℞ **FAMCICLOVIR**

PENVIR 250/500/750

250mg/500mg/750 mg film-coated tablet

Antiviral

Formulation :

PENVIR 250 (Famciclovir Tablets 250 mg)

Each film-coated tablet contains:
Famciclovir.....250 mg

PENVIR 500 (Famciclovir Tablets 500 mg)

Each film-coated tablet contains:
Famciclovir.....500 mg

PENVIR 750 (Famciclovir Tablets 750 mg)

Each film-coated tablet contains:
Famciclovir.....750 mg

Description

- **PENVIR 250** (Famciclovir 250 mg tablet):

  White to off-white, round, biconvex, film-coated tablets, debossed with "I" on one side and "49" on the other side.

- **PENVIR 500** (Famciclovir 500 mg tablet):

  White to off white, oval film coated, biconvex tablets, debossed with 'I' on one side and '48' on the other side.

- **PENVIR 750** (Famciclovir 750 mg tablet):

  White to off-white, Oval, biconvex, film-coated tablets, debossed with "I" on one side and "100" on the other side.

INDICATIONS AND USAGE

Immunocompetent Adult Patients

Herpes labialis (cold sores): Famciclovir is indicated for the treatment of recurrent herpes labialis.

Genital herpes:

Recurrent episodes: Famciclovir is indicated for the treatment of recurrent episodes of genital herpes. The efficacy of Famciclovir when initiated more than 6 hours after onset of symptoms or lesions has not been established.

Suppressive therapy: Famciclovir is indicated for chronic suppressive therapy of recurrent episodes of genital herpes. The efficacy and safety of Famciclovir for the suppression of recurrent genital herpes beyond 1 year have not been established.

Herpes zoster (shingles): Famciclovir is indicated for the treatment of herpes zoster. The efficacy of Famciclovir when initiated more than 72 hours after onset of rash has not been established.

HIV-Infected Adult Patients

Recurrent orolabial or genital herpes: Famciclovir is indicated for the treatment of recurrent episodes of orolabial or genital herpes in HIV-infected adults. The efficacy of Famciclovir when initiated more than 48 hours after onset of symptoms or lesions has not been established.

Limitation of Use

The efficacy and safety of Famciclovir have not been established for:

- Patients <18 years of age
- Patients with first episode of genital herpes
- Patients with ophthalmic zoster
- Immunocompromised patients other than for the treatment of recurrent orolabial or genital herpes in HIVinfected patients

DOSAGE AND ADMINISTRATION

Famciclovir may be taken with or without food.

Dosing Recommendation in Immunocompetent Adult Patients

Herpes labialis (cold sores): The recommended dosage of Famciclovir for the treatment of recurrent herpes labialis is 1500 mg as a single dose. Therapy should be initiated at the first sign or symptom of herpes labialis (e.g., tingling, itching, burning, pain, or lesion).

Genital herpes:

Recurrent episodes: The recommended dosage of Famciclovir for the treatment of recurrent episodes of genital herpes is 1000 mg twice daily for 1 day. Therapy should be initiated at the first sign or symptom of a recurrent episode (e.g., tingling, itching, burning, pain, or lesion).

Suppressive therapy: The recommended dosage of Famciclovir for chronic suppressive therapy of recurrent episodes of genital herpes is 250 mg twice daily.

Herpes zoster (shingles): The recommended dosage of Famciclovir for the treatment of herpes zoster is 500 mg every 8 hours for 7 days. Therapy should be initiated as soon as herpes zoster is diagnosed.

Dosing Recommendation in HIV-Infected Adult Patients

Recurrent orolabial or genital herpes: The recommended dosage of Famciclovir for the treatment of recurrent orolabial or genital herpes in HIV-infected patients is 500 mg twice daily for 7 days. Therapy should be initiated at the first sign or symptom of a recurrent episode (e.g., tingling, itching, burning, pain, or lesion).

Dosing Recommendation in Patients with Renal Impairment

Dosage recommendations for adult patients with renal impairment are provided in Table [see Use in Specific Populations, Clinical Pharmacology]

Dosage Recommendations for Adult Patients with Renal Impairment.

Indication and Normal Dosage Regimen	Creatinine Clearance (mL/min.)	Adjusted Dosage Regimen Dose (mg)	Dosing Interval
Single-Day Dosing Regimens Recurrent Genital Herpes 1000 mg every 12 hours for 1 day	≥60 40-59 20-39 <20 HD*	1000 500 500 250 250	every 12 hours for 1 day every 12 hours for 1 day single dose single dose single dose following dialysis
Recurrent Herpes Labialis 1500 mg single dose	≥60 40-59 20-39 <20 HD*	1500 750 500 250 250	single dose single dose single dose single dose single dose following dialysis

Dosage Recommendations for Adult Patients with Renal Impairment.

