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutations/chromosomal damage, caused chromosomal aberrations in human lymphocytes *in vitro* and was positive in a mouse micronucleus assay *in vivo* when administered intravenously at doses toxic to bone marrow.

Effects on Fertility

Testicular toxicity was observed in rats, mice and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of seminiferous tubules, reduction in sperm count and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of testicular toxicity was related to dose and duration of exposure and tended to reverse after the cessation of dosing. In male rats, decreased fertility was observed after 10 weeks dosing at 500 mg/kg/day, or approximately 3–20 times the human systemic exposure (AUC). Testicular toxicity was also seen in mice and dogs following chronic administration at exposures to penciclovir ranging from 2–14 times the human systemic exposure (AUC). However, there were no clinically significant effects on sperm count, morphology and motility in male patients receiving 250 mg famciclovir b.i.d. for 18 weeks. Famciclovir had no effect on fertility in female rats at doses of up to 1000 mg/kg/day, approximately 4–27 times the human systemic exposure (AUC).

Use in Pregnancy

Category B1 - *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.*

Famciclovir was tested for effects on embryo-foetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 4–27 times and 2–12 times the human systemic exposure to penciclovir in rats and rabbits, respectively [AUC]), and intravenous doses of 360 mg/kg/day in rats (1.9–12 times the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.2–7.1 times the human dose [BSA]). No adverse effects were observed on embryo-foetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.4–2.6 times the human dose [BSA]) or rabbits (60 mg/kg/day, 0.6–3.6 times the human dose [BSA]). Although animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir), the safety of famciclovir in human pregnancy has not been established. Famciclovir should therefore not be used during pregnancy unless the potential benefits are considered to outweigh the potential risks associated with treatment.

Use in Lactation

Famciclovir should not be used by nursing mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment. Following oral administration of famciclovir to lactating rats, penciclovir was excreted in milk at concentrations higher than those seen in plasma. There is no information on excretion in human milk.

Use in Children

Safety and efficacy in children has not been established.

Use in the Elderly

No special precautions are required for elderly patients with normal renal function and well-compensated hepatic impairment.

Effects on ability to drive and use machines

Patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking famciclovir should refrain from driving or operating machinery.

INTERACTIONS WITH OTHER MEDICINES

Effects of Other Medicines on Famciclovir

No clinically significant interactions have been identified with famciclovir or penciclovir (the active metabolite of famciclovir).

Probenecid: concurrent use of probenecid may result in increased plasma concentrations of penciclovir (the active metabolite of famciclovir, see **PHARMACOLOGY**).

Other drugs that affect renal physiology: could affect plasma levels of penciclovir (the active metabolite of famciclovir, see **PHARMACOLOGY**).

Evidence from preclinical studies has shown no potential for induction of cytochrome P450.

Zidovudine: In a phase I study, no significant drug interactions were observed after co-administration of zidovudine and famciclovir.

The conversion of the inactive metabolite 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme and/or inhibiting this enzyme could potentially occur. Clinical interaction studies of famciclovir with cimetidine and promethazine, *in vitro* inhibitors of aldehyde oxidase, did not show relevant effects on the formation of penciclovir. However, raloxifene, the most potent aldehyde oxidase inhibitor observed *in vitro*, could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifene is co-administered with famciclovir, the clinical efficacy should be monitored.

Effects of Famciclovir on Other Medicines

Although famciclovir is only a weak inhibitor of aldehyde oxidase *in vitro*, interactions with drugs metabolized by aldehyde oxidase could potentially occur. Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes or inhibition of CYP3A4.

ADVERSE EFFECTS

Famciclovir has been well tolerated in human studies. Headache, fatigue and nausea have been reported in clinical trials. These were generally mild or moderate and occurred at a similar incidence in patients receiving placebo treatment. Confusion, predominantly in the elderly, has been reported rarely.

