NOVARTIS

Famvir®

Composition
Active substance: Famciclovir

Excipients:
125 mg and 250 mg film-coated tablets
Tablet core: hydroxypropyl cellulose, lactose anhydrous, sodium starch glycollate, magnesium stearate.
Tablet coating: hypromellose/hydroxypropylmethyl-cellulose, polyethylene glycol 4000/Macrogol 4000, polyethylene glycol 6000/Macrogol 6000, titanium dioxide (CI 77891, E 171).

500 mg film-coated tablet
Tablet core: hydroxypropyl cellulose, lactose anhydrous (country specific), sodium starch glycollate, magnesium stearate.
Tablet coating: hypromellose/hydroxypropylmethyl-cellulose, polyethylene glycol 4000/Macrogol 4000, polyethylene glycol 6000/Macrogol 6000, titanium dioxide (CI 77891, E 171).

Pharmaceutical form and quantity of active substance per unit
Film-coated tablets containing 500 mg famciclovir
Film-coated tablets containing 250 mg famciclovir
Film-coated tablets containing 125 mg famciclovir

Indications / Potential uses
Immunocompetent patients
Famvir is indicated for the treatment of:

Herpes zoster, including ophthalmic zoster
(Treatment is initiated as soon as possible, within not more than 72 hours)

Genital herpes
Acute treatment (treatment of new and recurrent genital herpes infections);
Suppression of recurrent infections which do not respond adequately to other treatment and which cause frequent and persistent symptoms.
Immunocompromised patients
Famvir is indicated for the treatment of *herpes zoster* and *herpes simplex* infections.
Studies have not been conducted in patients with *herpes simplex* infections who were immunocompromised from causes other than HIV infection.

Dosage / Administration
Usual dosage
Immunocompetent adults:
1.a. Herpes zoster
One 500 mg tablet twice daily for 7 days.
There is an increased risk of post-herpetic neuralgia (PHN) in patients over 50 years of age. In this age group, one 500 mg tablet may be taken three times daily for 7 days. This can reduce the incidence of PHN during the acute phase of the disease.
Better results are achieved if treatment is initiated as soon as possible after appearance of the rash.

1.b. Ophthalmic zoster
One 500 mg tablet three times daily for 7 days.
Better results are achieved if treatment is initiated as soon as possible after appearance of the rash.

2. Genital herpes
Treatment of the first episode:
One 250 mg tablet three times daily for 5 days, or
Two 125 mg tablets three times daily for 5 days.
Treatment should be initiated as soon as possible after appearance of the lesions.

Recurrent genital herpes infections: One 125 mg tablet twice daily for 5 days. It is recommended that treatment be initiated during the prodromal period or as soon as possible after appearance of the lesions.

Suppression of recurrent infections: One 250 mg tablet twice daily. The duration of treatment depends on the severity of the disease. Treatment should be interrupted after 12 months at most in order to determine possible changes in the course of the disease. Treatment should be interrupted no earlier than after two recurrent infections.

Immunocompromised adults:
1. Herpes zoster
One 500 mg tablet three times daily for 10 days.

2. Herpes simplex infections
One 500 mg tablet twice daily for 7 days.
Treatment should be initiated as soon as possible after appearance of the rash.

Special dosage instructions
No dose adjustment is required in *elderly patients* who do not have kidney disease or renal impairment.

Children: No data are available on the use of famciclovir in children.
Black patients: A clinical study in immunocompetent black patients with recurrent genital herpes showed no difference in efficacy between patients who received 1,000 mg famciclovir twice daily for one day, and those who received placebo. There were no unexpected or new drug safety findings in this study.
The lack of efficacy in this 1-day treatment regimen cannot be extrapolated to the 5-day treatment regimen for recurrent genital herpes (125 mg twice daily for five days) or other indications in black patients (see "**Properties / Actions**" and "**Pharmacokinetics**").