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Acute renal failure: Cases of acute renal failure have been reported in patients with underlying renal disease who have received inappropriately high doses of Famciclovir for their level of renal function. Dosage reduction is recommended when administering Famciclovir to patients with renal impairment [see Dosage and Administration, Use in Specific Populations].

ADVERSE REACTIONS

Acute renal failure is discussed in greater detail in other sections of the label [see Warnings and Precautions]. The most common adverse events reported in at least 1 indication by >10% of adult patients treated with Famciclovir are headache and nausea.

SIDE EFFECTS

Acute renal failure is discussed in greater detail in other sections of the label [see Warnings and Precautions].

The most common adverse events reported in at least 1 indication by > 10% of adult patients treated with Famciclovir are headache and nausea.

Immunocompetent patients

The safety of Famciclovir has been evaluated in active- and placebo-controlled clinical studies involving 816 Famciclovir-treated patients with herpes zoster (Famciclovir, 250 mg three times daily to 750 mg three times daily); 163 Famciclovir-treated patients with recurrent genital herpes (Famciclovir, 1000 mg twice daily); 1,197 patients with recurrent genital herpes treated with Famciclovir as suppressive therapy (125 mg once daily to 250 mg three times daily) of which 570 patients received Famciclovir (open-labeled and/or double-blind) for at least 10 months; and 447 Famciclovir-treated patients with herpes labialis (Famciclovir, 1500 mg once or 750 mg twice daily). Table 2 lists selected adverse events.

Table: Selected Adverse Events (all grades and without regard to causality) Reported by ≥ 2% of Patients in Placebo-Controlled Famciclovir Trials*

Events	Herpes Famciclovir (n=273)%	Zoster† Placebo (n=146)%	Recurrent Genital Famciclovir (n=163)%	Herpes‡ Placebo (n=166)%	Genital Suppression§ Famciclovir (n=458)%	Herpes Placebo (n=63)%	Herpes Famciclovir (n=447)%	Labialis‡ Placebo (n=254)%
Nervous System								
Headache	22.7	17.8	13.5	5.4	39.3	42.9	8.5	6.7
Paresthesia	2.6	0.0	0.0	0.0	0.9	0.0	0.0	0.0
Migraine	0.7	0.6	0.6	0.6	3.1	0.0	0.2	0.0
Gastrointestinal								
Nausea	12.5	2.5	2.5	3.6	7.2	9.5	2.2	3.9
Diarrhea	7.7	4.8	4.9	1.2	9.0	9.5	1.6	0.8
Vomiting	4.8	3.4	1.2	0.6	3.1	1.6	0.7	0.0
Flatulence	1.5	0.7	0.6	0.0	4.8	1.6	0.2	0.0
Abdominal pain	1.1	3.4	0.0	1.2	7.9	7.9	0.2	0.4
Body as a Whole								
Fatigue	4.4	3.4	0.6	0.0	4.8	3.2	1.6	0.4
Skin and Appendages								
Pruritus	3.7	2.7	0.0	0.6	2.2	0.0	0.0	0.0
Rash	0.4	0.7	0.0	0.0	3.3	1.6	0.0	0.0
Reproductive (Female)								
Dysmenorrhea	0.0	0.7	1.8	0.6	7.6	6.3	0.4	0.0

* Patients may have entered into more than one clinical trail

† 7 days of treatment

‡ 1 day of treatment

§ daily treatment

Table: Selected Laboratory Abnormalities in Genital Herpes Suppression Studies*

Parameter	Famciclovir (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 (17% vs. 15%), nausea (11% vs. 13%), diarrhea (7% vs. 11%), vomiting (5% vs. 4%), fatigue (4% vs. 2%), and abdominal pain (3% vs. 6%).