Adverse Events (related, possibly related, unassessable or unknown) reported by ≥ 1% of immunocompetent subjects during clinical trials

Adverse Event	famciclovir (n=3996)	placebo (n=880)
Headache	5.3 %	4.8 %
Nausea	4.6 %	4.5 %
Dizziness	1.5 %	1.5 %
Diarrhoea	1.5 %	1.3 %
Fatigue	1.2 %	0.9 %
Abdominal pain	1.1 %	1.3 %
Vomiting	1.1 %	0.5 %
Somnolence	0.6 %	1.1 %

Adverse Events (related, possibly related, unassessable or unknown) reported by ≥ 1% of immunocompetent subjects during clinical trials in herpes labialis

	famciclovir 1500 mg q.d. n=227 n (%)	famciclovir 750 mg b.i.d. n=220 n (%)	placebo n=254 n (%)
Patients with AE(s)	63 (27.8)	54 (24.5)	53 (20.9)
AE preferred term			
Headache	22 (9.7)	16 (7.3)	17 (6.7)
Diarrhoea	4 (1.8)	3 (1.4)	2 (0.8)
Nausea	5 (2.2)	5 (2.3)	10 (3.9)
Nasopharyngitis	6 (2.6)	3 (1.4)	2 (0.8)

Adverse Events (related, possibly related, unassessable or unknown) reported by ≥ 1% of immunocompetent subjects during clinical trials comparing the 2-day and 5-day recurrent genital herpes treatments[a]

	famciclovir 2-day course (n=521 recurrences) n (%)	famciclovir 5-day course (n=517 recurrences) n (%)
Recurrences with ≥ 1 AE(s)	185 (35.5)	176 (34.0)
No. of AEs	377	336
MedDRA preferred term [b,c] :		
Headache	83 (15.9)	94 (18.2)
Nausea	15 (2.9)	22 (4.3)
Diarrhoea	12 (2.3)	16 (3.1)
Abdominal pain	12 (2.3)	5 (1.0)
Dizziness	10 (1.9)	10 (1.9)
Fatigue	9 (1.7)	13 (2.5)

2-day course 2-day famciclovir regimen (500 mg loading dose then 250 mg 12-hourly)
5-day course 5-day famciclovir regimen (125 mg 12-hourly).

a On or for 4 days after date of starting study medication

b The denominator is the number of recurrences in the safety recurrence population for each treatment group

c If a patient had more than 1 recurrence of a specific AE during a recurrence, the AE is counted only once for that recurrence

Adverse Events (related, possibly related, unassessable or unknown) reported by ≥ 1% of immunocompetent subjects during a clinical trial of 1 g b.i.d. for 1 day versus placebo in recurrent genital herpes

	famciclovir (n=163) n (%)	famciclovir (n=166) n (%)
Patients with AE(s)	43 (26.4)	40 (24.1)
AE preferred term :		
Headache	22 (13.5)	9 (5.4)
Diarrhoea	8 (4.9)	2 (1.2)
Nausea	4 (2.5)	6 (3.6)
Insomnia	3 (1.8)	2 (1.2)
Dysmenorrhea	3 (1.8)	1 (0.6)
Pharyngolaryngeal pain	3 (1.8)	1 (0.6)
Back pain	2 (1.2)	1 (0.6)
Anxiety	2 (1.2)	0
Dry mouth	2 (1.2)	0
Palpitations	2 (1.2)	0
Stomach discomfort	2 (1.2)	1 (0.6)
Vomiting	2 (1.2)	1 (0.6)
Abdominal pain upper	1 (0.6)	4 (2.4)
Dizziness	0	4 (2.4)
Abdominal pain	0	2 (1.2)
Fungal infection	0	2 (1.2)
Nasopharyngitis	0	2 (1.2)

Frequency of Adverse Events (≥ 5%) for patients receiving famciclovir 500 mg daily or placebo for > 10 months

Adverse Event	Famciclovir (n=154)	Placebo (n=63)
Headache	37.7%	42.9%
URTI	31.8%	31.7%
Infection (viral)	24.7%	25.4%
Injury	18.8%	23.8%

Sinusitis	19.5%	15.9%
Back pain	12.3%	14.3%
Pharyngitis	11.0%	14.3%
UTI	7.1%	4.8%
Dyspepsia	5.2%	11.1%

Famciclovir has also been well tolerated in immunocompromised patients. Undesirable effects reported from clinical studies were similar to those reported in the immunocompetent population.