Renal impairment: Because reduced clearance of penciclovir is related to impaired renal function, as measured by creatinine clearance, special caution is required in patients with impaired renal function.
The following dose adjustments are recommended in patients with impaired renal function:
Immunocompetent patients:

1 a) Treatment of herpes zoster:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
A) 500 mg twice daily for 7 days	≥40	500 mg twice daily for 7 days
	20-39	500 mg once daily for 7 days
	<20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis for 7 days
B) 500 mg three times daily for 7 days	≥60	500 mg three times daily for 7 days
(in patients >50 years)	40-59	500 mg twice daily for 7 days
	20-39	500 mg once daily for 7 days
	<20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis for 7 days

1 b) Treatment of ophthalmic zoster:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
500 mg twice daily for 7 days	≥60	500 mg three times daily for 7 days
	40-59	500 mg twice daily for 7 days
	20-39	500 mg once daily for 7 days
	<20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis for 7 days

2 a) Treatment of the first episode of genital herpes infections:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
250 mg three times daily for 5 days	≥40	250 mg three times daily for 5 days
	20-39	250 mg twice daily for 5 days
	<20	250 mg once daily for 5 days
	Haemodialysis patients	250 mg following each dialysis for 5 days

2 b) Treatment of recurrent genital herpes infections:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
125 mg twice daily for 5 days	≥20	125 mg twice daily
	<20 Haemodialysis patients	125 mg once daily 125 mg following each dialysis for 5 days

2 c) Suppression of recurrent genital herpes infections:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
250 mg twice daily	≥40	250 mg twice daily
	20-39	125 mg twice daily
	<20	125 mg once daily
	Haemodialysis patients	125 mg following each dialysis

Immunocompromised patients:
1) Treatment of herpes zoster:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
500 mg three times daily for 10 days	≥60	500 mg three times daily for 10 days
	40-59	500 mg twice daily for 10 days
	20-39	500 mg once daily for 10 days
	<20	250 mg once daily for 10 days
	Haemodialysis patients	250 mg following each dialysis for 10 days

2) Treatment of herpes simplex infections:

Nominal dose regimen	Creatinine clearance (ml/min.)	Adjusted dose regimen
500 mg twice daily for 7 days	≥40	500 mg twice daily for 7 days
	20-39	500 mg once daily for 7 days
	<20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis for 7 days

Dialysis patients
Since 4 hours of haemodialysis resulted in a reduction of up to 75% in plasma penciclovir concentrations, Famvir should be administered immediately following dialysis. Please refer to the tables above for the recommended dose in each case.

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see "**Pharmacokinetics**").

Method of administration
The tablets can be taken without regard to meals. They should be swallowed whole with water.

Contraindications
Known hypersensitivity to famciclovir, penciclovir or any of the excipients of Famvir.

Warnings and precautions
Dose adjustment, based on creatinine clearance, is required in patients with impaired renal function (see "**Special dosage instructions**").
Acute renal failure has been reported in patients with existing renal impairment following administration of inappropriately high doses of Famvir in relation to the extent of renal impairment.
No dose adjustment is required in patients with mild to moderate hepatic impairment. This also applies to elderly patients who do not have renal impairment. Famciclovir has not been studied in patients with severe hepatic impairment. Impaired conversion of famciclovir to the active metabolite may result in lower penciclovir plasma concentrations and thus decreased efficacy of famciclovir in these patients (see "**Pharmacokinetics**").

Transmission of genital herpes
Genital herpes is a sexually transmitted disease. The risk of transmission is increased during acute episodes. Patients should be advised to avoid sexual intercourse if symptoms are present, or even if treatment with a virostatic agent has been initiated.
Famvir 125 mg and 250 mg tablets contain lactose (26.9 mg and 53.7 mg, respectively). Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Famvir 125 mg or 250 mg tablets.

Interactions
Effects of other medicinal products on famciclovir
Concurrent use of probenecid and other medicinal products that affect renal physiology may affect the plasma concentrations of penciclovir, the active metabolite of famciclovir (see "**Pharmacokinetics**"). Therefore, patients receiving Famvir at a dose of 500 mg three times daily co-administered with probenecid on consecutive days should be monitored in particular for toxicity, and a dose reduction of Famvir may be considered.
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 or promethazine, or when given shortly after an antacid (magnesium hydroxide and aluminium 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.
The conversion of the inactive metabolite 6-deoxy penciclovir (formed by deacetylation of famciclovir) to penciclovir is catalysed by aldehyde oxidase. Interactions with other medicinal products 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 any relevant effects on the formation of penciclovir. However, raloxifene, the most potent aldehyde oxidase inhibitor tested *in vitro*, may affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifene is co-administered with famciclovir, the clinical efficacy of the antiviral therapy should be monitored.