Post marketing Experience

The adverse events listed below have been reported during post-approval use of Famciclovir. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Blood and lymphatic system disorders: Thrombocytopenia

Hepatobiliary disorders: Abnormal liver function tests, cholestatic jaundice

Nervous system disorders: Dizziness, somnolence

Psychiatric disorders: Confusion (including delirium, disorientation, and confusional state occurring predominantly in the elderly), hallucinations

Skin and subcutaneous tissue disorders: Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

DRUG INTERACTIONS

Potential for Famciclovir to Affect Other Drugs

The steady-state pharmacokinetics of digoxin were not altered by concomitant administration of multiple doses of Famciclovir (500 mg three times daily). No clinically significant effect on the pharmacokinetics of Zidovudine, its metabolite Zidovudine glucuronide, or Emtricitabine was observed following a single oral dose of 500 mg Famciclovir coadministered with Zidovudine or Emtricitabine. An in vitro study using human liver microsomes suggests that Famciclovir is not an inhibitor of CYP3A4 enzymes.

Potential for Other Drugs to Affect 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, Zidovudine, promethazine, when given shortly after an antacid (magnesium and aluminum hydroxide), or concomitantly with Emtricitabine. No clinically significant effect on penciclovir pharmacokinetics was observed following multiple dose (three times daily) administration of Famciclovir (500 mg) with multiple doses of digoxin.

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 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. Raloxifene, a potent aldehyde oxidase inhibitor in vitro, could decrease the formation of penciclovir. However, a clinical drug-drug interaction study to determine the magnitude of interaction between penciclovir and raloxifene has not been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy category B: After oral administration, Famciclovir (prodrug) is converted to penciclovir (active drug). There are no adequate and well-controlled studies of Famciclovir or penciclovir use in pregnant women. No adverse effects on embryofetal development were observed in animal reproduction studies using Famciclovir and penciclovir at doses higher than the maximum recommended human dose (MRHD) and human exposure. Because animal reproduction studies are not always predictive of human response, Famciclovir should be used during pregnancy only if needed. In animal reproduction studies, pregnant rats and rabbits received oral Famciclovir at doses (up to 1000 mg/kg/day) that provided 2.7 to 10.8 times (rats) and 1.4 to 5.4 times (rabbits) the human systemic exposure based on AUC. No adverse effects were observed on embryo-fetal development. In other studies, pregnant rats and rabbits received Intravenous, Famciclovir at doses (360 mg/kg/day) 1.5 to 6 times (rats) and (120 mg/kg/day) 1.1 to 4.5 times (rabbits) or penciclovir at doses (80/mg/kg/day) 0.3 to 1.3 times (rats) and (60 mg/kg/day) 0.5 to 2.1 times (rabbits) the MRHD based on body surface area comparisons. No adverse effects were observed on embryo-fetal development.

Pregnancy exposure reporting: To monitor maternal-fetal outcomes of pregnant women exposed to Famciclovir.

Nursing Mothers

It is not known whether Famciclovir (prodrug) or penciclovir (active drug) are excreted in human milk. Following oral administration of Famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. There are no data on the safety of Famciclovir in infants. Famciclovir should not be used in nursing mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment.

Pediatric Use

The efficacy and safety of Famciclovir tablets have not been established in pediatric patients. The pharmacokinetic profile and safety of Famciclovir experimental granules mixed with OraSweet® were studied in two open-label studies. Study 1 was a single-dose pharmacokinetic and safety study in infants 1 month to <1 year of age who had an active herpes simplex virus (HSV) infection or who were at risk for HSV infection. Eighteen subjects were enrolled and received a single dose of Famciclovir experimental granules mixed with OraSweet® based on the patient's body weight (doses ranged from 25 mg to 175 mg). These doses were selected to provide penciclovir systemic exposures similar to the penciclovir systemic exposures observed in adults after administration of 500 mg Famciclovir. The efficacy and safety of Famciclovir have not been established as suppressive therapy in infants following neonatal HSV infections. In addition, the efficacy cannot be extrapolated from adults to infants because there is no similar disease in adults. Therefore, Famciclovir is not recommended in infants. Study 2 was an open-label, single-dose pharmacokinetic, multiple-dose safety study of Famciclovir experimental granules mixed with OraSweet® in children 1 to <12 years of age with clinically suspected HSV or varicella zoster virus (VZV) infection. Fifty-one subjects were enrolled in the pharmacokinetic part of the study and received a single body weight adjusted dose of Famciclovir (doses ranged from 125 mg to 500 mg). These doses were selected to provide penciclovir systemic exposures similar to the penciclovir systemic exposures observed in adults after administration of 500 mg Famciclovir. Based on the pharmacokinetic data observed with these doses in children, a new weight-based dosing algorithm was designed and used in the multiple-dose safety part of the study. Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm. A total of 100 patients were enrolled in the multiple-dose safety part of the study; 47 subjects with active or latent HSV infection and 53 subjects with chickenpox.

