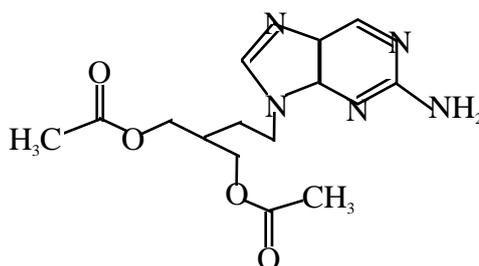


## PRODUCT INFORMATION

### FAMCICLOVIR SANDOZ<sup>®</sup> 125/250/500MG FILM-COATED TABLET

#### NAME OF THE MEDICINE

Active ingredient:	famciclovir
Chemical names:	9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine
CAS number:	104227-87-4
Molecular weight:	321.3
Molecular formula	C <sub>14</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub>
Chemical structure:	



#### DESCRIPTION

Famciclovir is a synthetic guanine derivative. It is a white to pale yellow crystalline solid.

All Famciclovir Sandoz film-coated tablets also contain hypromellose, sodium starch glycolate and magnesium stearate as excipients. Famciclovir Sandoz 125mg\* and 250mg tablets contain lactose (see "PRECAUTIONS"). Famciclovir Sandoz 500mg tablets do not contain lactose. The film coat, Opadry OY-S-28924, contains titanium dioxide (CI 77891, E171), hypromellose and macrogol.

#### PHARMACOLOGY

##### Pharmacodynamics

Pharmacotherapeutic group: Oral antiviral agent, ATC code: JO5A B09

##### Virology

Famciclovir is the oral form of the antiviral compound: penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has demonstrable *in vitro* activity against herpes simplex viruses (HSV types 1 and 2) and varicella zoster virus (VZV). The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir.

Penciclovir targets virus-infected cells where it is rapidly converted into penciclovir-triphosphate (mediated via virus-induced thymidine kinase). The triphosphate inhibits viral DNA polymerase by competition with deoxyguanosine triphosphate and is incorporated into the extending DNA chain, preventing significant chain elongation. Consequently, viral DNA synthesis and, therefore, viral replication are inhibited.

This triphosphate persists in infected cells in excess of 12 hours. The long intracellular half-life of penciclovir triphosphate ensures prolonged antiviral activity, as demonstrated in cell cultures with HSV-1 and HSV-2 and in animal studies.

Penciclovir is only readily phosphorylated in virus-infected cells. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Accordingly, uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

The most common form of resistance encountered with aciclovir among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would be expected to be cross-resistant to both penciclovir and aciclovir. However, penciclovir has been shown to be active against a clinically isolated aciclovir-resistant herpes simplex type 1 strain with an altered DNA polymerase.

The results from penciclovir and famciclovir patient studies, including studies of up to four months' treatment with famciclovir, showed that no resistance occurred as a result of treatment with either famciclovir or penciclovir. Penciclovir-resistant isolates were found at the start of treatment or in the placebo groups in 0.25% of the 1976 total isolates from HSV and VZV (5/1976), and in 0.19% of the 533 virus isolates from immunocompromised patients (1/533).

### **Pharmacokinetics**

Famciclovir is the oral prodrug of penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to the antivirally active compound penciclovir. Bioavailability of penciclovir after oral famciclovir is 77%. Mean peak plasma concentrations of penciclovir following a 125mg, 250mg, 500mg and 750mg oral dose of famciclovir were 0.8 microgram/mL, 1.6 microgram/mL, 3.3 microgram/mL and 5.1 microgram/mL respectively, and occurred at a median time of 45 minutes post-dose. There are no data on the pharmacokinetics of the 1500mg single dose.

**Table 1: Mean peak plasma concentrations ( $C_{max}$ ) of penciclovir after administration of single oral doses of famciclovir**

famciclovir single oral dose (mg)	$C_{max}$ ( $\mu\text{g/mL}$ )
125	0.8
250	1.6
500	3.3
750	5.1
1000	6.6

Plasma concentration-time curves of penciclovir are similar following single and repeat (b.i.d. and t.i.d.) dosing and there is no accumulation of penciclovir on repeated dosing. 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. No unchanged famciclovir has been detected in urine. Tubular secretion and glomerular filtration contribute to renal elimination of the compound. The terminal plasma half-life of penciclovir after both single and repeat dosing with

famciclovir is approximately 2.0 hours. There is no accumulation of penciclovir on repeated dosing with famciclovir.