Effects of famciclovir on other medicinal products
The pharmacokinetics of digoxin were not altered by concomitant administration of single or multiple (three times daily) doses of famciclovir (500 mg). No clinically significant effects on the pharmacokinetics of zidovudine, its metabolite zidovudine glucuronide or emtricitabine were observed following a single oral dose of 500 mg famciclovir co-administered with zidovudine or emtricitabine.
Although famciclovir is only a weak inhibitor of aldehyde oxidase *in vitro*, interactions with medicinal products metabolized by aldehyde oxidase could potentially occur.
Preclinical studies have shown no induction of CYP450 or inhibition of CYP3A4.

Pregnancy / Lactation
Pregnancy
Although reproductive toxicity studies in animals have not shown any risk to the fetus (see "**Preclinical data**"), there are insufficient data on the use of Famvir in pregnant women. Famciclovir should therefore not be prescribed for pregnant or breastfeeding women unless clearly necessary. There is no data available to support special recommendations for women of childbearing age.

Lactation
Following oral administration of famciclovir to lactating rats, penciclovir (the active metabolite of famciclovir) was excreted in breast milk. No information is available on excretion in human milk. Famvir should not be used by breastfeeding women unless the potential benefits of treatment are considered to outweigh the potential risks.

Effects on ability to drive and use machines
There are no studies on the effects of Famvir on alertness. However, patients who experience dizziness, somnolence, confusion or other central nervous system symptoms while taking Famvir should refrain from driving or using machines (see "**Adverse effects**").

Adverse effects
Headache (16.9%), nausea (8.4%), diarrhoea (5.1%) and – uncommonly – somnolence (1%) have been reported in clinical trials. These symptoms were generally mild to moderate and occurred at the same incidence in patients receiving placebo.
The following adverse effects have been reported from post-marketing experience:

Psychiatric disorders
Confusion (predominantly in elderly patients).
Hallucinations.

Nervous system disorders
Headache.
Dizziness, somnolence (predominantly in elderly patients).

Cardiac disorders
Palpitations.

Gastrointestinal disorders
Abdominal pain, nausea, diarrhoea, vomiting.
Hepatic disorders
Cholestatic jaundice, abnormal liver function tests.

Skin and subcutaneous tissue disorders
Erythema, pruritus.
Angioedema (e.g. facial oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria.

Renal and urinary disorders
Acute renal failure has been reported rarely in patients with renal disease in whom the dosage was not correctly adjusted.
Isolated cases of thrombocytopenia, angioedema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), leukocytoclastic vasculitis and pancreatitis have been reported, but no connection with Famvir treatment could be established.
Adverse effects observed in immunocompromised patients during clinical trials were similar to those in immunocompetent patients.
The precise incidence of adverse effects cannot be indicated, since it is generally assumed that the incidence of adverse effects calculated based on spontaneous post-marketing reports underestimates the true incidence.

Overdose
Overdose experience with famciclovir is limited. No symptoms occurred in one case of sudden acute overdose (10.5 g). In a case involving long-term use (10 g daily for 2 years), famciclovir was well tolerated.
In the event of an overdose, supportive and symptomatic therapy should be given.
There have been rare reports of acute renal failure in patients with renal disease when doses of famciclovir were not properly adjusted in line with renal function.
Penciclovir is dialyzable; plasma concentrations are reduced by approximately 75% following 4 hours of haemodialysis.

