FV:L17A

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PRESCRIBING INFORMATION

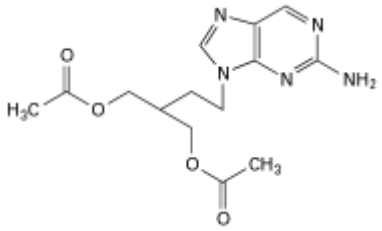
685633

FAMVIR ®

brand of
famciclovir
Tablets

DESCRIPTION

Famvir contains famciclovir, an orally administered prodrug of the antiviral agent penciclovir. Chemically, famciclovir is known as 2-[2-(2-amino-9*H*-purin-9-yl)ethyl]-1,3-propanediol diacetate. Its molecular formula is $C_{14}H_{19}N_5O_4$; its molecular weight is 321.3. It is a synthetic acyclic guanine derivative and has the following structure:



famciclovir

Famciclovir is a white to pale yellow solid. It is freely soluble in acetone and methanol, and sparingly soluble in ethanol and isopropanol. At 25°C famciclovir is freely soluble (>25% w/v) in water initially, but rapidly precipitates as the sparingly soluble (2-3% w/v) monohydrate. Famciclovir is not hygroscopic below 85% relative humidity. Partition coefficients are: octanol/water (pH 4.8) *P*=1.09 and octanol/phosphate buffer (pH 7.4) *P*=2.08.

Tablets for Oral Administration: Each white, film-coated tablet contains famciclovir. The 125 mg and 250 mg tablets are round; the 500 mg tablets are oval. Inactive ingredients consist of hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

MICROBIOLOGY

Mechanism of Antiviral Activity: Famciclovir undergoes rapid biotransformation to the active antiviral compound penciclovir, which has inhibitory activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). In cells infected with HSV-1, HSV-2 or VZV, viral thymidine kinase phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. *In vitro* studies demonstrate that penciclovir triphosphate

inhibits HSV-2 DNA polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited.

Penciclovir triphosphate has an intracellular half-life of 10 hours in HSV-1-, 20 hours in HSV-2- and 7 hours in VZV-infected cells cultured *in vitro*; however, the clinical significance is unknown.

Antiviral Activity *In Vitro* and *In Vivo*: In cell culture studies, penciclovir has antiviral activity against the following herpesviruses (listed in decreasing order of potency): HSV-1, HSV-2 and VZV. Sensitivity test results, expressed as the concentration of the drug required to inhibit the growth of the virus by 50% (IC_{50}) or 99% (IC_{99}) in cell culture, vary greatly depending upon a number of factors, including the assay protocols, and in particular the cell type used. See Table 1.

Table 1

Method of Assay	Virus Type	Cell Type	IC_{50} (mcg/mL)	IC_{99} (mcg/mL)
Plaque Reduction	VZV (c.i.)	MRC-5	5.0 ± 3.0	
	VZV (c.i.)	Hs68	0.9 ± 0.4	
	HSV-1 (c.i.)	MRC-5	0.2 – 0.6	
	HSV-1 (c.i.)	WISH	0.04 – 0.5	
	HSV-2 (c.i.)	MRC-5	0.9 – 2.1	
	HSV-2 (c.i.)	WISH	0.1 – 0.8	
Virus Yield	HSV-1 (c.i.)	MRC-5		0.4 – 0.5
Reduction	HSV-2 (c.i.)	MRC-5		0.6 – 0.7
DNA Synthesis	VZV (Ellen)	MRC-5	0.1	
Inhibition	HSV-1 (SC16)	MRC-5	0.04	
	HSV-2 (MS)	MRC-5	0.05	

(c.i.) = clinical isolates.

