PRODUCT MONOGRAPH

[Pr] AURO-FAMCICLOVIR

(famciclovir)

125 mg, 250 mg and 500 mg film-coated tablets

ANTIVIRAL AGENT

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CANADA

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	Tablets / 125 mg, 250 mg and 500 mg	Sodium starch glycollate, anhydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 400 & titanium dioxide.

INDICATIONS AND CLINICAL USE

AURO-FAMCICLOVIR (famciclovir) tablets are indicated :

- for the treatment of acute herpes zoster (shingles)
- for the treatment or suppression of recurrent episodes of genital herpes in immunocompetent adults.
- for the treatment of recurrent episodes of mucocutaneous herpes simplex infections in HIV-infected patients.

Early treatment of acute herpes zoster (shingles) in immune-competent individuals with oral famciclovir resulted in decreased time to loss of vesicles; decreased time to loss of crusts; and decreased viral shedding.

The results of clinical studies indicate that early treatment of acute herpes zoster with oral famciclovir resulted in decreased duration of post-herpetic neuralgia. Those most likely to benefit are patients who initiate treatment within 48 hours of onset of rash or are greater than 50 years of age or those patients with severe pain at the time of treatment initiation.

In clinical studies of immunocompetent patients with recurrent genital herpes (typically $\geq$ 6 episodes in a 12 month period) famciclovir suppressed lesional episodes, slowed the rate to first recurrence and patients were more likely to remain free from recurrences for a 12-month period.

Suppressive therapy in patients with fewer than 6 episodes of genital herpes in a 12 month period was not evaluated in these clinical studies.

Initiation of famciclovir treatment of recurrent genital herpes during the prodrome or as soon as possible after the onset of lesions resulted in decreased duration of viral shedding, decreased time to lesion healing and decreased time to resolution of symptoms (including pain, tenderness, itching and burning).

CONTRAINDICATIONS

Patients who have known hypersensitivity to AURO-FAMCICLOVIR (famciclovir) or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of this product monograph.

WARNINGS AND PRECAUTIONS

General:

The efficacy of famciclovir has not been established for first episode genital herpes infections, disseminated zoster, or in immunocompromised patients with herpes zoster (see Actions and Clinical Pharmacology). Dosage adjustment is required when administering famciclovir to patients with moderate or severe renal dysfunction (see Dosage and Administration). No special precautions are required for patients with mild or moderate hepatic impairment. Famciclovir has not been studied in patients with severe hepatic impairment (see Action and Clinical pharmacology). 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 Action and Clinical Pharmacology).

Genital herpes is a sexually transmitted disease with an increased risk of transmission during acute episodes. There are no data evaluating whether famciclovir will prevent transmission of infection to others. Patients should be advised to avoid intercourse when lesions and/or symptoms are present (even if treatment with an anti-viral has been initiated) in order to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding.

AURO-FAMCICLOVIR 125 mg, 250 mg and 500 mg tablets contain lactose (26.8 mg, 53.6 mg and 107.2 mg, respectively). Patients with rare heredity problems of galactose intolerance, a severe case of lactase deficiency or glucose-galactose malabsorption should not take AURO-FAMCICLOVIR 125mg, 250 mg and 500 mg tablets.

Pregnancy:

Although animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir), there are insufficient data on the use of famciclovir in pregnant women. Because animal reproductive studies are not always predictive of human response, famciclovir should, therefore, not be used in pregnancy unless the potential benefits are considered to outweigh the potential risks associated with treatment.

Breast-feeding:
Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk. It is not known whether it (penciclovir) is excreted in human milk, thus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Race
The impact of race on the safety and efficacy of famciclovir has not been established.

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 safety between younger and older patients (see Adverse Events).

Impairment of Fertility
As with other drugs of this class, testicular toxicity has been observed in animals receiving both famciclovir and penciclovir. 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
Famciclovir can cause dizziness, drowsiness or confusion in very rare cases. Patients who experience any of these symptoms while taking famciclovir should take special care when driving or using machines (see Adverse events - Post-marketing Experience).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

Immunocompetent Patients
The most frequent adverse reactions reported during herpes zoster clinical trials with oral famciclovir three times daily were as shown in the following table.

Patients (%) reporting A/Es related* to study medication by preferred term in famciclovir Zoster trials within 30 days of the last dose.

	Famciclovir	Placebo
Patients receiving study medication	816	146
Event:	%	%
Body as a Whole		
Headache	7.1	6.8
Fatigue	1.6	0.7
Fever	1.1	0.0
Rigors	0.6	1.4
Herpes Zoster Symptoms	0.5	1.4
Central Nervous System		
Dizziness	1.5	0.7
Somnolence	1.2	2.7
Gastrointestinal		
Nausea	4.3	8.2
Diarrhea	1.8	2.1
Abdominal Pain	1.5	0.0
Constipation	1.0	0.0
Vomiting	1.2	0.7
Anorexia	0.5	1.4
Dermatologic		
Pruritis	1.2	0.7
Sweating increased	1.0	0.0
Hepatic		
ALT (SGPT) Increased	0.6	1.4
Gamma GT Increased	0.6	1.4
Hepatic Enzymes Increased	0.2	1.4
Special Senses		
Tinnitus	0.0	1.4

* Includes events assessed by the investigator as related, probably related, possibly related and AEs where the relationship was unassessable or missing.

The most frequent adverse reactions reported within 30 days of the last dose, during genital herpes clinical trials with oral famciclovir were as shown in the following table.

Patients (%) reporting A/Es related* to study medication by preferred term in Famciclovir Genital Herpes trials

	Famciclovir	Placebo
Patients receiving study medication	1500	255
Event:	%	%
Body as a Whole		
Headache	5.5	3.9
Fatigue	1.5	1.6
Central Nervous System		
Dizziness	2.3	3.1
Gastrointestinal		
Nausea	4.9	3.9
Diarrhea	1.8	1.6
Dyspepsia	1.3	1.2
Abdominal Pain	0.9	1.6
Autonomic Nervous System		

Mouth Dry	0.3	1.2

* Includes events assessed by the investigator as related, probably related, possibly related or where relationship was unassessable or not given.

The most frequent adverse events (incidence of >1%) are listed in the following table for patients receiving double-blind famciclovir or placebo for at least 10 months in the two 12-month-long trials.