Post-marketing Data

In addition to the adverse events reported in the clinical trials, the following adverse reactions have been reported in post-marketing surveillance.

Adverse reactions are ranked under headings of frequency, using the following convention:

- very common (≥ 1/10);
- common (≥ 1/100, < 1/10);
- uncommon (≥ 1/1,000, <1/100);
- rare (≥ 10,000, < 1/1,000);
- very rare (< 1/10,000), including isolated reports.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia

Psychiatric disorders

Uncommon: Confusion (predominantly in the elderly)
Rare: Hallucinations

Nervous system disorders

Very commmon: Headache
Common: Dizziness,
Uncommon: Somnolence (predominantly in the elderly)

Cardiovascular disorders

Rare: Palpitations

Gastrointestinal disorders

Common: Vomiting, nausea, abdominal pain, diarrhoea

Hepatobiliary disorders

Common: Liver function test abnormal
Rare: Jaundice cholestatic

Skin and subcutaneous tissue disorders

Common: Rash, pruritus
Uncommon: Angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria
Very rare: Serious skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis)
Not known: Leukocytoclastic vasculitis

Musculoskeletal disorders

Very rare: Arthralgia, myalgia

DOSAGE AND ADMINISTRATION

Dosage

Immunocompetent

Herpes zoster

The recommended dosage of famciclovir is 250 mg three times daily for seven days. Treatment should be initiated as soon as possible after herpes zoster is diagnosed. Studies have shown famciclovir to be of

benefit when started within 72 hours of the onset of rash. Greatest benefit occurs if famciclovir is started within 48 hours.

Recurrent genital herpes infections (HSV)

The recommended dosage is either:

(i) 500 mg statim, then 250 mg 12 hourly for 3 doses; or
(ii) 125 mg twice daily for 5 days or
(iii) 1000 mg twice daily for 1 day.

Initiation of treatment is recommended during the prodromal period or as soon as possible after onset of lesions.

Suppression of recurrent genital herpes (HSV)

The recommended dose for the suppression of recurrent genital herpes is 250 mg twice daily. As studies conducted to date have not extended beyond 12 months, therapy should be re-evaluated after this period in order to observe possible changes in the natural history of the disease.

Recurrent herpes labialis (cold sores)

The recommended dosage is 1500 mg as a single dose or 750 mg twice daily at 12 hourly intervals for one day (see **CLINICAL TRIALS, Herpes Labialis (Cold Sores)**). Initiate therapy at the earliest sign or symptom of a cold sore (e.g. tingling, itching or burning). Treatment was initiated within 1 hour of symptom onset in the recurrent herpes labialis clinical study.

Immunocompromised

Herpes zoster

The recommended dosage of famciclovir is 500 mg three times daily for ten days. Initiation of treatment is recommended as soon as possible after rash onset. Studies have shown famciclovir to be of benefit when started within 72 hours of the onset of rash.

Recurrent HSV infections

For treating herpes simplex infections in immunocompromised adults, the recommended dose is 500 mg twice daily for seven days.

Initiation of treatment is recommended during the prodromal period or as soon as possible after onset of lesions.

Suppression of recurrent genital herpes (HSV) in HIV

For suppression of recurrent genital herpes infections, a dose of 500 mg twice a day has been shown to be efficacious in HIV patients.

Renal Impairment

As reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to dosages in patients with impaired renal function. The recommended modifications in dosage are tabulated below. As these recommendations are not based on repeated dose data, patients with impaired renal function should be closely monitored for adverse effects. There are insufficient data to recommend a dosage for patients with creatinine clearance less than 10 mL/min/1.73m^2.