Drug Resistance: Resistance of HSV and VZV to antiviral nucleoside analogs can result from mutations in the viral thymidine kinase (TK) and DNA polymerase genes. Mutations in the viral TK gene may lead to complete loss of viral TK activity (TK negative), reduced levels of TK activity (TK partial) or alteration in the ability of viral TK to phosphorylate the drug without an equivalent loss in the ability to phosphorylate thymidine (TK altered). The most commonly encountered acyclovir-resistant mutants are TK negative and they are also resistant to penciclovir. The possibility of viral resistance to penciclovir should be considered in patients who fail to respond or experience recurrent viral infections during therapy.

CLINICALPHARMACOLOGY

Pharmacokinetics

Absorption and Bioavailability: Famciclovir is the diacetyl 6-deoxy analog of the active antiviral compound penciclovir. Following oral administration, little or no famciclovir is detected in plasma or urine.

The absolute bioavailability of famciclovir is 77±8% as determined following the administration of a 500 mg famciclovir oral dose and a 400 mg penciclovir intravenous dose to 12 healthy male subjects.

Penciclovir concentrations increased in proportion to dose over a famciclovir dose range of 125 mg to 750 mg administered as a single dose. Single oral dose administration of 125 mg, 250 mg or 500 mg famciclovir to healthy male volunteers across 17 studies gave the following pharmacokinetic parameters:

Table 2

Dose	AUC (0-inf)[†] (mcg.hr./mL)	C_{max}[‡] (mcg/mL)	T_{max}[§] (h)
125 mg	2.24	0.8	0.9
250 mg	4.48	1.6	0.9
500 mg	8.95	3.3	0.9

[†]AUC (0-inf) (mcg.hr./mL)=area under the plasma concentration-time profile extrapolated to infinity.
[‡]C_{max} (mcg/mL)=maximum observed plasma concentration.
[§]T_{max} (h)= time to C_{max}.

Following single oral-dose administration of 500 mg famciclovir to seven patients with herpes zoster, the mean ± SD AUC, C_{max}, and T_{max} were 12.1±1.7 mcg.hr./mL, 4.0±0.7 mcg/mL, and 0.7±0.2 hours, respectively. The AUC of penciclovir was approximately 35% greater in patients with herpes zoster as compared to healthy volunteers. Some of this difference may be due to differences in renal function between the two groups.

There is no accumulation of penciclovir after the administration of 500 mg famciclovir t.i.d. for 7 days.

Penciclovir C_{max} decreased approximately 50% and T_{max} was delayed by 1.5 hours when a capsule formulation of famciclovir was administered with food (nutritional content was approximately 910 Kcal and 26% fat). There was no effect on the extent of availability (AUC) of penciclovir. There was an 18% decrease in C_{max} and a delay in T_{max} of about 1 hour when famciclovir was given 2 hours after a meal as compared to its administration 2 hours before a meal. Because there was no effect on the extent of systemic availability of penciclovir, it appears that *Famvir* can be taken without regard to meals.

Distribution: The volume of distribution (Vd_{β}) was 1.08±0.17 L/kg in 12 healthy male subjects following a single intravenous dose of penciclovir at 400 mg administered as a 1-hour intravenous infusion.

Penciclovir is <20% bound to plasma proteins over the concentration range of 0.1 to 20 mcg/mL. The blood/plasma ratio of penciclovir is approximately 1.

Metabolism: Following oral administration, famciclovir is deacetylated and oxidized to form penciclovir. Metabolites that are inactive include 6-deoxy penciclovir, monoacetylated penciclovir, and 6-deoxy monoacetylated penciclovir (5%, <0.5% and <0.5% of the dose in the urine, respectively). Little or no famciclovir is detected in plasma or urine.

An *in vitro* study using human liver microsomes demonstrated that cytochrome P450 does not play an important role in famciclovir metabolism. The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase.

Elimination: Approximately 94% of administered radioactivity was recovered in urine over 24 hours (83% of the dose was excreted in the first 6 hours) after the administration of 5 mg/kg radiolabeled penciclovir as a 1-hour infusion to three healthy male volunteers. Penciclovir accounted for 91% of the radioactivity excreted in the urine.

