New Zealand Datasheet

Name of Medicine

FAMVIR® ONCE
Famciclovir 500 mg tablets

Presentation

White, oval, biconvex film-coated tablets, debossed with “FV 500” on one side and no markings on the reverse side.

Uses

Actions

Pharmacotherapeutic group: Oral antiviral agent, ATC code: J05A B09

Famciclovir is the oral prodrug 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).

Clinical studies

Adults

In one large placebo-controlled trial, 701 immunocompetent adults with recurrent herpes labialis were treated with Famvir 1500 mg once (n=227), Famvir 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 analogs.

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 Famvir 1500 mg single-dose treated patients was 4.4 days compared to 4.0 days in Famvir 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 ($CI_{95\%}$ 1.3, 3.1) days, respectively. A single 1500 mg dose of Famvir 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 Famvir 750 mg b.i.d. (median time 2.1 days).

Paediatric patients

Safety and efficacy of famciclovir in the treatment of herpes labialis in children and adolescents under 18 years of age has not been investigated. Therefore, use of Famvir Once in this age group is not recommended.

Pharmacokinetic properties

General characteristics

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir is 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg, 750 mg and 1000 mg oral dose of famciclovir, was 0.8 microgram/mL, 1.6 micrograms/mL, 3.3 micrograms/mL, 5.1 micrograms/mL and 6.6 micrograms/mL respectively, and occurred at a median time of 45 minutes post-dose. No data is available on the pharmacokinetics of 1500 mg famiciclovir as a single dose. The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food. Plasma concentration-time curves of penciclovir are similar following single and repeated (t.i.d. and b.i.d.) dosing. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir, is approximately 2 hours. There is no

accumulation of penciclovir on repeated dosing with famciclovir. 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 and no unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir.

The terminal plasma half life of penciclovir after single dosing with famciclovir was approximately 2 hours.

Effect of food

Penciclovir C_{max} was decreased by approximately 50 % and T_{max} was delayed by 1.5 hour when a capsule formulation of famciclovir was administered 30 minutes after food. When Famvir 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.

Because the systemic availability (AUC) of penciclovir was not altered when famciclovir was administered with food, it appears that famciclovir can be taken without regard to meals.

Subjects with renal impairment

The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal insufficiency and should be managed by a medical practitioner (see Dosage and method of administration).

Patients who are at higher risk of renal impairment include those who:

- are over 50 years of age
- are smokers
- have diabetes mellitus, hypertension or established cardiovascular disease
- are obese
- have a family history of chronic kidney disease
- are of Aboriginal or Torres Strait Islander origin
- are taking medication that may impair renal function

Such at risk patients should be referred to a medical practitioner for a kidney health check which usually consists of a simple urine test (dipstick analysis for protein), blood test (measurement of eGFR or kidney function) and blood pressure measurement.

Therefore use of Famvir Once in patients who have or are at-risk of renal impairment should only be under medical advice.

Subjects with 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) or penciclovir following a single dose of 500 mg famciclovir. No dose adjustment is recommended for patients with mild to moderate hepatic impairment (see Dosage and method of administration and Special warnings and precautions for use). The pharmacokinetics of penciclovir have not been evaluated in patients with severe uncompensated hepatic impairment. Conversion of famciclovir to the active metabolite penciclvoir may be impaired in these patients, resulting in lower penciclovir plasma concentrations and thus possibly a decrease of efficacy of famciclovir.

Elderly subjects
Based on cross-study comparisons, the mean penciclovir AUC was about 40 % higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Some of this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see Dosage and method of administration).

Race
A retrospective evaluation was performed to compare pharmacokinetic data 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 difference in the pharmacokinetics of penciclovir between Black and Caucasian subjects.

Indications
Famvir Once is indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults aged 18 years and over.

Dosage and method of administration
1500 mg as a single dose for one day. Initiation of treatment is recommended at the earliest sign or symptom of a cold sore (e.g. tingling, itching or burning).

Dosage in renally impaired patients
Famvir Once should only be used in patients with or who are at-risk of renal impairment under medical advice. Because reduced clearance of penciclovir, the antivirally active metabolite of famciclovir (see Pharmacokinetic properties), is related to reduced renal function, as measured by creatinine clearance, special attention should be given to dosages in patients with impaired renal function.

Patients who are at higher risk of renal impairment include those who:
- are over 50 years of age
- are smokers
- have diabetes mellitus, hypertension or established cardiovascular disease
- are obese
- have a family history of chronic kidney disease
- are of Aboriginal or Torres Strait Islander origin
- are taking medication that may impair renal function

Such at risk patients should be referred to a medical practitioner for a kidney health check, which usually consists of a simple urine test (dipstick analysis for protein), blood test (measurement of eGFR or kidney function) and blood pressure measurement. and blood pressure measurement.