For a patient on haemodialysis who has been prescribed famciclovir for conditions other than herpes labialis, a dosage interval of 48 hours is recommended for periods between dialysis. Since 4-hour haemodialysis results in approximately 75% reduction in plasma concentrations of penciclovir, the full adjusted dose (for patients with severe renal impairment) of famciclovir should be administered immediately following dialysis.

	Creatinine Clearance (mL/min/1.73m^2)	**Dosage**
Immunocompetent		
For the treatment of herpes zoster infection	≥ 30	No dosage adjustment necessary
	10–29	250 mg / 24 hours
For the treatment or suppression of recurrent genital herpes infections: 5-day treatment	≥ 30	No dose adjustment necessary
	10–29	125 mg / 12 hours

	Creatinine Clearance ($mL/min/1.73m^2$)	Dosage
For the treatment or suppression of recurrent genital herpes infections: 1-day treatment	≥ 60	No dose adjustment necessary
	40–59	500 mg / 12 hours
	20–39	500 mg / 24 hours
	<20	250 mg / 24 hours
For the treatment of recurrent herpes labialis	≥ 60	No dose adjustment necessary
	40–59	750 mg single dose
	20–39	500 mg single dose
	10–20	250 mg single dose
	for patients on haemodialysis	250 mg single dose
Immunocompromised		
For the treatment of herpes zoster infection	≥ 50	No dose adjustment necessary
	30–49	250 mg / 8 hours
	10–29	250 mg / 24 hours
For the treatment of recurrent herpes simplex infections	≥ 50	No dose adjustment necessary
	30–49	250 mg / 12 hours
	10–29	125 mg / 24 hours
For suppression of genital herpes infections	≥ 50	No dose adjustment necessary
	30–49	250 mg / 12 hours
	10–29	125 mg / 12 hours

Hepatic Impairment

Dosage modification is not required for patients with well compensated hepatic impairment.

Black Patients with Recurrent Genital Herpes

A placebo-controlled study in immunocompetent Black patients with recurrent genital herpes showed no difference in efficacy between patients receiving famciclovir 1 g b.i.d. for 1 day and placebo. There were no unexpected or new safety findings in this trial in Black patients. The relevance of these study results to other indications in Black patients is unknown (see **CLINICAL TRIALS** and **PHARMACOLOGY, Pharmacokinetics**).

Administration

Famciclovir can be taken without regard to meals (see **PHARMACOLOGY, Pharmacokinetics, Effect of food**).

OVERDOSAGE

Symptomatic and supportive therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease. The famciclovir dosage in these patients had not been appropriately reduced for the level of renal function.

Penciclovir, the active metabolite of famciclovir, is dialysable; plasma concentrations are reduced by approximately 75% following 4-hour haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Famciclovir is intended for oral administration.

Each tablet contains 125mg, 250mg or 500mg famciclovir as the active ingredient.

125 mg tablets:

White, round, biconvex, film-coated and engraved *"FAM"* over *"125"* on one side and *"APO"* on the other side. Blister pack of 10, 28, 40 and 56 tablets (AUST R 160559). Bottle pack of 28, 40, 56 tablets (AUST R 160558).

250 mg tablets:

White, round, biconvex, film-coated and engraved *"FAM"* over *"250"* on one side and *"APO"* on the

other side. Blister pack of 5, 14, 20, 21, 28, 30, 56 tablets (AUST R 160556). Bottle pack of 14, 20, 21, 28, 40, 56 tablets (AUST R 160560).

500 mg tablets:

White, oval, biconvex, film-coated and engraved *"FAM500"* on one side and *"APO"* on the other side.Blister pack of 3, 12, 14, 16, 20, 28, 30, 56 tablets (AUST R 172443).Bottle pack of 12, 14, 16, 20, 28, 30, 56 tablets (AUST R 172445).

Storage

Store below 25°C.

POISONS SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
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