Following the oral administration of a single 500 mg dose of radiolabeled famciclovir to three healthy male volunteers, 73% and 27% of administered radioactivity were recovered in urine and feces over 72

hours, respectively. Penciclovir accounted for 82% and 6-deoxy penciclovir accounted for 7% of the radioactivity excreted in the urine. Approximately 60% of the administered radiolabeled dose was collected in urine in the first 6 hours.

After intravenous administration of penciclovir in 48 healthy male volunteers, mean ± S.D. total plasma clearance of penciclovir was 36.6±6.3 L/hr (0.48±0.09 L/hr/kg). Penciclovir renal clearance accounted for 74.5±8.8% of total plasma clearance.

Renal clearance of penciclovir following the oral administration of a single 500 mg dose of famciclovir to 109 healthy male volunteers was 27.7±7.6 L/hr.

The plasma elimination half-life of penciclovir was 2.0±0.3 hours after intravenous administration of penciclovir to 48 healthy male volunteers and 2.3±0.4 hours after oral administration of 500 mg famciclovir to 124 healthy male volunteers. The half-life in seven patients with herpes zoster was 3.0±1.1 hours.

HIV-Infected Patients: Following oral administration of a single dose of 500 mg famciclovir (the oral prodrug of penciclovir) to HIV-positive patients, the pharmacokinetic parameters of penciclovir were comparable to those observed in healthy subjects.

Renal Insufficiency: Apparent plasma clearance, renal clearance, and the plasma-elimination rate constant of penciclovir decreased linearly with reductions in renal function. After the administration of a single 500 mg famciclovir oral dose (n=27) to healthy volunteers and to volunteers with varying degrees of renal insufficiency (CL_{CR} ranged from 6.4 to 138.8 mL/min.), the following results were obtained (Table 3):

Table 3

Parameter (mean ± S.D.)	CL_{CR} † ≥ 60 (mL/min.)	CL_{CR} 40-59 (mL/min.)	CL_{CR} 20-39 (mL/min.)	CL_{CR} <20 (mL/min.)
CL_{CR} (mL/min)	88.1 ± 20.6	49.3 ± 5.9	26.5 ± 5.3	12.7 ± 5.9
CL_R (L/hr)	30.1 ± 10.6	13.0 ± 1.3‡	4.2 ± 0.9	1.6 ± 1.0
CL/F§ (L/hr)	66.9 ± 27.5	27.3 ± 2.8	12.8 ± 1.3	5.8 ± 2.8
Half-life (hr)	2.3 ± 0.5	3.4 ± 0.7	6.2 ± 1.6	13.4 ± 10.2
n	15	5	4	3

† CL_{CR} is measured creatinine clearance.
‡ n=4.
§ CL/F consists of bioavailability factor and famciclovir to penciclovir conversion factor.

In a multiple dose study of famciclovir conducted in subjects with varying degrees of renal impairment (n=18), the pharmacokinetics of penciclovir were comparable to those after single doses.

A dosage adjustment is recommended for patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Well-compensated chronic liver disease (chronic hepatitis [n=6], chronic ethanol abuse [n=8], or primary biliary cirrhosis [n=1]) had no effect on the extent of availability (AUC) of penciclovir following a single dose of 500 mg famciclovir. However, there was a 44% decrease in penciclovir mean maximum plasma concentration and the time to maximum plasma concentration was increased by 0.75 hours in patients with hepatic insufficiency compared to normal volunteers. No dosage adjustment is recommended for patients with well-compensated hepatic impairment. The pharmacokinetics of penciclovir have not been evaluated in patients with severe uncompensated hepatic impairment.

Elderly Subjects: Based on cross-study comparisons, mean penciclovir AUC was 40% larger and penciclovir renal clearance was 22% lower after the oral administration of famciclovir in elderly volunteers (n=18, age 65 to 79 years) compared to younger volunteers. Some of this difference may be due to differences in renal function between the two groups.

