

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 plain on the reverse side.

Uses

Actions

Pharmacotherapeutic group: Oral antiviral agent, ATC code: JO5A 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), varicella zoster virus, Epstein-Barr virus 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, the viral thymidine kinase (TK) phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. This triphosphate persists in infected cells in excess of 12 hours and inhibits replication of viral DNA. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Hence the probability of toxicity to mammalian host cells is low and uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

Like with acyclovir, the most common form of penciclovir resistance encountered with acyclovir among HSV strains is a deficiency in the production of the (TK) enzyme. Such TK deficient strains would be expected to be cross-resistant to both penciclovir and acyclovir.

Results from 11 worldwide clinical studies involving penciclovir (topical or intravenous formulations) or famciclovir in immunocompetent or immunocompromised patients, including studies of up to 12 months treatment with famciclovir, have shown a small overall frequency of penciclovir resistant isolates: 0.2% (2/913) in immunocompetent patients and 2.1% (6/288) in immunocompromised patients. The resistant isolates were mostly found at the start of treatment or in a placebo group, with resistance occurring on or after treatment with famciclovir or penciclovir only in two immunocompromised patients

Clinical studies

Adults

A randomised, double-blind, placebo-controlled trial was conducted in 701 immunocompetent adults with recurrent herpes labialis. Patients self-initiated therapy within 1 hour of first onset of signs or symptoms of a recurrent herpes labialis episode with FAMVIR 1500 mg as a single dose (n=227), FAMVIR 750 mg twice daily (n=220) or placebo (n=254) for 1 day. The median time to healing among patients with non-aborted lesions (progressing beyond the papule stage) was 4.4 days in the FAMVIR 1500 mg single-dose group (n=152) as compared to 4.0 days in the FAMVIR 750 mg twice-daily group (n=157) and 6.2 days in

the placebo group (n=168). The median difference in time to healing was 1.8 days (95% CI: 0.9 – 2.7) between placebo and FAMVIR 1500 mg treated groups and 2.2 days (95% CI: 1.3 – 3.1) between placebo and FAMVIR 750 mg twice daily groups. No differences in proportion of patients with aborted lesions (not progressing beyond the papule stage) were observed between patients receiving FAMVIR or placebo: 33% for FAMVIR 1500 mg single dose, 29% for FAMVIR 750 mg twice daily and 34% for placebo. The median time to loss of pain and tenderness was 1.7 days in FAMVIR 1500 mg single dose-treated patients, 2.1 days in FAMVIR 750 mg twice daily-treated patients and 2.9 days in placebo-treated patients.

Paediatric patients

The efficacy of FAMVIR ONCE in paediatric patients under the age of 18 years has not been established. The safety of famciclovir experimental oral granules was evaluated in 169 paediatric patients 1 month to ≤12 years of age. One hundred of these patients were 1 to ≤12 years of age and were treated with famciclovir oral granules (doses ranged from 150 mg to 500 mg) either twice (47 patients with herpes simplex virus infections) or three times (53 patients with chickenpox) daily for 7 days. The remaining 69 patients (18 patients 1 to ≤12 months, 51 patients 1 to ≤12 years) participated in single-dose pharmacokinetic and safety studies using famciclovir oral granules (doses ranged from 25 mg to 500 mg). The frequency, intensity, and nature of adverse events and laboratory abnormalities reported in the clinical trials were similar to those seen in adults.

The available data are insufficient to support the use of famciclovir for the treatment of chickenpox or infections due to herpes simplex virus in this patient population (see Method of administration). No efficacy studies have been conducted in paediatric patients and there are no efficacy data in adults with diseases similar to the ones evaluated in the safety and pharmacokinetics paediatric studies (i.e. chickenpox or gingivostomatitis).

Pharmacokinetics

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 and 750 mg oral dose of famciclovir, was 0.8 microgram/mL, 1.6 micrograms/mL, 3.3 micrograms/mL and 5.1 micrograms/mL respectively, and occurred at a median time of 45 minutes post-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 repeat (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.

Characteristics in special populations

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 (see Dosage and Administration).

Subjects with hepatic impairment

Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral 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 penciclovir 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).

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.

Paediatric patients

In the paediatric studies described in Pharmacodynamic properties, the famciclovir doses were based on the patient's body weight and were selected to provide systemic exposures similar to the penciclovir systemic exposure 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 studies in patients 1 to ≤ 12 years of age. Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm.

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).