**Effect of food:**

Penciclovir  $C_{max}$  was decreased by approximately 50 % and  $T_{max}$  was delayed by 1.5 hour when a capsule formulation of famciclovir was administered 30 minutes after food. When famciclovir tablets were administered 30 minutes after food, penciclovir  $C_{max}$  was reduced by approximately 20 % and  $T_{max}$  was delayed by 0.75 hour. The systemic availability (AUC) of penciclovir following either preparation was unaffected. The clinical consequences of these effects on plasma concentration are unknown.

**Characteristics in special populations**

**Patients with Herpes Zoster:**

Uncomplicated Herpes virus does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration of famciclovir.

**Renal impairment:**

Plasma clearance, renal clearance and plasma elimination rate constant decreased linearly with reductions in renal function. A dosage interval adjustment is recommended for patients with renal impairment (see "DOSAGE AND ADMINISTRATION").

**Hepatic impairment:**

Well-compensated chronic liver disease (chronic hepatitis [n=6], chronic ethanol abuse [n=8] or biliary cirrhosis [n=1]) has no effect on the extent of availability (AUC) of penciclovir following a single dose of 500mg famciclovir. No dose adjustment is recommended for patients with well-compensated hepatic impairment (see section "DOSAGE AND ADMINISTRATION – Hepatic impairment" and "PRECAUTIONS"). However, there was a 43% decrease in penciclovir mean maximum plasma concentration and the time to maximum plasma concentration was increased by a median of 0.75 hour in patients with hepatic impairment compared to normal volunteers. The pharmacokinetics have not been evaluated in patients with severe uncompensated hepatic impairment.

**Elderly patients:**

Based on cross-study comparisons of single dose studies, the mean penciclovir AUC was approximately 30 % higher, half-life 23 % longer and penciclovir body weight adjusted renal clearance reduced by 19% in healthy elderly male volunteers (n=18, aged 65 to 79 years) compared to younger volunteers. Some of this difference may be due to differences in renal function between the two groups. No dose adjustment based on age is recommended unless renal function is impaired (see section "DOSAGE AND ADMINISTRATION").

**HIV patients:**

Extrapolated data from a study (n=8) where famciclovir was given as a single dose resulted in a mean AUC of 24 microgram.h/mL, which is similar to that obtained in healthy subjects.

### **Race:**

A retrospective evaluation was performed to compare the pharmacokinetic parameters 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 differences in the pharmacokinetics of penciclovir between Black and Caucasian subjects.

### **Transplant patients:**

In a study of allogeneic bone marrow transplant or peripheral blood stem cell transplant or allogeneic renal transplant patients (n=21), intravenous penciclovir for one month was followed by oral use of famciclovir. The doses of penciclovir and famciclovir were adjusted according to creatinine clearance. During repeat dosing with famciclovir, the AUC of penciclovir was found to be 66 microgram.h/mL in subjects with creatinine clearance greater than 50mL/min. No safety concerns were identified despite the higher than normal AUCs reported, and additional dosage adjustment in renal transplant patients is not recommended.

## **CLINICAL TRIALS**

### **Herpes Zoster**

#### **Placebo-controlled trial:**

Famciclovir was studied in a placebo-controlled, double-blind trial of 419 otherwise healthy patients with uncomplicated herpes zoster who were treated with famciclovir 500mg t.i.d. (n=138), famciclovir 750mg t.i.d. (n=135) or placebo (n=146). Treatment was begun within 72 hours of initial lesion appearance and therapy was continued for 7 days.

**Dermatology and virology:** The times to full crusting, loss of vesicles, loss of ulcers and loss of crusts were shorter for famciclovir 500mg-treated patients than for placebo-treated patients in the overall study population. The median time to full crusting in famciclovir 500mg-treated patients was 5 days compared to 7 days in placebo-treated patients. No additional efficacy was demonstrated with the higher dose of famciclovir (750mg t.i.d.) when compared to famciclovir 500mg t.i.d. In the total population, 65.2% of patients had a positive viral culture at some time during their acute infection. Patients treated with famciclovir 500mg had a shorter median duration of viral shedding (time to last positive viral culture) than did placebo-treated patients (1 day and 2 days, respectively).

**Acute pain and postherpetic neuralgia:** There were no overall differences in the duration of acute pain (i.e. pain before rash healing) between famciclovir and placebo-treated groups. In addition, there was no difference in the incidence of postherpetic neuralgia (i.e. pain after rash healing) 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 famciclovir 500mg than in those treated with placebo (63 days and 119 days, respectively).