Gender: The pharmacokinetics of penciclovir were evaluated in 18 healthy male and 18 healthy female volunteers after single-dose oral administration of 500 mg famciclovir. AUC of penciclovir was 9.3±1.9 mcg.hr./mL and 11.1±2.1 mcg.hr./mL in males and females, respectively. Penciclovir renal clearance was 28.5±8.9 L/hr and 21.8±4.3 L/hr, respectively. These differences were attributed to differences in renal function between the two groups. No famciclovir dosage adjustment based on gender is recommended.

Pediatric Patients: The pharmacokinetics of famciclovir or penciclovir have not been evaluated in patients <18 years of age.

Race: The pharmacokinetics of famciclovir or penciclovir with respect to race have not been evaluated.

Drug Interactions

Effects on penciclovir

No clinically significant alterations in penciclovir pharmacokinetics were observed following single-dose administration of 500 mg famciclovir after pre-treatment with multiple doses of allopurinol, cimetidine, theophylline, or zidovudine. No clinically significant effect on penciclovir pharmacokinetics was observed following multiple-dose (t.i.d.) administration of famciclovir (500 mg) with multiple doses of digoxin.

Effects of famciclovir on co-administered drugs

The steady-state pharmacokinetics of digoxin were not altered by concomitant administration of multiple doses of famciclovir (500 mg t.i.d.). No clinically significant effect on the pharmacokinetics of zidovudine or zidovudine glucuronide was observed following a single oral dose of 500 mg famciclovir.

CLINICAL TRIALS

Herpes Zoster

Famvir (famciclovir) was studied in a placebo-controlled, double-blind trial of 419 immunocompetent adults with uncomplicated herpes zoster. Comparisons included *Famvir* 500 mg t.i.d., *Famvir* 750 mg t.i.d., or placebo. Treatment was begun within 72 hours of initial lesion appearance and therapy was continued for 7 days.

The median time to full crusting in *Famvir*-treated patients was 5 days compared to 7 days in placebo-treated patients. The times to full crusting, loss of vesicles, loss of ulcers, and loss of crusts were shorter for *Famvir* 500 mg-treated patients than for placebo-treated patients in the overall study population. The effects of *Famvir* were greater when therapy was initiated within 48 hours of rash onset; it was also more pronounced in patients 50 years of age or older. Among the 65.2% of patients with at least one positive viral culture, *Famvir*-treated patients had a shorter median duration of viral shedding than placebo-treated patients (1 day and 2 days, respectively).

There were no overall differences in the duration of pain before rash healing between *Famvir* and placebo-treated groups. In addition, there was no difference in the incidence of pain after rash healing (postherpetic neuralgia) between the treatment groups. In the 186 patients (44.4% of total study population) who did develop postherpetic neuralgia, the median duration of postherpetic neuralgia was shorter in patients treated with *Famvir* 500 mg than in those treated with placebo (63 days and 119 days, respectively). No additional efficacy was demonstrated with higher doses of *Famvir*.

A double-blind controlled trial in 545 immunocompetent adults with uncomplicated herpes zoster treated within 72 hours of initial lesion appearance compared three doses of *Famvir* to acyclovir 800 mg 5 times per day. Times to full lesion crusting and times to loss of acute pain were comparable for all groups and there were no statistically significant differences in the time to loss of postherpetic neuralgia between *Famvir* and acyclovir-treated groups.

Herpes Simplex Infections

Recurrent Genital Herpes: In two placebo-controlled trials, 626 immunocompetent adults with a recurrence of genital herpes were treated with *Famvir* 125 mg b.i.d. (n=160), *Famvir* 250 mg b.i.d. (n=169), *Famvir* 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 *Famvir* 125 mg-treated patients was 4 days compared to 5 days in placebo-treated patients and the median time to cessation of viral shedding was 1.8 vs. 3.4 days in *Famvir* 125 mg and placebo recipients, respectively. The median time to loss of all symptoms was 3.2 days in *Famvir* 125 mg-treated patients vs. 3.8 days in placebo-treated patients. No additional efficacy was demonstrated with higher doses of *Famvir*.