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

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. The following modifications in dosage are recommended:

Creatinine (mL/min/1.73m²)	Clearance	Dosage
≥60		1500 mg single dose
40-59		750 mg single dose
20-39		500 mg single dose
<20		250 mg single dose

Renally impaired patients on haemodialysis

Since 4 h haemodialysis results in approximately 75% reduction in plasma penciclovir concentrations, famciclovir should be administered in a single dose of 250 mg 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 penciclovir may be impaired in these patients, resulting in lower penciclovir plasma concentrations and thus possibly a decrease of efficacy of famciclovir (see Pharmacokinetics).

Elderly

Dosage modification is not required unless renal function is impaired.

Paediatric patients

The efficacy and safety of famciclovir has not been investigated in paediatric patients. Famciclovir should therefore not be used in children unless the potential benefits are considered to justify the potential risks associated with treatment.

Mode of administration

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 (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.

Warnings and Precautions

Special attention should be paid to patients with impaired renal function and dosage adjustment is necessary (see Dosage and Administration and Overdosage). No special precautions are required for elderly patients with normal renal function and patients with well-compensated hepatic impairment. Famciclovir has not been studied in patients with severe uncompensated hepatic impairment (see Pharmacokinetics).

Use in Pregnancy

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

Studies in rats show that penciclovir is excreted in the breast milk of lactating females given oral FAMVIR (famciclovir). There is no information on excretion in human milk. Famciclovir should not be used in nursing mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment.

Fertility

Famciclovir has been shown to have no significant effects on sperm count, morphology, or motility in man. Clinical data do not indicate an impact of famciclovir on male fertility following long-term treatment at an oral dose of 250 mg twice daily.

Effects on Ability to Drive and Use Machines

There is no evidence that FAMVIR ONCE will affect the ability of a patient to drive or to use machines. However, 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 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.

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* ($\geq 1/10$); *common* ($\geq 1/100, < 1/10$); *uncommon* ($\geq 1/1,000, < 1/100$); *rare* ($\geq 1/10,000, < 1/1,000$); *very rare* ($< 1/10,000$), including isolated reports.

Table 1

Blood and lymphatic system disorders	
Rare:	Thrombocytopenia.
Psychiatric disorders	
Uncommon:	Confusion (predominantly in the elderly).
Rare:	Hallucinations.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness
Uncommon:	Somnolence (predominantly in the elderly).
Gastrointestinal disorders	
Common:	Nausea and vomiting
Hepatobiliary disorders	
Common:	Abnormal liver function tests.
Rare:	Cholestatic jaundice
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Angioedema (eg face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria.
Not known:	Serious skin reactions (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis).

Famciclovir has also been well tolerated in immunocompromised patients. Undesirable effects reported from clinical studies were similar to those reported in the immunocompetent population.

Interactions

Effects of other medicinal products on famciclovir

Concurrent use of probenecid may result in increased plasma concentrations of penciclovir (active metabolite of famciclovir, see Pharmacokinetics).

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 and aluminium hydroxide), or concomitantly with emtricitabine. 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.

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.

Effects of famciclovir on other medicinal products

The pharmacokinetics of digoxin were not altered by concomitant administration of single or multiple (t.i.d) 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 drugs metabolized by aldehyde oxidase could potentially occur. Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

Overdosage

Overdose experience with famciclovir is limited. In the event of an overdose 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 h haemodialysis.

Pharmaceutical Precautions

Do not store above 30°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.

Medicine Classification

Pharmacist Only Medicine

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

Carcinogenicity

In 2 year studies there were no changes seen at 200 mg/kg/d. At the maximally tolerated dose of 600 mg/kg/d in female rats there was an increased incidence of mammary adenocarcinoma, a common tumour in this strain of rats used in the studies. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

Genotoxicity

Famciclovir was not found to be genotoxic in a comprehensive battery of *in vivo* and *in vitro* tests designed to detect gene mutation, chromosomal damage and repairable damage to DNA. Penciclovir, in common with other drugs of this class, has been shown to cause chromosomal damage, but did not induce gene mutation in bacterial or mammalian cell systems, nor was there evidence of increased DNA repair *in vitro*.

Reproductive toxicity

Famciclovir is well tolerated in laboratory animals. In common with other drugs of this class, degenerative changes of the testicular epithelium were noted.

Famciclovir has been shown to have no significant effects on sperm count, morphology, or motility in man. Impaired fertility was observed in male rats given 500 mg/kg. There were no significant effects on fertility in female rats given famciclovir.

Juvenile toxicity study in rats

In juvenile rats, famciclovir was administered daily at doses of 0, 40, 125, or 400 mg/kg/day for 10 weeks beginning on post-partum Day 4. There were no treatment related deaths or clinical observations. The toxicity of famciclovir was not enhanced in juvenile rats compared to that in the adult animals.

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