Patients with active or latent HSV infection received Famciclovir twice a day for seven days. The daily dose of Famciclovir ranged from 150 mg to 500 mg twice daily depending on the patient's body weight. Patients with chickenpox received Famciclovir three times daily for seven days. The daily dose of Famciclovir ranged from 150 mg to 500 mg three times daily depending on the patient's body weight. The clinical adverse events and laboratory test abnormalities observed in this study were similar to these seen in adults. The available data are insufficient to support the use of Famciclovir for the treatment of children with chickenpox or infections due to HSV for the following reasons:

Chickenpox: The efficacy of Famciclovir for the treatment of chickenpox has not been established in either pediatric or adult patients. Famciclovir is approved for the treatment of herpes zoster in adult patients. However, extrapolation of efficacy data from adults with herpes zoster to children with chickenpox would not be appropriate. Although chickenpox and herpes zoster are caused by the same virus, the diseases are different.

Genital herpes: Clinical information on genital herpes in children is limited. Therefore, efficacy data from adults cannot be extrapolated to this population. Further, Famciclovir has not been studied in children 1 to <12 years of age with recurrent genital herpes. None of the children in Study 2 had genital herpes.

Herpes labialis: There are no pharmacokinetic and safety data in children to support a Famciclovir dose that provides penciclovir systemic exposures comparable to the penciclovir systemic exposures in adults after a single dose administration of 1500 mg.

Geriatric Use

Of 816 patients with herpes zoster in clinical studies who were treated with Famciclovir, 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. Of 610 patients with recurrent herpes simplex (type 1 or type 2) in clinical studies who were treated with Famciclovir, 26 (4.3%) were >65 years of age and 7 (1.1%) were >75 years of age. Clinical studies of Famciclovir in patients with recurrent genital herpes did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. No

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Antiviral

300 x 350 mm
Color Black

Famciclovir dosage adjustment based on age is recommended unless renal function is impaired [see Dosage and Administration, Clinical Pharmacology]. In general, appropriate caution should be exercised in the administration and monitoring of Famciclovir in elderly patients reflecting the greater frequency of decreased renal function and concomitant use of other drugs.

Patients with Renal Impairment

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 impairment (CL_{CR} ranged from 6.4 to 138.8 mL/min), the following results were obtained.

Pharmacokinetic Parameters of Penciclovir in Subjects with Different Degrees of Renal Impairment

Parameter (Mean ± S.D.)	CL_{CR} =60 (mL/min) (n=15)	CL_{CR} 40-59 (mL/min) (n=5)	CL_{CR} 20-39 (mL/min) (n=4)	CL_{CR} <20 (mL/min) (n=3)
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

† CLCR 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 impairment [see Dosage and Administration].

Patients with Hepatic Impairment

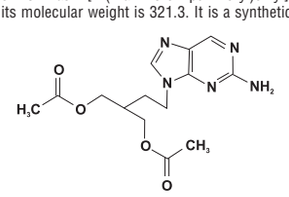
Well-compensated chronic liver disease (chronic hepatitis [n=6], chronic ethanol abuse [n=8], or primary biliary cirrhosis [n=1]) had no effect on the extent of availability (AUC) of penciclovir following a single dose of 500-mg Famciclovir. However, there was a 44% decrease in penciclovir mean maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (t_{max}) was increased by 0.75 hours in patients with hepatic impairment 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.

OVERDOSAGE

Appropriate symptomatic and supportive therapy should be given. Penciclovir is removed by hemodialysis.

DESCRIPTION

The active ingredient in Famciclovir tablets is orally administered prodrug of the antiviral agent penciclovir. Chemically, Famciclovir is known as 2-[2-(2-amino-*9H*-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.

Famciclovir tablets contain 125 mg, 250 mg or 500 mg of Famciclovir, together with the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Famciclovir is an orally administered prodrug of the antiviral agent penciclovir [see Clinical Pharmacology].

Pharmacokinetics

Famciclovir is the diacetyl 6-deoxy analog of the active antiviral compound penciclovir. Following oral administration Famciclovir undergoes rapid and extensive metabolism to penciclovir and little or no Famciclovir is detected in plasma or urine. Penciclovir is predominantly eliminated unchanged by the kidney. Therefore, the dose of Famciclovir needs to be adjusted in patients with different degrees of renal impairment [see Dosage and Administration].

Pharmacokinetics in adults:

Absorption and Bioavailability: The absolute bioavailability of penciclovir 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 1000 mg administered as a single dose. Table shows the mean pharmacokinetic parameters of penciclovir after single administration of Famciclovir to healthy male volunteers.

