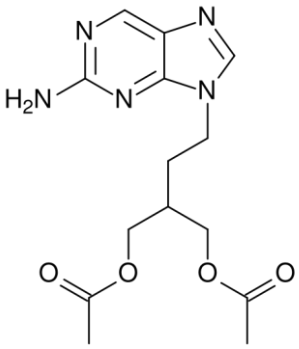
APOHEALTH FAMCICLOVIR ONCE

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 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 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 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. Bioavailability of penciclovir after oral famciclovir 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 h 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 0.75h. 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 h in patients with hepatic insufficiency compared to normal volunteers. Pharmacokinetics has 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% larger, 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 allogenic bone marrow transplant or peripheral blood stem cell transplant or allogenic 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 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

APOHEALTH FAMCICLOVIR ONCE is indicated for:
- treatment of recurrent herpes labialis (cold sores) in immunocompetent adult patients.

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.

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[1]

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.

[1] *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.*

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.

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.

Carcinogenicity
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.

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).

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)

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 rarely 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
Rare: Confusion (predominantly in the elderly)
Very rare: Hallucinations

Nervous system disorders
Rare: Headache
Very rare: Dizziness, somnolence (predominantly in the elderly)

Gastrointestinal disorders
Rare: Nausea
Very rare: Vomiting

Hepatobiliary disorders
Very rare: Cholestatic jaundice and abnormal liver function tests

Skin and subcutaneous tissue disorders
Very rare: Rash, pruritus, urticaria, serious skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis)
Uncommon: Angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria

Musculoskeletal disorders
Very rare: Arthralgia, myalgia

DOSAGE AND ADMINISTRATION

The recommended dosage is 1500 mg taken as a single dose. 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.

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

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**
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

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

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.

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

PRESENTATION AND STORAGE CONDITIONS

APOHEALTH FAMCICLOVIR ONCE 500 mg tablets are white, oval, biconvex, film-coated and engraved *"FAM500"* on one side and *"APO"* on the other side.

They are available in blister packs containing 3 tablets. AUST R 201911.

APOHEALTH FAMCICLOVIR ONCE is intended for oral administration.

Storage
Store below 25°C.

POISONS SCHEDULE OF THE MEDICINE

S3 - Pharmacist Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

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