#### Active-control trial:

A second double-blind controlled trial in 545 otherwise healthy patients with uncomplicated herpes zoster treated within 72 hours of initial lesion appearance compared famciclovir 250mg t.i.d. (n=134), famciclovir 500mg t.i.d. (n=134), famciclovir 750mg t.i.d. (n=138) and aciclovir 800mg 5 times per day (n=139) for 7 days. In this study, patients treated with famciclovir at each dose and aciclovir had comparable times to full lesion crusting and times to loss of acute pain. There were no statistically significant differences in the time to loss of postherpetic neuralgia between famciclovir and aciclovir-treated groups.

Higher doses of famciclovir (500mg t.i.d.; 750mg t.i.d.) have not been shown to confer greater benefit. The minimum effective dose of famciclovir in the treatment of herpes zoster has not been established

#### Immunocompromised:

A double-blind, controlled clinical trial was conducted in 148 oncology and transplant patients with herpes zoster infections who received famciclovir 500mg t.i.d. (n=71) or aciclovir 800mg 5 times per day (n=77) for 10 days. Patients started study medication within 72 hours of rash onset. Overall famciclovir and aciclovir showed comparable efficacy. The median times to full crusting and complete healing were 8 and 20 days for the famciclovir group and 9 and 21 days for the aciclovir group. The median times to loss of all pain were 14 and 17 days for the famciclovir and aciclovir groups, respectively. Withdrawal due to dissemination of zoster and continued new lesion formation beyond 10 days of onset was reported in 7% of the famciclovir group and 9% of the aciclovir group.

### **Genital Herpes**

#### Placebo-controlled trials (episodic therapy):

**5-day treatment:** In two placebo-controlled trials, 626 otherwise healthy patients with a recurrence of genital herpes were treated with famciclovir 125mg b.i.d. (n=160), famciclovir 250mg b.i.d. (n=169), famciclovir 500mg 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 famciclovir 125mg-treated patients was 4 days compared to 5 days in placebo-treated patients. The median time to cessation of viral shedding was 1.8 vs 3.4 days in famciclovir 125mg and placebo recipients, respectively. The median time to loss of all symptoms was 3.2 days in famciclovir 125mg-treated patients vs. 3.8 days in placebo-treated patients. When used to treat acute recurrent genital herpes, no additional efficacy was demonstrated with higher doses of famciclovir (250mg b.i.d. or 500mg b.i.d.) when compared to famciclovir 125mg b.i.d. over 5 days.

#### Active-control trial (episodic therapy):

**2-day treatment:** In a randomised, double-blind, non-inferiority, multi-centre study (59 sites in Australia and 7 in Canada), famciclovir 500mg statim then 250mg bd for 2 days (short-course) was compared to the standard regimen of 125mg bd for 5 days in the treatment of adult patients with recurrent genital herpes. HIV-infected patients were eligible if CD4  $\geq$  500 cells/ $\mu$ L and/or CD4%  $\geq$  25%.

The study was designed to treat and follow each eligible patient for two complete and consecutive recurrences. A total of 1038 recurrences occurred in 616 patients that were randomised and treated. Treatment was initiated by patients within 12 hours of development of a lesion or onset of symptoms.

Patients attended for assessment within 24 hours and then 5.5 days following initiation of treatment. A daily diary was used to record treatment compliance, progression of lesions and symptoms, functional impact and side effects from the treatment.

The primary endpoint was the estimated probability of being not lesion-free at 5.5 elapsed days (132 hours) after patient self-initiation of therapy. The estimated probability was 24.4% for recurrences treated with the 2-day regimen and was 27.6 % for recurrences treated with the 5-day regimen. The upper one-sided 97.5% confidence limit of the treatment difference was 1.7 % which was within the pre-defined margin for claiming non-inferiority. Non-inferiority was maintained in five sensitivity analyses, confirming a robust result.

Over the course of treatment, there were no differences between the mean symptom and functional impact scores for either the famciclovir short-course or the standard-course treatment groups.

The study concluded that the 2-day famciclovir regimen was equivalent to the 5-day regimen in the treatment of adult patients with recurrent genital herpes.

#### Placebo-controlled trials (suppressive therapy)

In two placebo controlled suppression studies, immunocompetent patients (n=934) with at least six recurrences of genital herpes per year received 125mg t.i.d. (n=233), 250mg b.i.d. (n=236), 250mg t.i.d. (n=232) or placebo (n=233) for 52 weeks. Treatment was initiated during an asymptomatic period. Among those who received famciclovir 250mg b.i.d., the proportion of patients who remained free from virologically confirmed recurrence at the 12 month end point was 68% in one trial and 72% in the second trial compared with approximately 21% in the placebo groups. Median days to first clinically confirmed recurrence for the famciclovir 250mg b.i.d. treatment groups were >365 days for the famciclovir 250mg b.i.d. treatment groups compared to 67 days for the placebo treated group in one of the studies and 336 days for the famciclovir groups compared to 47 days for the placebo group in the second study.