Patients (%) reporting A/Es related* to study medication by preferred term in Famciclovir Genital Herpes Suppression trials

	Famciclovir	Placebo
Patients receiving study medication	458	63
Event:	%	%
Body as a whole		
Headache	8.7	9.5
Central Nervous System		
Dizziness	1.5	0
Gastrointestinal		
Abdominal Pain	2.4	4.8
Dyspepsia	2.0	3.2
Nausea	1.5	3.2
Diarrhea	1.3	0
Flatulence	1.1	0
Enzyme Abnormality†	2.2	3.2
Bilirubinemia	1.3	1.6
Leukopenia	1.3	0

* Includes events assessed by the investigator as related, probably related, possibly related and AEs where the relationship was unassessable or missing.

† Reports of elevated lipase.

HIV-Infected Patients

In a controlled study of HIV-infected patients, the overall percentages of patients reporting adverse events were comparable for famciclovir and acyclovir. The most frequently reported events (≥2% in any group) are listed below.

Adverse events* reported by preferred term in HIV-infected patients

	Famciclovir	Acyclovir
Patients receiving study medication	150	143
Event:	%	%
Headache	13.3	9.1
Nausea	8.7	8.4
Diarrhea	4.7	4.9
Vomiting	3.3	2.1
Fatigue	2.0	0.7
Creatine phosphokinase increased	2.0	0.7
Abdominal Pain	1.3	3.5

* Includes adverse events considered by the investigators to be related, possibly related or of unknown relationship to study medication.

Post-Market Adverse Drug Reactions

Because they are reported spontaneously from a population of unknown size, estimates of frequency of post-marketing adverse events cannot be made. The following events have been chosen for inclusion due to their seriousness, frequency of reporting, potential causal connection to famciclovir, or a combination of these factors: headache, abdominal pain, diarrhea, nausea and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly), rash, urticaria, pruritus, serious skin reactions (e.g. erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis), angioedema (e.g. face edema, eyelid edema, periorbital edema, pharyngeal edema), vomiting, dizziness, somnolence (predominantly in the elderly), hallucinations, palpitations, jaundice and abnormal liver function tests, seizure, anaphylactic shock and anaphylactic reaction.

Abnormal Hematological and Clinical Chemistry Findings: In post-market experience, thrombocytopenia has been reported.

DRUG INTERACTIONS

Effects of other medicinal products on famciclovir

No clinically significant alterations in penciclovir (active metabolite of famciclovir) pharmacokinetics were observed following single dose administration of 500 mg famciclovir after pretreatment with multiple doses of cimetidine, allopurinol, theophylline, zidovudine, or promethazine or when given shortly after an antacid (magnesium and aluminium hydroxide), or concomitantly with emtricitabine. Furthermore, 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 of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir (see Action and Clinical Pharmacology). Therefore, patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid on consecutive days should be monitored for toxicity and a dose reduction of famciclovir may be considered.

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. 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 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.

DOSAGE AND ADMINISTRATION

Recommended dose

Herpes zoster infections:

The recommended dose is 500 mg 3 times per day for 7 days. Therapy should be initiated within 72 hours of the onset of the rash.

Herpes simplex infections:

Immunocompetent Patients

Recurrent genital herpes episodes: The recommended dosage is 125 mg twice a day for 5 days. Initiation of treatment is recommended during the prodromal period or as soon as possible at the first sign or symptom of a recurrent episode (e.g. tingling, itching, burning, pain, or lesion).

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

HIV-Infected Patients

For recurrent episodes of mucocutaneous herpes simplex infection, the recommended dosage is 500 mg twice a day for 7 days. Treatment should be initiated at the first sign or symptom of a recurrent episode (e.g. tingling, itching, burning, pain, or lesion).

AURO-FAMCICLOVIR (famciclovir) tablets should be swallowed whole and may be taken with or without food.

Dosage Adjustment

Dosage in renally impaired patients:

In patients with moderately or severely reduced renal function, dosage reduction is recommended:

Indication	Creatinine clearance ($mL/min/1.73m^2$)	Dosage
Herpes Zoster	>60	500 mg every 8 hours
	40-59	500 mg every 12 hours
	20-39	500 mg every 24 hours
	<20	250 mg every 24 hours
	hemodialysis patients	250 mg following each dialysis during 7 days
Recurrent Genital Herpes	>20	125 mg every 12 hours

Indication	Creatinine clearance ($mL/min/1.73m^2$)	Dosage
	<20	125 mg every 24 hours
	hemodialysis patients	125 mg following each dialysis during 5 days
Suppression of Recurrent Genital Herpes	>40	250 mg every 12 hours
	20-39	125 mg every 12 hours
	<20	125 mg every 24 hours
	hemodialysis patients	125 mg following each dialysis
Recurrent episodes of mucocutaneous herpes simplex infections in HIV-infected patients	>40	500 mg every 12 hours
	20-39	500 mg every 24 hours
	<20	250 mg every 24 hours
	hemodialysis patients	250 mg following each dialysis during 7 days

Dosage in hepatically impaired patients:
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see ACTION and CLINICAL PHARMACOLOGY).

Missed Dose
If a dose of AURO-FAMCICLOVIR is missed, it should be taken as soon as the patient remembers.
The next dose should be taken at the normal time.
The patient should carry on as normal until they have finished all the tablets.
Do not double-dose.

OVERDOSAGE

For management of suspected overdose, contact the regional poison control centre immediately.

No acute overdosage has been reported. Appropriate symptomatic and supportive therapy should be given. Penciclovir, the active metabolite of famciclovir, is dialyzable; plasma concentrations are reduced by approximately 75% following 4 h hemodialysis.

In patients with underlying renal disease who have received inappropriately high doses of famciclovir for their level of renal function, acute renal failure has been reported frequently.

ACTION AND CLINICAL PHARMACOLOGY

Famciclovir is the orally administered pro-drug of the antiviral agent penciclovir. Famciclovir itself has no antiviral activity until it is biotransformed to penciclovir. Studies in volunteers have shown that famciclovir is well absorbed and produces plasma penciclovir concentrations superior to those obtained following oral administration of penciclovir alone.
The mean bioavailability of penciclovir after administration of oral famciclovir is 77%. The mean peak plasma concentration of penciclovir, following a 500 mg oral dose of famciclovir was 3.3 mcg/mL and occurred at a mean time of 0.89 hours post-dose. Plasma concentration

time curves of penciclovir are similar following single and repeat dosing. The terminal plasma elimination half-life of penciclovir after both single and repeat oral dosing with famciclovir is 2.3 hours. The elimination of famciclovir is by metabolism, principally to penciclovir and its 6-deoxy precursor, which are subsequently excreted in urine (See Pharmacokinetics).