The following modifications in dosage are recommended and which should be managed by a medical practitioner:

Creatinine Clearance (mL/min/1.73m2)	Dosage
≥60	No dose adjustment necessary (1500 mg single dose)
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

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/1.73^2.

Renally impaired patients on haemodialysis
Since 4 hour haemodialysis results in approximately 75% reduction in plasma penciclovir concentrations, famciclovir should be administered in a single dose of 250 mg immediately following dialysis (single-day regimen).

Hepatically impaired patients
No dosage adjustment is required in patients with well-compensated hepatic impairment. No data are available for patients with severe uncompensated hepatic impairment. Conversion of famciclovir to the active metabolite penciclvoir may be impaired in these patients, resulting in lower penciclovir plasma concentrations and thus possibly a decrease of efficacy of famciclovir (see Pharmacokinetic properties).

Mode of administration
It appears that famciclovir can be taken without regard to meals (see Pharmacokinetic properties).

Contraindications

Famvir Once is contraindicated in patients with known hypersensitivity to famciclovir or other constituents of Famvir Once. It is also contraindicated in those patients who have shown hypersensitivity to penciclovir, the active metabolite of famciclovir.

Famvir is not recommended for use in:

- patients who are immunocompromised
- children and adolescents under 18 years of age

Warnings and precautions

Special attention should be paid to patients with impaired renal function and dosage adjustment is necessary (see Dosage and method of administration and Overdose). 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 (see Pharmacokinetic properties).

Refer the patient to a medical practitioner if they have symptoms and signs of an infection other than the cold sore.

Use in Pregnancy

Famciclovir was tested for effects on embryo-foetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 4 to 27 times and 2 to 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 to 12 times the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.2 to 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 to 2.6 times the human dose [BSA]) or rabbits (60 mg/kg/day, 0.6 to 3.6 times the human dose [BSA]).

Although animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir, 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

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. Famciclovir should not be used in breastfeeding mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment.

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 to 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 to 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 to 27 times the human systemic exposure (AUC).

Effects on Ability to Drive and Use Machines

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

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 in nature and occurred at a similar incidence in patients receiving placebo treatment. Confusion, predominately in the elderly has been reported rarely.

The following table specifies the estimated frequency of adverse reactions based on all the spontaneous reports and literature cases that have been reported for Famvir Once since its introduction to the market.

Adverse reactions (Table 1) 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 (≥ 1/10,000, < 1/1,000); very rare (<1/10,000), not known (cannot be estimated from available data)*.

Table 1

Blood and lymphatic system disorders		
	Very Rare:	Thrombocytopenia.
Psychiatric disorders		
	Uncommon:	Confusional state (predominantly in the elderly).
	Rare	Hallucination.
Nervous system disorders		
	Very common:	Headache.
	Common:	Dizziness.
	Uncommon:	Somnolence (predominantly in the elderly).
Cardiac 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.
	Not known:	Serious skin reactions (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis), leukocytoclastic vasculitis.
Musculoskeletal disorders		
	Very rare:	Arthralgia, myalgia

Interactions

Effects of other medicinal products on famciclovir

No clinically significant interactions have been identified with famciclovir or penciclovir.

Probenecid: Concurrent use of probenecid may result in increased plasma concentrations of penciclovir (active metabolite of famciclovir, see Pharmacokinetic properties).

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

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 (formed by deacetylation of famciclovir) to penciclovir is catalysed 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 medicinal products
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.

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Overdose

Contact the Poisons Information Centre (New Zealand) on 0800 POISON or 0800 764 766 for advice on management.

Supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dosage has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 hour haemodialysis.

Pharmaceutical Precautions

Store below 25°C. Store in the original package.
Famvir Once must be kept out of the reach and sight of children.

Shelf life

3 years.

Special precautions for disposal

No specific instructions.

Package Quantities

PVC/PVDC/aluminium blister packs containing 3 tablets.

Further information

List of excipients

Tablet core: hydroxypropyl cellulose (E 463), sodium starch glycollate, magnesium stearate (E 572).

Tablet coating: hypromellose (E464), macrogol, titanium dioxide (E 171).

Incompatibilities

Not applicable.

Preclinical safety data

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 microgram.h/mL at 125 mg b.i.d. for acute recurrent genital herpes, and a penciclovir AUC of 27 microgram.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 are similar to the pharmacokinetics in immunocompromised subjects, as shown in the study on HIV patients (see "**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.

Carcinogenicity

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 microgram.h/mL respectively, or approximately 1 to 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 microgram.h/mL respectively, or approximately 2 to 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 IV at doses toxic to bone marrow.

Medicine Classification

Pharmacist Only Medicine

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