#### Immunocompromised:

A randomised, double-blind controlled trial in 293 HIV-infected patients with a recurrence of genital herpes compared famciclovir 500mg b.i.d. (n=150) and aciclovir 400mg 5 times per day (n=143) for 7 days. Treatment was initiated within 48 hours of lesion onset. Famciclovir and aciclovir were equally effective in prevention of new lesion formation while patients were receiving treatment. Efficacy in the three main time to event parameters were also comparable. The median times to complete healing of lesions, cessation of viral shedding and loss of lesion pain were 7 days, 2 days and 3 days for both the famciclovir and aciclovir treatment groups, respectively.

A further double-blind, placebo-controlled crossover study was conducted in 48 patients with HIV to assess famciclovir (500mg b.i.d.) in the suppression of HSV recurrence for 8 weeks. Famciclovir showed statistically significant superiority over placebo in the

efficacy parameters measured. There was an approximate 10-fold reduction in the percentage of days with HSV shedding ( $p=0.0003$ ) and a 6.7-fold reduction in the proportion of patients with HSV shedding from anogenital sites ( $p=0.0065$ ) in the famciclovir treated group. There was also an 8.7-fold reduction in the proportion of patients with HSV shedding from any site. Overall in the famciclovir group, the proportion of days of asymptomatic, symptomatic, subclinical or lesional HSV shedding from any site was significantly reduced compared to placebo ( $p=0.0012$ ).

In the famciclovir treatment group there was a 2.6-fold reduction in the percentage of days with lesions ( $p=0.0101$ ), and a 3.6-fold reduction in the percentage of days with lesions/symptoms ( $p=0.0089$ ) over the placebo group.

### **Herpes Labialis (Cold Sores)**

#### **Placebo-controlled trial**

In one large placebo-controlled trial, 701 immunocompetent adults with recurrent herpes labialis were treated with famciclovir 1500mg once ( $n=227$ ), famciclovir 750mg b.i.d. ( $n=220$ ) or placebo ( $n=254$ ) for 1 day. As well, patients also had to be in good general health, aged at least 18 years, have normal renal and hepatic function, had prior pregnancy tests if they were females of reproductive age, and have experienced 3 or more episodes of cold sores in the preceding 12 months. Patients were required to have a history of prodromal symptoms preceding at least 50% of the recurrent episodes, and at least 50% of these episodes had to have progressed to the vesicular lesion stage. Women of childbearing potential had to agree to use reliable birth control measures during the study. Pregnant or breast-feeding women were excluded. Patients were excluded if they had received an investigational drug in the 4 weeks prior to the study, had been previously vaccinated against herpes, or were using a topical immunosuppressive agent on or near the face or a systemic immunosuppressive agent within 1 month of screening. Patients were also excluded if they were immunosuppressed due to underlying disease or concomitant treatment had a recent history of drug or alcohol abuse, were suffering from inflammatory skin diseases (e.g. eczema or dermatitis) that would interfere with the assessment of lesions, or were allergic or hypersensitive to products containing aciclovir, penciclovir, famciclovir or other nucleoside analogs.

Patients were instructed to take the first dose of study medication within 1 hour of symptom onset. However, some patients commenced treatment after 1 hour of onset of symptoms. Both famciclovir regimens significantly reduced time to healing of primary vesicular herpes labialis lesions (the primary efficacy variable) in the modified ITT population compared with placebo. The median time to healing in famciclovir 1500mg single-dose treated patients was 4.4 days compared to 4.0 days in famciclovir 750mg bid and 6.2 days in placebo-treated patients. This translates to treatment effects of 1.8 ( $CI_{95\%}$  0.9, 2.7) and 2.2 ( $CI_{95\%}$  1.3, 3.1) days, respectively. A single 1500mg dose of famciclovir reduced the time to resolution of pain and tenderness (median time 1.7 days versus 2.9 days) compared with placebo and was marginally more effective than famciclovir 750mg b.i.d. (median time 2.1 days).

## INDICATIONS

Famciclovir Sandoz is indicated for the treatment of herpes zoster infection in adult patients who commence therapy within 72 hours of the onset of rash. Greatest benefit occurs if the drug is started within 48 hours.

Efficacy has not been demonstrated in patients less than 50 years of age, although the occasional younger patient with severe herpes zoster may benefit from therapy with famciclovir. Herpes zoster infection is generally a milder condition in younger patients.