Mechanism of Action

Penciclovir is a substituted guanine analogue with potent and selective antiviral activity against varicella zoster virus and other human herpes viruses (see Virology). Penciclovir is in the same class of antiviral drugs as acyclovir, and both are phosphorylated by viral thymidine kinase and then by cellular kinases to the active triphosphate form in virus-infected cells. Penciclovir triphosphate inhibits viral DNA polymerase competitively 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. Inhibition of the virus reduces the period of viral shedding, limits the degree of spread and level of pathology, and thereby facilitates healing.

Penciclovir is not readily phosphorylated in uninfected cells and does not inhibit cellular DNA synthesis even at concentrations > 20 times those achieved in clinical usage.

Pharmacokinetics

Absorption

Following oral administration, famciclovir is rapidly, extensively and consistently absorbed and converted to the antivirally active compound, penciclovir. The mean (range) bioavailability of penciclovir after oral famciclovir is 77% (69.5 - 84.5%). The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

In a healthy male volunteer study using a single oral dose of famciclovir, the pharmacokinetics of penciclovir were linear over the famciclovir dose range 125 to 750 mg. The mean (range) peak plasma concentration of penciclovir, calculated from dose normalised estimates across all single dose healthy male volunteer studies, following a single 500 mg dose of famciclovir was 3.3 ug/ml (range 1.3-6.3 ug/ml) and occurred at a mean time of 0.89 hours post-dose (range 0.5-5.0 hours). The mean terminal half-life of penciclovir was 2.3 hours (range 0.99-5.26 hours)

Pharmacokinetic parameter estimates of penciclovir following oral administration of a single dose of famciclovir to patients with uncomplicated herpes zoster were essentially identical to values reported in healthy volunteers matched for age. Repeated oral dosing of famciclovir every 8 hours for up to 7 days in patients with herpes zoster infections had no significant effect on the pharmacokinetics of penciclovir compared to that described after single doses of famciclovir. The terminal plasma half-life of penciclovir in patients with herpes zoster was 2.8 h and 2.7 h, respectively, after single and repeated doses of famciclovir.

Distribution

Plasma protein binding of penciclovir and its 6-deoxy precursor is low (<20%) and penciclovir distributes freely between plasma and blood cells.

Metabolism

Following oral administration little or no famciclovir is detected in plasma or urine since famciclovir is rapidly converted via deacetylation and oxidation to penciclovir. An *in vitro* study using human liver microsomes demonstrated that cytochrome P450 does not play an important role in famciclovir metabolism. The conversion of B-deoxy penciclovir is catalyzed by aldehyde oxidase.

Excretion

Little or no famciclovir is detected in plasma or urine since famciclovir undergoes extensive first-pass metabolism to penciclovir. The major metabolites identified in plasma and urine are penciclovir (67 ± 4% of radioactivity in plasma at 1.5 h following a 500 mg oral dose of [^{14}C]famciclovir and 82 ± 2.2% of radioactivity in 0-24 h urine) and, to a lesser extent, its 6-deoxy precursor, which has no antiviral activity (11 ± 4% in plasma and 7 ± 0.5% in urine at the corresponding time points). Other minor, virally inactive metabolites identified in human urine are monoacetylated penciclovir and 6-deoxy monoacetylated penciclovir (each < 0.5% of the dose).

Renal clearance values for penciclovir exceed creatinine clearance indicating that net active tubular secretion and glomerular filtration contribute to renal elimination.

Renal impaired patients:

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).

Hepatically impaired patients:

Following single oral administration of famciclovir to patients with mild or moderate hepatic impairment, there was no change in the extent of availability of penciclovir compared with healthy volunteers. There was, however, a decrease in the rate of availability of penciclovir in the hepatically impaired subjects. Mean maximum plasma concentrations of penciclovir were decreased by 43% and the time to maximum plasma concentrations increased by 0.75 hours.
However, no dosage adjustment for patients with mild or moderate hepatic impairment is recommended. The pharmacokinetics of penciclovir following oral famciclovir in patients with severe hepatic impairment has not been studied. 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 Warnings and Precautions).

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.

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 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.

STORAGE AND STABILITY
Store at room temperature (15°C to 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form	Film-Coated Tablets		
Strength	125 mg	250 mg	500 mg
Description	White to pale yellow colored, round film-coated, biconvex tablets with beveled edges, debossed with 'X' on one side and '48' on the other side.	White to pale yellow colored, round film-coated, biconvex tablets with beveled edges, debossed with 'X' on one side and '49' on the other side.	White to pale yellow colored, oval film-coated, biconvex tablets, debossed with 'X' on one side and '34' on the other side.
Composition	125 mg famciclovir	250 mg famciclovir	500 mg famciclovir
	Non-Medicinal Ingredients: Sodium starch glycollate, anhydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 400 & titanium dioxide.		
Packaging	Blister packs of 10's Bottle packs of 30's, 100's & 500's.	Blister packs of 30's Bottle packs of 30's, 100's & 500's.	Blister packs of 21's Bottle packs of 30's, 100's & 500's.

PART II: SCIENTIFIC INFORMATION

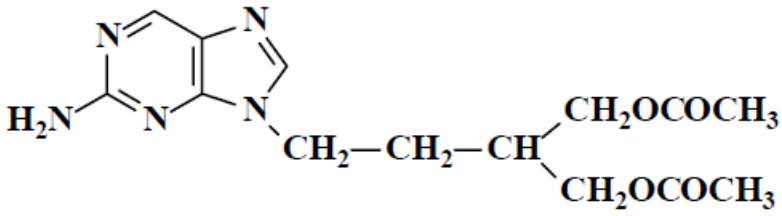
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Famciclovir

Chemical Name: 2-[2-(2-Amino-9H-Purin-9-YL) Ethyl]-1,3-propanediol diacetate

Molecular structure:



Molecular Formula: C14H19N5O4

Molecular Weight: 321.34 g/mol

Description: A white to pale yellow powder

Solubility: Freely soluble in methanol and acetone, sparingly soluble in ethanol and in isopropyl alcohol.

CLINICAL TRIALS

A double blind, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of AURO-FAMCICLOVIR 500 mg Tablets (Test) of Aurobindo Pharma Limited, India manufactured for Auro Pharma Inc., and Famvir® (Famciclovir) 500 mg Tablets (Reference) of Novartis Pharmaceuticals Canada Inc. was conducted in 28 healthy, adult, male subjects under fasting conditions.

Summary Table of the Comparative Bio-availability Data

Analyte: Penciclovir (1 X 500 mg famciclovir) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference †**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$AUC_{0\rightarrow t}$ (hr.ng/mL)	11390.7 11625.2 (20.9)	11091.0 11270.8 (18.9)	102.7	99.3-106.3
$AUC_{0\rightarrow \infty}$ (hr.ng/mL)	11550.1 11792.7 (21.2)	11253.8 11436.4 (18.9)	102.6	99.1-106.3
C_{max} (ng/mL)	4242.5 4426.3 (31.6)	4016.8 4177.9 (30.5)	105.6	98.4-113.3
T_{max} [§] (h)	0.8 (0.5-1.8)	0.8 (0.5-3.0)		
$T_{½}$ [$] (h)	2.5 (19.6)	2.7 (20.1)		

***** AURO-FAMCICLOVIR (Famciclovir) 500 mg Tablets by Auro Pharma Inc.
† FAMVIR® (Famciclovir) 500 mg Tablets is manufactured by Novartis Pharmaceuticals Canada Inc. and was purchased in Canada.
§ Expressed as median (range) only.
$ Expressed as arithmetic mean (CV%) only.

Herpes Zoster and Post-Herpetic Neuralgia:
In patients with uncomplicated herpes zoster, famciclovir has been shown to significantly reduce the duration of virus shedding and to relieve the signs and symptoms of the disease.

A 7-day double-blind placebo-controlled trial was conducted in 419 patients with uncomplicated herpes zoster treated within 72 hours of initial lesion appearance. According to the randomization scheme, 138 patients were given famciclovir 500 mg t.i.d., 135 patients famciclovir 750 mg t.i.d. and 146 patients given placebo. No additional efficacy was demonstrated with the higher dose of famciclovir (750 mg t.i.d.), when compared to famciclovir 500 mg 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 500 mg 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; p=0.0001).

The times to loss of vesicles (p=0.01), loss of ulcers (p=0.01), and loss of crusts (p=0.05), were shorter for famciclovir 500 mg-treated patients than for placebo-treated patients in the overall study population.

The follow-up phase of this trial was designed to monitor the progression of post-herpetic neuralgia (PHN) after treatment with either famciclovir or placebo for seven days during acute infection. There was no difference in the incidence of postherpetic neuralgia between the treatment groups at the time of rash resolution. 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 500 mg than in those treated with placebo (63 days and 119 days, respectively; p=0.02).

A second 7-day double-blind controlled trial involved 545 patients with uncomplicated herpes zoster treated within 72 hours of initial lesion appearance. According to the randomization scheme, 134 patients received 250 mg t.i.d. of famciclovir, 134 patients received 500 mg t.i.d. of famciclovir, 138 patients received 750 mg t.i.d. of famciclovir and 139 patients received 800 mg of acyclovir given 5 times a day. Famciclovir was found to be as effective as acyclovir at all dose levels for cutaneous lesion healing parameters, time to loss of pain and viral shedding.

A double-blind controlled trial in 497 adult patients with ophthalmic zoster treated within 72 hours of initial lesion appearance compared famciclovir 500 mg three times daily for 7 days (n=251) to acyclovir 5 times per day for 7 days (n=246). Famciclovir was comparable to acyclovir in preventing ocular complications due to herpes zoster infection.

Herpes Simplex Infections:

Treatment of Recurrent Genital Herpes Episodes:

Famciclovir was studied in two placebo-controlled trials of 626 otherwise healthy patients with a recurrence of genital herpes who were treated with famciclovir 125 mg b.i.d. (n=160), famciclovir 250 mg b.i.d. (n=169), famciclovir 500 mg b.i.d. (n=154) or placebo (n=143) for 5 days. In the two studies combined, the median time to healing in famciclovir 125 mg-treated patients was 4 days compared to 5 days in placebo treated patients (p= 0.0001) and the median time to cessation of viral shedding was 1.8 vs. 3.4 days in famciclovir 125 mg and placebo recipients, respectively (p= 0.0001). The median time to loss of all symptoms was 3.2 days in famciclovir 125 mg-treated patients vs. 3.8 days in placebo treated patients (p= 0.0001). Pre-treatment, self-obtained viral cultures were positive in 31%, 25%, 30% and 24% for the famciclovir 125 mg, 250 mg, 500 mg and placebo recipients respectively in the patient-initiated study. Of those patients whose pre-treatment culture was negative, significantly fewer patients self-initiating famciclovir treatment went on to become viral culture positive compared to placebo. Patients initiating treatment early (during the prodrome) were half as likely to commence viral shedding compared to placebo patients. Additionally, in the clinic-initiated study, famciclovir reduced the number of patients who developed new lesions.

Famciclovir was also studied in three acyclovir-controlled, double-blind trials in 951 otherwise healthy patients with first episode genital herpes.

Famciclovir for 5 or 10 days provided comparable efficacy to acyclovir although the studies were not powered to show statistical equivalence.

Suppression of Recurrent Genital Herpes Episodes:
A total of 934 otherwise healthy adults with frequently recurring genital herpes, were enrolled in two 12-month, placebo-controlled studies. Patients either had at least six recurrences 12 months prior to study entry or a history of at least six recurrences per year while not receiving other suppressive therapies. Sixty-two percent of patients had experienced at least 12 genital herpes recurrences in the previous 24 months. Treatment arms consisted of famciclovir 125 mg t.i.d. (n=233), 250 mg b.i.d. (n=236), 250 mg t.i.d. (n=232) and placebo (n=233). Compared to placebo, famciclovir 250 mg b.i.d. significantly delayed the time to developing the first clinically confirmed recurrence by 10 months in one study (medians: >365 days for famciclovir vs. 67 days for placebo; p=0.0001) and 9.5 months in another study (medians: 336 days for famciclovir vs. 47 days for placebo; p=0.0001). Approximately 80% of famciclovir-treated patients in both studies remained free from HSV recurrences documented by viral culture for up to 6 months compared with approximately 25% of patients treated with placebo ($p<0.001$). Treatment effects were sustained for 12 months.

Treatment of Recurrent Mucocutaneous Herpes Simplex Infection in HIV-Infected Patients:
A randomized, double-blind, multicenter study compared famciclovir 500 mg twice daily for 7 days (n=150) with oral acyclovir 400 mg 5 times daily for 7 days (n=143) in HIV-infected patients with mucocutaneous HSV infection. Approximately 40% of patients had a CD4 count below 200 cells/mm^3; 54% of patients had anogenital lesions and 35% had orolabial lesions. Twice-daily oral famciclovir was comparable to five-times daily oral acyclovir in preventing new lesion formation, in time to complete healing (median of 7 days in both groups), time to loss of all lesion-associated symptoms (median of 4 days in both groups) and time to cessation of viral shedding (median of 2 days in both groups). Efficacy was maintained regardless of the degree of immunosuppression or location of lesions.

VIROLOGY

Penciclovir is a highly potent and selective antiviral agent. Inhibitory activity in animals has been shown against herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) infections. It also has inhibitory activity in cell cultures against HSV-1, HSV-2 and varicella zoster virus (VZV).

Penciclovir enters cells rapidly. In HSV-1, HSV-2 and VZV infected cells, viral thymidine kinase rapidly converts penciclovir to a monophosphate, which host cell enzymes convert to penciclovir triphosphate. The triphosphate inhibits viral DNA polymerase competitively 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.

Following the removal of the acyclonucleoside from MRC-5 cell culture medium, the stability of intracellular penciclovir triphosphate was much greater than that of acyclovir triphosphate. The intracellular half-life of penciclovir triphosphate was: 10 hours for HSV-1; 20 hours for HSV-2; 7 hours for VZV-infected cells grown in culture. The corresponding values for

acyclovir triphosphate were 0.7 hours for HSV-1 and 1.0 hours for HSV-2. No value was derived for VZV-infected cells since acyclovir triphosphate concentrations were undetectable. In other human cells, penciclovir triphosphate was invariably a more stable entity than acyclovir triphosphate. The long intracellular half-life of penciclovir triphosphate ensures prolonged antiviral activity as demonstrated in cell cultures with HSV-1, HSV-2 and VZV, and in animal studies with HSV-1 and HSV-2.

In cell culture, penciclovir has the highest antiviral activity against the following herpes viruses (listed in decreasing order of potency and detailed below): HSV-1, HSV-2, VZV, Epstein-Barr virus (EBV) and cytomegalovirus (CMV). The degree of inhibition is dependent upon a number of variables, including the assay method, the host cell, virus type and multiplicity of infection.

Comparative in vitro data for the antiviral potency of penciclovir and acyclovir are shown in the following table.

Assay Method	Virus*	Cell Type	Penciclovir	Acyclovir
			IC_{50} (mcg/mL)	
Plaque reduction	VZV	MRC-5	2.0 - 10.9	2.8 - 8.5
	VZV	Hs68	0.4 - 1.8	0.4 - 1.6
	HSV-1	WISH	0.04 - 0.5	0.2 - 1.2
	HSV-1	MRC-5	0.2 - 0.6	0.1 - 0.6
	HSV-2	WISH	0.1 - 0.8	0.4 - 1.8
	HSV-2	MRC-5	0.9 - 2.1	0.2 - 1.1
DNA synthesis inhibition	VZV (Ellen) HSV-1 (SC-16)	MRC-5 MRC-5	0.1 0.04	0.2 0.15
	HSV-2 (MS)	MRC-5	0.05	0.04
			IC99 (mcg/mL)	
Virus yield reduction	HSV-1 HSV-2	MRC-5 MRC-5	0.4 - 0.6 0.6 - 0.7	0.8 - 2.5 0.2 - 0.9

* Data were obtained using clinical isolates, except for DNA synthesis assays in which the specified laboratory strains were used.

In an assay measuring inhibition of EBV DNA synthesis in P_3HR1 cells, the IC_{50} for penciclovir was 1.5 mcg/mL. In plaque-reduction assays in MRC-5 cells against CMV, the IC_{50} for penciclovir was 52 mcg/mL.

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 in the DNA polymerase gene. Most aciclovir-resistant HSV and VZV clinical isolates are also resistant to penciclovir, but cross-resistance is not universal. In plaque-reduction assays against laboratory-produced mutants with altered DNA polymerase, Vero (human lung fibroblast) cells infected with HSV-1 were inhibited by penciclovir to the same extent as the wild type (IC_{50} was 1.5 mcg/mL for the mutant and 1.0 mcg/mL for the wild type). In contrast, resistance to acyclovir was demonstrated as the IC_{50} of acyclovir was 47

fold higher (20 mcg/mL) for the mutant compared to (0.43 mcg/mL) the wild type. In a clinically isolated strain of acyclovir-resistant HSV-1 tested in Hs68 (human foreskin fibroblast) cells, resistance to acyclovir was demonstrated, whereas the IC_{50} values for penciclovir in the wild type and mutant strains were almost identical (1.3 mcg/mL vs. 1.0 mcg/mL, respectively).

Penciclovir sensitivity testing was performed on 84 HSV-2 isolates from 50 famciclovir-treated patients (59 isolates) and 21 placebo-treated patients (25 isolates) who participated in a 4-month genital herpes suppression trial. All HSV-2 isolates on-treatment and after-treatment were sensitive (mean IC_{50} 1.7 mcg/mL for famciclovir recipients and 1.5 mcg/mL for placebo recipients).

Short-term treatment of HSV-1-infected MRC-5 cells with penciclovir (3 mM) for 2 hours reduced viral DNA by 76% compared with only 17% following similar treatment with acyclovir (3 mM). Treatment of HSV-2-infected cells with penciclovir (3 mM) for 1.5 hours reduced viral DNA by 52% vs. 20% with acyclovir (3 mM).

Studies of VZV-infected MRC-5 cells exposed to pulse treatment for 8 hours on days 0, 1, 2 and 3 produced an IC50 of 5.0 mcg/mL for penciclovir and 24 mcg/mL for acyclovir. The activity of penciclovir seen after short or pulse treatment is consistent with the stability of intracellular penciclovir triphosphate.

The presence of penciclovir at 10 or 100 mcg/mL did not decrease the activity of zidovudine against human immunodeficiency virus in M8166 cells.

As there is no appropriate animal model that mimics VZV infection in humans, the antiviral activity of penciclovir has not been evaluated in animals infected with VZV. However, penciclovir has been shown to have inhibitory activity against HSV-1 and HSV-2 infections in mice and guinea pigs. The level of antiviral activity depends on a number of factors including the route of infection, route of administration of penciclovir and time between virus infection and treatment with penciclovir.

The clinical significance of inhibitory activity of penciclovir against HSV-1 and HSV-2 in *in vitro* animal models is unknown at this time.

TOXICOLOGY

Both famciclovir and its active metabolite penciclovir have undergone a comprehensive toxicological evaluation; principal findings from the key studies are summarised below. Exposure to drug-related material in animals compared with that in humans given 500 mg famciclovir t.i.d. is expressed, where appropriate, as multiples of the amount of penciclovir and 6-deoxy-penciclovir systemically available.

Acute Toxicity:
Famciclovir has a low order of acute toxicity, with median lethal doses in excess of 5000 mg/kg orally and around 500 mg/kg or higher intravenously; penciclovir intravenously was slightly better tolerated. With both compounds the majority of adverse effects were indicative of central nervous system disturbances, undoubtedly reflecting the high doses administered since no such effects were detected at the lower doses used in the studies to assess general pharmacological actions.

Subacute Toxicity Studies:
In studies of 1 month's duration, famciclovir was administered at oral doses of up to 4000 mg/kg/day in the rat and up to 500 mg/kg/day in the dog.

In rats, there were early degenerative changes in the seminiferous epithelium at 4000 and 400 mg/kg/day (35- and 9- fold human exposure to penciclovir respectively), but the effects at the lower dose were minimal. Microscopically there was also a slight reduction in the number of lymphocytes in the thymic cortex confined to the high dose of 4000 mg/kg/day; there were no effects at 400 mg/kg/day.

In dogs, doses of up to 500 mg/kg/day (3-fold human exposure to penciclovir), which was the maximum practicable dose, were tolerated with no indications of definitive target organ toxicity.

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 clinical observations or adverse developmental effects. The toxicity of famciclovir was not enhanced in juvenile rats compared to that in the adult animals.

Chronic Toxicity Studies:
In 6 and 12 month studies with famciclovir, oral doses of up to 600 mg/kg/day in rats and up to 500 mg/kg/day in dogs were without significant effect on any tissue except the testes (See Reproduction). At these doses, a high systemic exposure to both penciclovir (4- and 3-fold human values in rat and dog respectively) and 6-deoxy penciclovir (at least 40- and 150-fold human values in rat and dog respectively) were achieved.

Carcinogenicity Studies:
Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. There was an increase in the incidence of mammary adenocarcinoma in female rats receiving the maximum tolerated dose of 600 mg/kg/day (4- and 40-fold human exposure to penciclovir and 6-deoxy penciclovir respectively), but not in the number of high dose females with mammary tumours of any type (benign or malignant). No effects were seen in females receiving 200 mg/kg/day (2- and 8-fold human exposure to penciclovir and 6-deoxy penciclovir respectively) or in males treated at doses of up to 240 mg/kg/day, the maximum tolerated dose. There was also no effect on the incidence or type of tumours in mice given the maximum tolerated dose of 600 mg/kg/day (6- and 65-fold human exposure to penciclovir and 6-deoxy penciclovir respectively).

Mutagenicity Studies:

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 system. There was also no 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.

Reproduction:

As with other drugs of this class, testicular toxicity has been observed in animals receiving both famciclovir and penciclovir, but there was evidence of a return towards normal on withdrawal of treatment. The testicular effects seen following famciclovir are very likely attributable to penciclovir; therefore, systemic exposure comparisons in animals and man are shown for penciclovir.

Mating performance was unaffected in male rats treated with famciclovir for up to 6 months, but fertility decreased after 10 weeks of dosing at 500 mg/kg/day (5-fold human exposure) and there were abnormal sperm profiles, degenerative changes in the seminiferous epithelium and raised FSH levels. Fertility was unaffected at 150 mg/kg/day (2-fold human exposure).

Only minimal testicular degeneration was apparent in rats after 1 month's dosing at 400 mg/kg/day (9-fold human exposure), and no effects were seen following 240 mg/kg/day for 2 years (3-fold human exposure).

In dogs there were no effects after 1 month's dosing at 500 mg/kg/day (3-fold human exposure) and, except for minor histological changes in a single dog after 12 months' treatment, testicular toxicity was confined to chronic dosing with ≥150 mg/kg/day.

There were no significant effects on fertility or on peri- and post-natal development in female rats given famciclovir at doses up to 1000 mg/kg/day.

Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day, and intravenous doses of 360 mg/kg/day in rats or 120 mg/kg/day in rabbits. No adverse effects were observed on embryo-fetal development. Similarly, no embryotoxic or teratogenic effects were observed following intravenous administration of penciclovir to rats (up to 80 mg/kg/day) or rabbits (up to 60 mg/kg/day).

There were no clinically significant effects on sperm count, morphology or motility in male patients receiving famciclovir 250 mg b.i.d. for 18 weeks. Although the daily dosage in this study was lower than the recommended dose for zoster, the duration of treatment was longer at 18 weeks compared with 7 days, and patients therefore received a cumulative (total) dose which was 6-fold higher.

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PART III: CONSUMER INFORMATION

[Pr]AURO-FAMCICLOVIR

(famciclovir)

125 mg, 250 mg and 500 mg film-coated tablets

This leaflet is part III of a three-part "Product Monograph "published when **[Pr]AURO-FAMCICLOVIR** (famciclovir) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **[Pr]AURO-FAMCICLOVIR** (famciclovir). Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AURO-FAMCICLOVIR is an antiviral medicine that is used to treat a number of viral infections described below. It stops the infecting virus from reproducing. Since the virus reproduces very early in the infection, the best results in the treatment are obtained if AURO-FAMCICLOVIR is started as soon as possible after the first symptoms appear.

Herpes zoster:
AURO-FAMCICLOVIR is used to treat herpes zoster (Shingles). Herpes zoster is an infection caused by a virus called varicella zoster (the same virus that causes chickenpox). AURO-FAMCICLOVIR stops the virus from spreading in the body so that healing can occur faster if taken within 72 hours of the first lesion, and reduces the blistering, pain, and rash.

Genital herpes:
AURO-FAMCICLOVIR is used to treat or prevent recurrence of the viral infections which cause genital herpes. Genital herpes is a viral infection caused by herpes simplex virus type 1 or 2, and is normally spread by sexual contact. It causes blisters and burning or itching around the genitals, which may be painful.

AURO-FAMCICLOVIR does not stop you from spreading herpes to another person. It is important to understand that the drug must be taken as early as possible as soon as you know that an attack is starting. Although AURO-FAMCICLOVIR does not cure the viral infection, it helps to shorten the duration of symptoms and allows the infections to heal faster.

What it does:
AURO-FAMCICLOVIR helps stop the virus from multiplying and shortens the time the virus is released and spread, which helps healing.

When it should not be used:
Do not use AURO-FAMCICLOVIR if:

- you have a known hypersensitivity to AURO-FAMCICLOVIR (famciclovir), to penciclovir (a compound formed from famciclovir by your body and an ingredient of some other medicines) (See: What the important nonmedicinal ingredients are) or to any ingredient of the formulation or packaging

What the medicinal ingredient is:
Each AURO-FAMCICLOVIR tablet contains 125 mg, 250 mg or 500 mg of Famciclovir

What the important nonmedicinal ingredients are:
The tablets also contain some inactive ingredients to make up the bulk of each tablet: Sodium starch glycollate, anhydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 400 & titanium dioxide.

The tablets are gluten-free.
The tablets do not contain sucrose, tartrazine or any other azo dyes.

What Dosage Form it comes in:
HERPES ZOSTER
AURO-FAMCICLOVIR tablets are white to pale yellow colored, oval film-coated, biconvex tablets, debossed with 'X' on one side and '34' on the other side. Check with your doctor or pharmacist if your tablets look different from this.

GENITAL HERPES
125 mg tablet - white to pale yellow colored, round film-coated, biconvex tablets with beveled edges, debossed with 'X' on one side and '48' on the other side.
250 mg tablet - White to pale yellow colored, round film-coated, biconvex tablets with beveled edges, debossed with ‘X’ on one side and ‘49’ on the other side.
Check with your doctor or pharmacist if the identifying markings or colour of your tablets are not the same as these.

WARNINGS AND PRECAUTIONS

Before you take AURO-FAMCICLOVIR, **talk to your doctor if:**

- You have an intolerance to some sugars, galactose intolerance, a severe lactase deficiency or glucose-galactose malabsorption, then you should not take AURO-FAMCICLOVIR, as this product contains lactose
- You have an allergy (including itching) or other unwanted (side) effects when previously taking AURO-FAMCICLOVIR

- You are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed
- You have a past history or current kidney disease
- You have severe liver problems
- You have other medical conditions

It is important to tell your doctor, dentist or pharmacist if you are taking other medication, as combining drugs can sometimes result in a change from the expected drug effects, or cause harmful effects.

INTERACTIONS WITH THIS MEDICATION

Always tell your doctor about other medical conditions you have or any medicines you are taking. This means medicines you bought for yourself as well as medicines on prescription. Your doctor or pharmacist will know if it is safe to take AURO-FAMCICLOVIR as well.

It is particularly important that you tell your doctor or pharmacist if you are taking any of the following medicines:

- Probenecid (used to treat high blood levels of uric acid associated with gout and to increase blood levels of penicillin type antibiotics), or any other medicine that can affect your kidneys.
- Raloxifene (used to prevent and treat osteoporosis).

You can take AURO-FAMCICLOVIR with or without food.

PROPER USE OF THIS MEDICATION

How do I use AURO-FAMCICLOVIR?
You should take AURO-FAMCICLOVIR only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

Be sure to take AURO-FAMCICLOVIR regularly as prescribed. Try to take your tablets at the same time each day. You should continue to take your medicine even if you do not feel better, as it may take a few days for your medicine to work.

If your kidneys are not working very well, your doctor will probably have you take this medicine less often, check with your doctor if you have kidney problems. AURO-FAMCICLOVIR will work whether or not you take it with food. You should swallow the tablets whole, with water. Do not chew them.

How long do I use AURO-FAMCICLOVIR?
The usual adult dose is one AURO-FAMCICLOVIR tablet three times a day for shingles. Follow your doctor's instructions about how and when to take your tablets. Start taking them as soon as you can for the best effect.

Most people take one tablet when they get up in the morning, one in the middle of the afternoon and one before going to bed at night.

Finish all the tablets you have been given even if you start to feel better. The treatment lasts for seven days.

Treating an outbreak of recurrent genital herpes:
If you have had herpes infections of the genitals before (called recurrent genital herpes), your doctor may decide to treat the outbreak. You will likely be told to take 125 mg twice a day for 5 days or if you are HIV-positive, 500 mg t twice a day for 7 days. Most people with recurrent genital herpes take one tablet when waking, and one tablet just before going to bed. AURO-FAMCICLOVIR should be taken as soon as possible after the early symptoms (pain, burning, blisters, itching, tingling) begin to appear.

Preventing outbreaks of recurrent genital herpes:
If you have had herpes infections of the genitals before (called recurrent genital herpes), then your doctor may decide to prevent future outbreaks. Your doctor will likely tell you that you should continually take 250 mg twice a day. Most people with recurrent genital herpes take one tablet when waking, and one tablet just before going to bed

Missed Dose:
If you miss taking a AURO-FAMCICLOVIR tablet, don't worry. Take it as soon as you remember. Take your next tablet at the normal time. However, do not take two doses within a time interval of less than 1 hour, in that case you should skip the missed dose. Carry on as normal until you have finished all the tablets. It is important that you finish all the tablets you have been given, unless your doctor tells you to stop taking them. Do not double-dose.

Overdose

If you think you have taken too much AURO-FAMCICLOVIR, contact a health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Taking too much of any type of medicine is risky.

Taking too much AURO-FAMCICLOVIR may affect the kidneys. In people who already have kidney problems it may, rarely, lead to kidney failure if their dose is not correctly lowered.

Important: Your doctor may give you different instructions better suited to your specific needs. If you

need more information on how to take AURO-FAMCICLOVIR properly, double-check with your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine can cause side effects. With AURO-FAMCICLOVIR, some people may feel sick or get a headache, or experience confusion or dizziness. Other side effects include drowsiness (usually in older people), hallucinations (seeing or hearing things that are not really there), vomiting, yellowing of the skin and/or eyes, abnormal liver function test results, palpitations (signs of abnormal heart beat), skin rash, itching or blistering, diarrhea, tiredness and abdominal pain.
If you get these or any other problems while you are taking AURO-FAMCICLOVIR, tell your doctor or pharmacist.

Some effects could be serious:

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Signs of serious skin reaction: pruritus, (e.g. itching, erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis), severe blistering of the skin and/or mucous membranes of the lips, eyes, mouth, nasal passages or genitals, angioedema (e.g. swelling of tissues such as face, mouth, eyes, throat, skin, hands and feet)			√
Serious allergic reaction with symptoms such as difficulty of breathing or swallowing, rash, itching, hives, wheezing or coughing, light-headedness, dizziness, changes in levels of consciousness, hypotension, with or without generalized itching, skin reddening, facial/throat swelling, blue discoloration of the lips, tongue or skin			√
Seizures or fits			√
Signs of decrease in the number of blood platelets: Unexplained bruising, reddish or purplish patches on the skin or nosebleeds			√
Purple skin patches, itching, burning (signs of inflamed blood vessels)			√

Tell your doctor immediately or go to the emergency department at your nearest hospital if any of the following side effects occur:

If you experience anything unusual, while you are receiving treatment with AURO-FAMCICLOVIR, you should report it to your physician. A more complete listing of side effects reported to date, is contained in the Product Monograph supplied to your physician.

Driving and using machines
AURO-FAMCICLOVIR can cause dizziness, drowsiness or confusion in very rare cases. If you have any of these symptoms while taking AURO-FAMCICLOVIR, you should take special care when driving or using machines.

This is not a complete list of side effects. If you have any unexpected effects after receiving AURO-FAMCICLOVIR*, contact your doctor or pharmacist.*

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada,
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

- Keep AURO-FAMCICLOVIR in the bottle or package provided by the pharmacist.
- Store at room temperature (15°C to 30°C).
- AURO-FAMCICLOVIR must be kept out of the reach and sight of children.
- Don't take your tablets if they are past their expiry date.
- Never let anyone else take your tablets, even if they have shingles as well.
- Finish all the tablets in the way you have been told.

More information about shingles.

What is shingles like?

- At first you might feel burning and tingly where the rash is coming. You may get pain for a few days before you see the rash.
- Most people with shingles get a blistery rash down one side of their body or face. This can be painful.
- New blisters will keep coming for about five days. After this, the blisters will dry to form scabs.
- You may feel weak and tired.
- The rash usually lasts for two to three weeks. Afterwards, people can have pain where the rash was, sometimes for several months.

Who gets shingles?

People of any age can get shingles. Most people who get it are middle-aged or older.

You can only get shingles if you have had chickenpox. 50% of people have had shingles by the age of 85.

What causes shingles?

- Shingles is caused by the same virus that causes chickenpox.
- After you have had chickenpox, the inactive virus stays in your body.
- Many years later the virus can start to work again. This may happen when you are run down or tired.

How is shingles treated?

Tablets for shingles, such as AURO-FAMCICLOVIR, stop the virus spreading. They cut down blistering and pain of the rash. They help you get better quicker if you take them early in your illness.

What else can you do?

- To stop the rash itching, have cool baths - do not use perfumed soap or bath oils. You can also put ice cubes wrapped in a washcloth on the rash, or cover it with a soothing lotion like calamine for the first three days.
- Keep the rash clean and dry.
- Wear loose clothes.
- Do not scratch the rash. It could get infected and take longer to get better.
- Rest when you feel tired.
- Try to eat well and drink plenty of fluids.
- Tell your doctor right away if you start to have trouble with your eyes. Shingles can sometimes cause eye problems which can be treated.

Can other people catch your shingles?

Shingles is caused by the same virus that causes chickenpox. Most doctors agree that people do not catch shingles from each other. When you have shingles, you can give chickenpox to someone who has never had chickenpox before - but this is unlikely.

What is Genital Herpes?

Genital Herpes is a viral infection of the genital (sex organ) area which is caused by the Herpes Simplex Virus. You might suspect the onset of this infection if you see the appearance of sores or blisters or feel a burning sensation in your genital region.

Type II herpes simplex virus is the main cause of the sores and blisters that develop in your genital area, but you can also catch genital herpes from herpes simplex Type I which can be the cause of cold sores which occur around your mouth.

Genital Herpes can occur as a first-episode attack or recurrent infection. Unlike many other viruses, recovery from the first attack does not leave you with lifelong protection from re-infection. The virus is able to remain hidden in the nerves after the initial infection and stays there until reactivated.

Since your body still carries the highly infectious virus, you can easily infect someone else, even if you feel fine and you have no symptoms of genital herpes. This explains why genital herpes is one of the most common sexually transmitted diseases (STD).

The risk is higher for people who are more sexually active and have more sexual partners. It is therefore recommended that you avoid sexual activity if you or your partner have any symptoms of herpes, even if you have started your treatment.

If you are taking AURO-FAMCICLOVIR to treat or to suppress genital herpes, or you have had genital herpes in the past, you should still practice "safer sex", including the use of condoms. This is important to prevent you passing the infection on to others.

While taking this medication:

- remember that your infection is contagious.
- tell any other doctor, pharmacist or dentist you see, that you are taking AURO-FAMCICLOVIR.
- contact your doctor if you develop any unusual discomfort.
- you should not take AURO-FAMCICLOVIR when pregnant or breastfeeding unless your doctor tells you to.
- do not give AURO-FAMCICLOVIR to others because it may not be suitable for them.
- store your tablets in a dry place at room temperature in the original container provided by the pharmacy.
- keep this medication out of reach of children.
- read your prescription label carefully; consult your doctor or pharmacist if you have any questions or require further information.

MORE INFORMATION

If you want more information about AURO-FAMCICLOVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.auropharma.ca, or by calling 1-855-648-6681.

This leaflet was prepared by:

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