Suppression of Recurrent Genital Herpes: 934 immunocompetent adults with a history of 6 or more recurrences per year were randomized into two double-blind, 1-year, placebo-controlled trials. Comparisons included *Famvir* 125 mg t.i.d., 250 mg b.i.d., 250 mg t.i.d. and placebo. At one-year, 60% to 65% of patients were still receiving *Famvir* and 25% were receiving placebo treatment. Patient reported recurrence rates for the 250 mg b.i.d. dose at 6 and 12 months are shown in Table 4.

Table 4

	Recurrence Rates at 6 Months		Recurrence Rates at 12 Months	
	Famvir 250 mg b.i.d.	Placebo	*Famvir* 250 mg b.i.d.	Placebo
n	236	233	236	233
Recurrence-free	39%	10%	29%	6%
Recurrences†	47%	74%	53%	78%
Lost to Follow-up‡	14%	16%	17%	16%

†Based on patient reported data; not necessarily confirmed by a physician.
‡Patients recurrence-free at time of last contact prior to withdrawal.

Famvir-treated patients had approximately 1/5 the median number of recurrences as compared to placebo-treated patients.

Higher doses of *Famvir* were not associated with an increase in efficacy.

Recurrent Mucocutaneous Herpes Simplex Infection in HIV-Infected Patients

A randomized, double-blind, multicenter study compared famciclovir 500 mg twice daily for 7 days (n=150) with oral acyclovir 400 mg 5 times daily for 7 days (n=143) in HIV-infected patients with recurrent mucocutaneous HSV infection treated within 48 hours of lesion onset. Approximately 40% of patients had a CD_4 count below 200 cells/mm^3, 54% of patients had anogenital lesions and 35% had orolabial lesions. Famciclovir therapy was comparable to oral acyclovir in reducing new lesion formation and in time to complete healing.

INDICATIONS AND USAGE

Herpes Zoster: Famvir (famciclovir) is indicated for the treatment of acute herpes zoster (shingles).

Herpes Simplex Infections: *Famvir* is indicated for:

- treatment or suppression of recurrent genital herpes in immunocompetent patients
- treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

CONTRAINDICATIONS

Famvir (famciclovir) is contraindicated in patients with known hypersensitivity to the product, its components, and Denavir® (penciclovir cream).

PRECAUTIONS

General

The efficacy of *Famvir* has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering *Famvir* to patients with creatinine clearance values <60 mL/min. (see DOSAGE AND ADMINISTRATION). In patients with underlying renal

disease who have received inappropriately high doses of *Famvir* for their level of renal function, acute renal failure has been reported.

Information for Patients

Patients should be informed that *Famvir* is not a cure for genital herpes. There are no data evaluating whether *Famvir* will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

Drug Interactions

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis: Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.5 to 9.0x the human systemic exposure at the recommended daily oral doses of 500 mg t.i.d., 250 mg b.i.d., or 125 mg b.i.d. based on area under the plasma concentration curve comparisons [24 hr AUC] for penciclovir). No increases in tumor incidence were reported in male rats treated at doses up to 240 mg/kg/day (0.9 to 5.4x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.4 to 2.4x the human AUC).

Mutagenesis: Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutations in bacteria (*S. typhimurium* and *E. coli*) and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5000 mcg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/mL), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 mcg/mL). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 mcg/mL). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/mL). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility: Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous

tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.9 to 11.4x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.2 to 1.2x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.4 to 2.4x the human AUC) and 150 mg/kg/day (1.7 to 10.2x the human AUC), respectively.

Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (3.6 to 21.6x the human AUC).

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8-week baseline period and recurrent genital herpes receiving oral *Famvir* (250 mg b.i.d.) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8-week follow-up.