Famciclovir Sandoz is also indicated for the treatment of recurrent episodes of genital herpes in adults and adolescents 12 years of age and older.

Famciclovir Sandoz is also indicated for suppression of recurrent genital herpes.

Famciclovir Sandoz is also indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adult patients.

Famciclovir Sandoz is also indicated in immunocompromised patients for:

- treatment of uncomplicated herpes zoster
- treatment of recurrent herpes simplex
- suppression of recurrent herpes simplex.

## CONTRAINDICATIONS

Famciclovir Sandoz is contraindicated in patients with known hypersensitivity to famciclovir or other constituents of Famciclovir Sandoz.

It is also contraindicated in those patients who have shown hypersensitivity to penciclovir, the active metabolite of famciclovir.

## PRECAUTIONS

Famciclovir Sandoz 125mg\* and 250mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, a severe lactase deficiency or glucose-galactose malabsorption should not take Famciclovir Sandoz tablets.

Efficacy has not been studied in ophthalmic zoster, chicken pox or zoster encephalomyelitis patients.

Special attention should be paid to patients with impaired renal function and dosage adjustment may be necessary. Appropriate dosage adjustments for renally impaired patients are provided (see "DOSAGE AND ADMINISTRATION"). No special precautions are required for elderly patients with normal renal function and patients with mild or moderate hepatic impairment. Famciclovir has not been studied in patients with severe hepatic impairment. 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 "PHARMACOLOGY").

Genital herpes is a sexually transmitted disease. The risk of transmission is increased during acute episodes. Patients should be advised to use condoms between episodes to reduce the risk of transmission and to avoid sexual intercourse when symptoms are present, even if treatment with an antiviral has been initiated. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. Therefore, in addition to therapy with Famciclovir Sandoz, it is recommended that patients use “safer sex” practices.

#### **Effects on ability to drive and use machines**

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

#### **Carcinogenesis, mutagenesis and impairment of fertility**

Data presented below include reference to area under the plasma concentration curve (24 hour AUC) for penciclovir in humans following the lowest and highest recommended doses for famciclovir (i.e. penciclovir AUC of 4.5 microgram.h/mL at 125mg b.i.d. for acute recurrent genital herpes, and a penciclovir AUC of 27 microgram.h/mL at 500mg t.i.d. for herpes infections in immunocompromised patients). This is based on the assumption that the pharmacokinetics in immunocompetent subjects are similar to the pharmacokinetics in immunocompromised subjects, as shown in the study on HIV patients (see "Pharmacokinetics"). If the higher values of AUC obtained in the renal transplant patients were used as a basis for comparison, the multiples specified here would be decreased. Exposures in animal studies are expressed as multiples of human exposures at the highest and lowest dosing schedules based on penciclovir AUC or body surface area.

#### Carcinogenesis

The carcinogenic potential of famciclovir was evaluated in 2 year dietary studies in rats and mice. A significant increase in the incidence of mammary adenocarcinoma was seen in female rats receiving 600mg/kg/day. No increases in tumour incidences were reported for male rats treated at doses of up to 240mg/kg/day or in mice of either sex at doses of up to 600mg/kg/day. At the no effect levels of 240 and 200mg/kg/day in male and female rats, the daily exposures to penciclovir based on AUC were about 40 and 29 microgram.h/mL respectively, or approximately 1 to 8 times the human systemic exposures at 500mg t.i.d or 125mg b.i.d. Systemic exposures at the no effect dose in male and female mice were 65 and 46 microgram.h/mL respectively, or approximately 2 to 12 times the human systemic exposure (AUC).

#### Genotoxicity

Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a series of *in vitro* and *in vivo* assays. Famciclovir showed no genotoxic potential in a series of assays for gene mutations, chromosomal damage and DNA damage. Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutations/ chromosomal damage, caused chromosomal aberrations in human lymphocytes *in vitro* and was positive in a mouse micronucleus assay *in vivo* when administered IV at doses toxic to bone marrow.

### Effects on fertility

Testicular toxicity was observed in rats, mice and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of seminiferous tubules, reduction in sperm count and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of testicular toxicity was related to dose and duration of exposure and tended to reverse after the cessation of dosing. In male rats, decreased fertility was observed after 10 weeks dosing at 500mg/kg/day, or approximately 3 to 20 times the human systemic exposure (AUC). Testicular toxicity was also seen in mice and dogs following chronic administration at exposures to penciclovir ranging from 2 to 14 times the human systemic exposure (AUC). However, there were no clinically significant effects on sperm count, morphology and motility in male patients receiving 250mg famciclovir b.i.d. for 18 weeks. Famciclovir had no effect on fertility in female rats at doses of up to 1000mg/kg/day, approximately 4 to 27 times the human systemic exposure (AUC).