Properties / Actions
ATC code: J05AB09

Mechanism of action / Pharmacodynamics
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), varicella/zoster viruses (VZV), and cytomegalovirus. The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir. In virus-infected cells, virus-induced thymidine kinase (TK) rapidly and efficiently converts penciclovir to a monophosphate form that, in turn, is converted to a triphosphate by cellular kinases. This triphosphate inhibits DNA-dependent replication. 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.
In healthy cells, concentrations of penciclovir triphosphate are only barely detectable. It is therefore unlikely that healthy cells will be negatively affected by therapeutic doses of penciclovir.
Like with aciclovir, penciclovir resistance is associated with mutations principally in the TK gene resulting in deficiency or altered substrate specificity of this enzyme, and to a much lesser extent with mutations in the DNA polymerase gene. Most aciclovir-resistant HSV and VZV clinical isolates are also resistant to penciclovir, but cross-resistance is not universal.
The most common form of aciclovir resistance among HSV strains is a deficiency in the thymidine kinase (TK) enzyme. TK-deficient strains are cross-resistant to penciclovir and aciclovir.

Clinical efficacy
Results from 11 worldwide clinical studies involving penciclovir and famciclovir, including studies of up to 12 months' treatment with famciclovir, have shown a small average frequency of penciclovir-resistant isolates: 0.2% of a total of 913 tested isolates from immunocompetent patients and 2.1% of a total of 288 tested isolates from immunocompromised patients. The resistant isolates were found at the start of treatment or in a placebo group; only two cases of resistance occurred in immunocompromised patients during or after treatment with penciclovir or famciclovir.
Available data show that famciclovir had a favourable effect on the incidence of post-herpetic neuralgia (PHN) in patients over 50 years of age with herpes zoster when administered at doses of 500 mg or higher three times daily, as soon as possible after appearance of the rash (within 72 hours).
A clinical study of suppression of recurrent genital herpes infections in HIV-positive patients has shown that 500 mg famciclovir twice daily noticeably decreases the number of days with symptomatic and asymptomatic HSV-related lesions.
The efficacy and good tolerability of famciclovir in the treatment of ophthalmic zoster were demonstrated in a large-scale clinical trial.
Two studies in which 125 mg famciclovir was administered twice daily for five days demonstrated its efficacy in the treatment of immunocompetent patients with recurrent genital herpes. A clinical study in immunocompetent black patients with recurrent genital herpes showed no difference in efficacy between 1000 mg famciclovir twice daily for one day, and placebo.

Pharmacokinetics
Absorption
Following oral administration, famciclovir is rapidly and extensively absorbed and metabolized into the antiviral active substance penciclovir. Bioavailability of penciclovir after oral administration of famciclovir is 77%. Penciclovir plasma concentrations increased in proportion to the dose over a famciclovir dose range of 125 mg to 1000 mg administered as a single dose. In one study, the mean peak plasma concentration of penciclovir following a 125 mg, 250 mg, 500 mg or 750 mg dose of famciclovir was 0.8 µg/ml, 1.6 µg/ml, 3.3 µg/ml or 5.1 µg/ml, respectively, at a median time of 45 minutes post-dose. The corresponding mean area under the concentration-time curve (AUC) of penciclovir was 2.2 µg•h/ml, 4.3 µg•h/ml, 9.3 µg•h/ml or 14.1 h•µg/ml. In another study, the mean peak plasma concentration of penciclovir following a 250 mg, 500 mg or 1000 mg dose of famciclovir was 1.5 µg/ml, 3.2 µg/ml or 5.8 µg/ml, respectively, and the mean AUC of penciclovir was 4.0 µg•h/ml, 8.7 µg•h/ml or 16.9 µg•h/ml. Plasma concentration-time curves are similar following single and repeat (three times daily and twice daily) dosing. There is no accumulation of penciclovir following repeat administration of famciclovir.
Meals reduce penciclovir C_{max} and T_{max}, but penciclovir bioavailability is not affected.

Distribution
Penciclovir and its 6-deoxy precursor are poorly (<20%) bound to plasma proteins.
Studies in rats have shown that penciclovir is excreted in the milk after oral administration of famciclovir. No information is available on excretion in human milk.
The volume of distribution (Vd) of penciclovir is approx. 1 litre/kg.
There are no significant differences in the distribution and elimination characteristics of penciclovir following oral famciclovir administration or parenteral penciclovir administration in immunocompetent or immunocompromised patients.

Metabolism
Famciclovir is the prodrug of the antivirally active metabolite penciclovir.