Pregnancy

Teratogenic Effects–Pregnancy Category B. Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 3.6 to 21.6x and 1.8 to 10.8x the human systemic exposure to penciclovir based on AUC comparisons for the rat and rabbit, respectively) and intravenous doses of 360 mg/kg/day in rats (2 to 12x the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.5 to 9.0x the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.4 to 2.6x the human dose [BSA]) or rabbits (60 mg/kg/day, 0.7 to 4.2x the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to *Famvir,* SmithKline Beecham maintains a *Famvir* Pregnancy Registry. Physicians are encouraged to register their patients by calling (800) 366-8900, ext. 5231.

Nursing Mothers

Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of *Famvir* in infants.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.

Geriatric Use

Of 816 patients with herpes zoster in clinical studies who were treated with *Famvir*, 248 (30.4%) were ≥65 years of age and 103 (13%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

ADVERSE REACTIONS

Immunocompetent Patients

The safety of *Famvir* has been evaluated in clinical studies involving 816 *Famvir*-treated patients with herpes zoster (*Famvir*, 250 mg t.i.d. to 750 mg t.i.d.); 528 *Famvir*-treated patients with recurrent genital herpes (*Famvir*, 125 mg b.i.d. to 500 mg t.i.d.); and 1,197 patients with recurrent genital herpes treated with *Famvir* as suppressive therapy (125 mg q.d. to 250 mg t.i.d.) of which 570 patients received *Famvir* (open-labeled and/or double-blind) for at least 10 months. Table 5 lists selected adverse events.

Table 5

Selected Adverse Events Reported by ≥2% of Patients in Placebo-controlled Famvir (famciclovir) Trials*

	Incidence					
	Herpes Zoster		Recurrent Genital Herpes		Genital Herpes-Suppression	
Event	*Famvir* (n=273) %	Placebo (n=146) %	*Famvir* (n=640) %	Placebo (n=225) %	*Famvir* (n=458) %	Placebo (n=63) %
Nervous System						
Headache	22.7	17.8	23.6	16.4	39.3	42.9
Paresthesia	2.6	0.0	1.3	0.0	0.9	0.0
Migraine	0.7	0.7	1.3	0.4	3.1	0.0
Gastrointestinal						
Nausea	12.5	11.6	10.0	8.0	7.2	9.5
Diarrhea	7.7	4.8	4.5	7.6	9.0	9.5
Vomiting	4.8	3.4	1.3	0.9	3.1	1.6
Flatulence	1.5	0.7	1.9	2.2	4.8	1.6
Abdominal Pain	1.1	3.4	3.9	5.8	7.9	7.9
Body as a Whole						
Fatigue	4.4	3.4	6.3	4.4	4.8	3.2
Skin and Appendages						
Pruritus	3.7	2.7	0.9	0.0	2.2	0.0
Rash	0.4	0.7	0.6	0.4	3.3	1.6
Reproductive Female						
Dysmenorrhea	0.0	0.7	2.2	1.3	7.6	6.3

* Patients may have entered into more than one clinical trial.

The following adverse events have been reported during post-approval use of *Famvir*: urticaria, hallucinations and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Table 6 lists selected laboratory abnormalities in genital herpes suppression trials.

Table 6
Selected Laboratory Abnormalities in Genital Herpes Suppression Studies*

Parameter	*Famvir* (n = 660)† %	Placebo (n = 210)† %
Anemia (<0.8 x NRL)	0.1	0.0
Leukopenia (<0.75 x NRL)	1.3	0.9
Neutropenia (<0.8 x NRL)	3.2	1.5
AST (SGOT) (>2 x NRH)	2.3	1.2
ALT (SGPT) (>2 x NRH)	3.2	1.5
Total Bilirubin (>1.5 x NRH)	1.9	1.2
Serum Creatinine (>1.5 x NRH)	0.2	0.3
Amylase (>1.5 x NRH)	1.5	1.9
Lipase (>1.5 x NRH)	4.9	4.7

* Percentage of patients with laboratory abnormalities that were increased or decreased from baseline and were outside of specified ranges.