### **Use in Pregnancy (Category B1)**

*Category B1 - Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*

Famciclovir was tested for effects on embryo-foetal development in rats and rabbits at oral doses up to 1000mg/kg/day (approximately 4 to 27 times and 2 to 12 times the human systemic exposure to penciclovir in rats and rabbits, respectively [AUC]), and intravenous doses of 360mg/kg/day in rats (1.9 to 12 times the human dose based on body surface area [BSA] comparisons) or 120mg/kg/day in rabbits (1.2 to 7.1 times the human dose [BSA]). No adverse effects were observed on embryo-foetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80mg/kg/day, 0.4 to 2.6 times the human dose [BSA]) or rabbits (60mg/kg/day, 0.6 to 3.6 times the human dose [BSA]). Although animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir), the safety of famciclovir in human pregnancy has not been established. Famciclovir Sandoz should therefore not be used during pregnancy unless the potential benefits are considered to outweigh the potential risks associated with treatment.

### **Use in Lactation**

Famciclovir should not be used by nursing mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment. Following oral administration of famciclovir to lactating rats, penciclovir was excreted in milk at concentrations higher than those seen in plasma. There is no information on excretion in human milk.

### **Use in Children**

Safety and efficacy in children has not been established.

### **Use in the Elderly**

No special precautions are required for elderly patients with normal renal function and well-compensated hepatic impairment.

## INTERACTIONS WITH OTHER MEDICINES

### *Effects of other medicinal products on famciclovir:*

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

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

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

Evidence from preclinical studies has shown no potential for induction of cytochrome P450.

**Zidovudine:** In a phase I study, no significant drug interactions were observed after coadministration of zidovudine and famciclovir.

The conversion of the inactive metabolite 6-deoxy penciclovir to penciclovir is catalysed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme and/or inhibiting this enzyme could potentially occur. Clinical interaction studies of famciclovir with cimetidine and promethazine, *in vitro* inhibitors of aldehyde oxidase, did not show relevant effects on the formation of penciclovir. However, raloxifene, the most potent aldehyde oxidase inhibitor observed *in vitro*, could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifene is co-administered with famciclovir, the clinical efficacy should be monitored.

### *Effects of famciclovir on other medicinal products*

Although famciclovir is only a weak inhibitor of aldehyde oxidase *in vitro*, interactions with drugs metabolized by aldehyde oxidase could potentially occur. Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes or inhibition of CYP3A4.

## ADVERSE EFFECTS

Famciclovir has been well tolerated in human studies. Headache, fatigue and nausea have been reported in clinical trials. These were generally mild or moderate and occurred at a similar incidence in patients receiving placebo treatment. Confusion, predominantly in the elderly, has been reported rarely.

**Table 2: Adverse Events (related, possibly related, unassessable or unknown) reported by  $\geq 1\%$  of immunocompetent subjects during clinical trials:**

Adverse Event	Famciclovir (n=3996)	Placebo (n=880)
Headache	5.3 %	4.8 %
Nausea	4.6 %	4.5 %
Dizziness	1.5 %	1.5 %
Diarrhoea	1.5 %	1.3 %

Fatigue	1.2 %	0.9 %
Abdominal pain	1.1 %	1.3 %
Vomiting	1.1 %	0.5 %
Somnolence	0.6 %	1.1 %

**Table 3: Adverse Events (related, possibly related, unassessable or unknown) reported by  $\geq 1\%$  of immunocompetent subjects during clinical trials in *Herpes labialis*:**

Adverse Event	Famciclovir 1500mg q.d. N=227 N (%)	Famciclovir 750mg b.i.d. N=220 N (%)	Placebo N=254 N (%)
Patients with AE(s)	63 (27.8)	54 (24.5)	53 (20.9)
<b>AE preferred term</b>			
Headache	22 (9.7)	16 (7.3)	17 (6.7)
Diarrhoea	4 (1.8)	3 (1.4)	2 (0.8)
Nausea	5 (2.2)	5 (2.3)	10 (3.9)
Nasopharyngitis	6 (2.6)	3 (1.4)	2 (0.8)

**Table 4: Adverse Events (related, possibly related, unassessable or unknown) reported by  $\geq 1\%$  immunocompetent subjects during a clinical trial comparing the 2-day and 5-day recurrent genital herpes treatments<sup>a</sup>:**

Adverse Event	Famciclovir 2-day course (n=521 recurrences) N (%)	Famciclovir 5-day course (n=517 recurrences) N (%)
Recurrences with $\geq 1$ AE(s)	185 (35.5)	176 (34.0)
No. of AEs	377	336
MedDRA preferred term <sup>b,c</sup> :		
Headache	83 (15.9)	94 (18.2)
Nausea	15 (2.9)	22 (4.3)
Diarrhoea	12 (2.3)	16 (3.1)
Abdominal pain	12 (2.3)	5 (1.0)
Dizziness	10 (1.9)	10 (1.9)
Fatigue	9 (1.7)	13 (2.5)

**Where:** **2-day course:** 2-day famciclovir regimen (500mg loading dose then 250mg 12-hourly)

**5-day course:** 5-day famciclovir regimen (125mg 12-hourly)

<sup>a</sup>On or for 4 days after date of starting study medication

<sup>b</sup>The denominator is the number of recurrences in the safety recurrence population for each treatment group

<sup>c</sup>If a patient had more than 1 recurrence of a specific AE during a recurrence, the AE is counted only once for that recurrence

**Table 5: Adverse Events ( $\geq 5\%$ ) of patients receiving Famciclovir 500mg daily or placebo for >10 months**

Adverse Event	Famciclovir (n=154)	Placebo (n=63)
Headache	37.7 %	42.9 %
URTI	31.8 %	31.7 %
Infection (viral)	24.7 %	25.4 %
Injury	18.8 %	23.8 %
Sinusitis	19.5 %	15.9 %
Back pain	12.3 %	14.3 %
Pharyngitis	11.0 %	14.3 %
UTI	7.1 %	4.8 %
Dyspepsia	5.2 %	11.1 %

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

#### **Post-marketing Data**

In addition to the adverse events reported in the clinical trials, the following events have been reported rarely in post-marketing surveillance:

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

#### **Adverse Events reported by patients receiving Famciclovir**

##### **Blood and lymphatic system disorders**

Very rare : Thrombocytopenia

##### **Psychiatric disorders**

Uncommon : Confusional state (predominantly in the elderly)

Rare : Hallucinations

##### **Nervous system disorders**

Very common : Headache

Common : Dizziness

Uncommon : Somnolence (predominantly in the elderly)

Not known : Seizure

##### **Cardiac disorders**

Rare : Palpitations

##### **Gastrointestinal disorders**

Common : Vomiting, nausea, abdominal pain, diarrhoea

##### **Hepatobiliary disorders**

Common : Liver function test abnormal

Rare : Jaundice cholestatic

### **Immune system disorders**

Not known : Anaphylactic shock, anaphylactic reaction

### **Skin and subcutaneous tissue disorders**

Common : Rash, pruritus

Uncommon : Angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticarial

Very Rare : Serious skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)

Not known : Hypersensitivity vasculitis

### **Musculoskeletal disorders**

Very rare: Arthralgia, myalgia

## **DOSAGE AND ADMINISTRATION**

### **Dosage**

#### **Immunocompetent**

##### *Herpes zoster:*

The recommended dosage of Famciclovir Sandoz is 250mg three times daily for seven days. Treatment should be initiated as soon as possible after herpes zoster is diagnosed. Studies have shown Famciclovir Sandoz to be of benefit when started within 72 hours of the onset of rash. Greatest benefit occurs if Famciclovir Sandoz is started within 48 hours.

##### *Recurrent genital herpes infections (HSV):*

The recommended dosage is a total dose of 1250mg famciclovir administered as either: (i) 500mg statim, then 250mg 12 hourly for 3 doses or (ii) 125mg\* twice each day for 5 days.

Initiation of treatment is recommended during the prodromal period or as soon as possible after onset of lesions.

##### *Suppression of recurrent genital herpes (HSV):*

The recommended dose for the suppression of recurrent genital herpes is 250mg twice daily. As studies conducted to date have not extended beyond 12 months, therapy should be re-evaluated after this period in order to observe possible changes in the natural history of the disease.

##### *Recurrent herpes labialis (cold sores):*

The recommended dosage is 1500mg as a single dose or 750mg twice daily at 12 hourly intervals for one day [see “CLINICAL TRIALS – herpes labialis (cold sores)”.]. Initiate therapy at the earliest sign or symptom of a cold sore (e.g. tingling, itching or burning). Treatment was initiated within 1 hour of symptom onset in the recurrent herpes labialis clinical study.

## **Immunocompromised**

### *Herpes zoster:*

The recommended dosage of Famciclovir Sandoz is 500mg three times daily for ten days. Initiation of treatment is recommended as soon as possible after rash onset. Studies have shown Famciclovir Sandoz to be of benefit when started within 72 hours of the onset of rash.