Mean Pharmacokinetic Parameters of Penciclovir in Healthy Adult Subjects*

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
1000 mg	17.9	6.6	0.9

* Based on pharmacokinetic data from 17 studies

† 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 oral single-dose administration of 500-mg Famciclovir to seven patients with herpes zoster, the AUC (mean ± SD), C_{max}, and Tmax 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 three times daily for 7 days.

Penciclovir C_{max} decreased approximately 50% and Tmax 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, Famciclovir can be taken without regard to meals.

Distribution: The volume of distribution (Vdß) 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. Cimetidine and promethazine, in vitro inhibitors of aldehyde oxidase, did not show relevant effects on the formation of penciclovir in vivo [see Drug Interactions].

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. Active tubular secretion contributes to the renal elimination of penciclovir. 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 17 patients with herpes zoster was 2.8±1.0 hours and 2.7±1.0 hours after single and repeated doses, respectively.

Special populations:

Geriatric patients: Based on cross study comparison, penciclovir AUC was 40% higher and penciclovir renal clearance was 22% lower in elderly subjects (n=18, age 65-79 years) as compared with younger subjects Some of this difference may be due to differences in renal function between the two groups. No Famciclovir dosage adjustment based on age is recommended unless renal function is impaired [see Dosage and Administration, Use in Specific Populations].

Patients with renal impairment: In subjects with varying degrees of renal impairment, apparent plasma clearance, renal clearance, and the plasma-elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing [see Use Specific Populations (8.6)]. A dosage adjustment is recommended for patients with renal impairment [see Dosage and Administration].

Patients with hepatic impairment: Well-compensated chronic liver disease had no effect on the extent of availability (AUC) of penciclovir [see Use in Specific Populations]. No dosage adjustment is recommended for patients with well-compensated hepatic impairment.

HIV-infected patients: Following oral administration of a single dose of 500-mg Famciclovir to HIV-positive patients, the pharmacokinetic parameters of penciclovir were comparable to those observed in healthy subjects.

Gender: The pharmacokinetics of penciclovir was 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.

Race: The effect of race on the pharmacokinetics of penciclovir after oral administration of Famciclovir has not been evaluated.

Virology

Mechanism of action: Famciclovir is a prodrug of penciclovir, which has demonstrated 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, the viral thymidine kinase phosphorylates penciclovir to a monophosphate form that, in turn, is converted by cellular kinases to the active form penciclovir triphosphate. Biochemical 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 grown in culture; however, the clinical significance is unknown.

Antiviral activity: In cell culture studies, penciclovir is inhibitory to the following herpes viruses: HSV-1, HSV-2 and VZV. The antiviral activity of penciclovir against wild type strains grown on human foreskin fibroblasts was assessed with a plaque reduction assay and staining with crystal violet 3 days postinfection for HSV and 10 days postinfection for VZV. The median EC50 values of penciclovir against laboratory and clinical isolates of HSV-1, HSV-2, and VZV were 2 µM (range 1.2 to 2.4 µM, n = 7), 2.6 µM (range 1.6 to 11 µM, n = 6), and 34 µM (range 6.7 to 71 µM, n = 6), respectively.

Resistance: Penciclovir-resistant mutants of HSV and VZV 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 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 that are TK negative are also resistant to penciclovir. The median EC50 values observed in a plaque reduction assay with penciclovir resistant HSV-1, HSV-2, and VZV were 69 µM (range 14 to 115 µM, n = 6), 46 µM (range 4 to >395 µM, n = 9), and 92 µM (range 51 to 148 µM, n = 4), respectively. The possibility of viral resistance to penciclovir should be considered in patients who fail to respond or experience recurrent viral shedding during therapy.

Availability

Pack style : Blister pack of 10's ALU/PVC/PVDC (Box of 30's).

STORAGE: Store at temperatures not exceeding 30°C.

Caution: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR Reporting Statement:

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction.

Manufactured by:

HETERO LABS LIMITED
Unit-V, Block V and V-A TSIIC Formulation SEZ,
Sy.Nos.439, 440, 441 & 458, Polepally Village,
Jadcherla Mandal, Mahaboobnagar District,
Telangana State, 509 301, India.

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CAMBER PHARMACEUTICALS, INC.
Unit 503-A ITC Bldg., 337 Sen. Gil Puyat Avenue,
Bel-Air, Makati City, Philippines.

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