† n values represent the minimum number of patients assessed for each laboratory parameter.

NRH = Normal Range High.

NRL = Normal Range Low.

HIV-Infected Patients

In HIV-infected patients, the most frequently reported adverse events for famciclovir (500 mg twice daily; n=150) and acyclovir (400 mg, 5x/day; n=143), respectively, were headache (16.7 vs 15.4%), nausea (10.7 vs 12.6%), diarrhea (6.7 vs 10.5%), vomiting (4.7 vs 3.5%), fatigue (4.0 vs 2.1%), and abdominal pain (3.3 vs 5.6%).

OVERDOSAGE

Appropriate symptomatic and supportive therapy should be given. Penciclovir is removed by hemodialysis (see PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

Herpes Zoster

The recommended dosage is 500 mg every 8 hours for 7 days. Therapy should be initiated promptly as soon as herpes zoster is diagnosed. No data are available on efficacy of treatment started greater than 72 hours after rash onset.

Herpes Simplex Infections

Recurrent genital herpes: The recommended dosage is 125 mg twice daily for 5 days. Initiate therapy at the first sign or symptom if medical management of a genital herpes recurrence is indicated. The efficacy of *Famvir* has not been established when treatment is initiated more than 6 hours after onset of symptoms or lesions.

Suppression of recurrent genital herpes: The recommended dosage is 250 mg twice daily for up to 1 year. The safety and efficacy of *Famvir* therapy beyond 1 year of treatment have not been established.

HIV-Infected Patients

For recurrent orolabial or genital herpes simplex infection, the recommended dosage is 500 mg twice daily for 7 days.

In patients with reduced renal function, dosage reduction is recommended (see PRECAUTIONS, General).

Table 7

Indication and Normal Dosage Regimen	Creatinine Clearance (mL/min.)	Adjusted Dosage Regimen Dose (mg)	Dosing Interval
Herpes Zoster			
500 mg every 8 hours	>60	500	every 8 hours
	40–59	500	every 12 hours
	20–39	500	every 24 hours
	<20	250	every 24 hours
	HD*	250	following each dialysis
Recurrent Genital Herpes			
125 mg every 12 hours	≥40	125	every 12 hours
	20–39	125	every 24 hours
	<20	125	every 24 hours
	HD*	125	following each dialysis
Suppression of Recurrent Genital Herpes			
250 mg every 12 hours	≥40	250	every 12 hours
	20–39	125	every 12 hours
	<20	125	every 24 hours
	HD*	125	following each dialysis
Recurrent Orolabial and Genital Herpes Simplex Infection in HIV-Infected Patients			
500 mg every 12 hours	≥40	500	every 12 hours
	20–39	500	every 24 hours
	<20	250	every 24 hours
	HD*	250	following each dialysis

*Hemodialysis

Administration with Food

When famciclovir was administered with food, penciclovir C_{max} decreased approximately 50%. Because the systemic availability of penciclovir (AUC) was not altered, it appears that *Famvir* may be taken without regard to meals.

HOW SUPPLIED

Famvir is supplied as film-coated tablets as follows: 125 mg in bottles of 30; 250 mg in bottles of 30; and 500 mg in bottles of 30 and Single Unit Packages of 50 (intended for institutional use only).

Famvir 125 mg tablets are white, round, debossed with FAMVIR on one side and 125 on the other.
125 mg 30's: NDC 0007-4115-13

Famvir 250 mg tablets are white, round, debossed with FAMVIR on one side and 250 on the other.
250 mg 30's: NDC 0007-4116-13

Famvir 500 mg tablets are white, oval, debossed with FAMVIR on one side and 500 on the other.

500 mg 30's: NDC 0007-4117-13
500 mg SUP 50's: NDC 0007-4117-19

Store between 15°C and 30°C (59°F and 86°F).

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