### *Recurrent HSV infections:*

For treating herpes simplex infections in immunocompromised adults, the recommended dose is 500mg twice daily for seven days.

Initiation of treatment is recommended during the prodromal period or as soon as possible after onset of lesions.

### *Suppression of recurrent genital herpes (HSV) in HIV:*

For suppression of recurrent genital herpes infections, a dose of 500mg twice a day has been shown to be efficacious in HIV patients.

## **Renal impairment**

As reduced clearance of penciclovir 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:

## **Immunocompetent:**

### *For the treatment of herpes zoster infection:*

<u>Creatinine Clearance (mL/min/1.73m<sup>2</sup>)</u>	<u>Dosage</u>
≥ 30	No dosage adjustment necessary
10 - 29	250mg / 24 hours

### *For the treatment or suppression of recurrent genital herpes infections:*

#### 5-day treatment

<u>Creatinine Clearance (mL/min/1.73m<sup>2</sup>)</u>	<u>Dosage</u>
≥ 30	No dose adjustment necessary
10 - 29	125mg* / 12 hours

### *For the treatment of recurrent herpes labialis:*

<u>Creatinine Clearance (mL/min/1.73m<sup>2</sup>)</u>	<u>Dosage</u>
≥ 60	No dose adjustment necessary
40 - 59	750 single dose
20 - 39	500 single dose
10 - 20	250 single dose
for patients on haemodialysis	250 single dose

**Immunocompromised:**

*For the treatment of herpes zoster infection:*

<u>Creatinine Clearance (mL/min/1.73m<sup>2</sup>)</u>	<u>Dosage</u>
≥ 50	No dose adjustment necessary
30 - 49	250mg / 8 hours
10 - 29	250mg / 24 hours

*For the treatment of recurrent herpes simplex infections:*

<u>Creatinine Clearance (mL/min/1.73m<sup>2</sup>)</u>	<u>Dosage</u>
≥ 50	No dose adjustment necessary
30 - 49	250mg / 12 hours
10 - 29	125mg* / 24 hours

*For suppression of genital herpes infections:*

<u>Creatinine Clearance (mL/min/1.73m<sup>2</sup>)</u>	<u>Dosage</u>
≥ 50	No dose adjustment necessary
30 - 49	250mg / 12 hours
10 - 29	125mg* / 12 hours

As these recommendations are not based on repeated dose data, patients with impaired renal function should be closely monitored for adverse effects. There are insufficient data to recommend a dosage for patients with creatinine clearance less than 10mL/min/1.73m<sup>2</sup>.

For a patient on haemodialysis, who has been prescribed famciclovir for conditions other than herpes labialis, a dosage interval of 48 hours is recommended for periods between dialysis. Since 4 hour of haemodialysis results in approximately 75% reduction in plasma concentrations of penciclovir, the full adjusted dose (for patients with severe renal impairment) of famciclovir should be administered immediately following dialysis.

**Hepatic impairment**

Dosage modification is not required for patients with well compensated hepatic impairment.

**Administration**

Famciclovir can be taken without regard to meals (see “Pharmacokinetics - Effect of food” section in PHARMACOLOGY).

**OVERDOSAGE**

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

Symptomatic and supportive therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease. The famciclovir dosage in these patients had not been appropriately reduced for the level of renal function.

Penciclovir, the active metabolite of famciclovir, is dialysable; plasma concentrations are reduced by approximately 75% following 4 hour of haemodialysis.

## **PRESENTATION AND STORAGE CONDITIONS**

Famciclovir Sandoz 125mg tablets\* - (white, round, film coated, biconvex) in blister packs of 40, debossed with “FV” on one side and 125 on the reverse side.

Famciclovir Sandoz 250mg tablets - (white, round, film coated, biconvex) in blister packs of 14\*, 20, 21, and 56, debossed with “FV” on one side and 250 on the reverse side.

Famciclovir Sandoz 500mg tablets - (white, oval, film coated, biconvex) in blister packs of 3\*, 30 and 56, debossed with “FV 500” on one side and no markings on the reverse side.

\*Not currently marketed in Australia

Store below 30°C in a dry place. Keep out of the reach of children.

## **NAME AND ADDRESS OF THE SPONSOR**

Sandoz Pty Ltd  
ABN 60 075 449 533  
54 Waterloo Road  
Macquarie Park NSW 2113  
Australia  
Tel: 1800 634 500

## **POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 09/02/2010

**DATE OF MOST RECENT AMENDMENT:** 19/09/2016