Elimination
Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted renally. No unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir.
The terminal elimination half-life of penciclovir is approx. 2 hours. Renal clearance of penciclovir is 80% of total clearance.

Pharmacokinetics in special patient populations
Patients with herpes zoster
Uncomplicated herpes zoster does not significantly alter the pharmacokinetics of penciclovir after the oral administration of famciclovir. The terminal plasma half-life of penciclovir in patients with herpes zoster was 2.8 hours and 2.7 hours, respectively, after single and repeat doses of famciclovir.

Elderly patients: Based on cross-study comparisons, 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 is probably 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 / Administration**").

Gender: Small differences in renal clearance of penciclovir between females and males have been reported and were attributed to gender differences in renal function. No dose adjustment based on gender is recommended.

Ethnicity: There were no differences in the pharmacokinetics of penciclovir between black and Caucasian volunteers.

Renal impairment: Elimination of penciclovir is decreased in renal impairment.
The apparent plasma clearance, renal clearance and plasma elimination rate constant of penciclovir decreased linearly with reduced renal function, both after single and repeat administration. Dose adjustment is therefore necessary in patients with *renal impairment* (see "**Dosage / Administration**").

Hepatic impairment: Mild to moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following administration of famciclovir. Therefore, no dose adjustment is recommended in such cases (see "**Dosage / Administration**" and "**Warnings and precautions**").
The pharmacokinetics of penciclovir have not been evaluated in patients with severe hepatic impairment. Conversion of famciclovir to penciclovir may be impaired in these patients, possibly resulting in lower penciclovir plasma concentrations and thus a decrease in the efficacy of famciclovir (see "Warnings and precautions").

Preclinical data
Carcinogenicity
Two-year oral carcinogenicity studies were conducted in rats and mice. At the maximum tolerated dose of 600 mg/kg/day, there was an increased incidence of mammary adenocarcinoma in female rats, a common tumour in the strain of rats used in this study. No effect was observed on the incidence of neoplasia in male rats given doses of up to 240 mg/kg/day or in mice of either sex at doses of up to 600 mg/kg/day.

Genotoxicity
Famciclovir was not found to be genotoxic in a battery of *in vivo* and *in vitro* tests designed to detect gene mutation, chromosomal damage and irreversible damage to DNA. Penciclovir, like other drugs of this class, causes chromosomal damage *in vitro*, but does not induce gene mutation in cell systems, nor is there evidence of increased DNA repair *in vitro*.
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 and above) but not when administered orally at 2,400 and 4,800 mg/kg.

Reproductive toxicity
The effects of famciclovir on embryofetal development in rats and rabbits were investigated using oral doses of up to 1000 mg/kg/day and intravenous doses of 360 mg/kg/day in rats and 120 mg/kg/day in rabbits. Based on AUC comparisons with rats and rabbits, the oral doses were, respectively, approx. 3.6-21.6 times and 1.8-10.8 times the systemic exposure to penciclovir in humans. The intravenous doses in rats and rabbits were, respectively, 2-12 times and 1.5-9.0 times the human dose based on comparisons of body surface area (BSA). No harmful effects on embryofetal development were observed. In addition, no effects were determined following intravenous administration of penciclovir in rats (80 mg/kg/day, 0.4-2.6 times the human dose [BSA]) and rabbits (60 mg/kg/day, 0.7-4.2 times the human dose [BSA]). However, there have been no corresponding well-controlled studies in pregnant women. Results from reproductive toxicity studies in animals cannot always be extrapolated to humans, and Famvir should therefore only be used during pregnancy if the benefit to the patient clearly outweighs the risk to the fetus.
Famciclovir has no negative effects on sperm count, morphology or motility in humans.
Impaired fertility was observed in male rats given 500 mg/kg/day famciclovir for 10 weeks. No effects on fertility were observed in female rats at doses of up to 1,000 mg/kg/day.

Other information
Incompatibilities
No specific incompatibilities are known.

Shelf life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Protect from moisture and do not store above 30 °C.
Keep out of the reach of children.

Pack sizes
Country specific pack sizes.

Manufacturer
See folding box

Information last revised
February 2013

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists