AUSTRALIAN PRODUCT INFORMATION

EZOVIR® COLD SORE RELIEF

Famciclovir

1 NAME OF THE MEDICINE

Famciclovir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg famciclovir. Famciclovir is a synthetic guanine derivative. It is a white to pale yellow crystalline solid.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

EZOVIR COLD SORE RELIEF tablets are white, oval, coated tablets with FM on one side and 500 on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EZOVIR COLD SORE RELIEF is indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults aged 18 years and over.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage: Adults 18 years and older

The recommended dosage is 1500 mg as a single dose. 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.

Renal Impairment

As reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, patients who have or at-risk of renal impairment should be referred to their medical practitioner for screening for renal impairment and any subsequent dosage adjustment if necessary. Therefore, use of EZOVIR COLD SORE RELIEF in patients with renal impairment should only be under medical advice. The following modifications in dosage are recommended.

If the creatinine clearance is $\geq$ 60 mL/min/1.73 m^2, no dosage adjustment is necessary. If the creatinine clearance is 40-59 mL/min/1.73 m^2, the dose is 750 mg as a single dose; 20-39 mL/min/1.73 m^2, the dose is 500 mg as a single dose; 10-20 mL/min/1.73 m^2 and for patients on haemodialysis, the dose is 250 mg as a single dose.

EZOVIR COLD SORE RELIEF is only available as tablets containing 500 mg of famciclovir.

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 10 mL/min/1.73 m^2.

Since 4 hours 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 mild to moderate hepatic impairment.

Administration

Famciclovir can be taken without regard to meals (see section 5.2 PHARMACOKINETICS PROPERTIES - EFFECT OF FOOD).

4.3 CONTRAINDICATIONS

EZOVIR COLD SORE RELIEF is contraindicated in patients with known hypersensitivity to famciclovir or other constituents of EZOVIR COLD SORE RELIEF.

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

EZOVIR COLD SORE RELIEF is not recommended for use in:

- patients who are immunocompromised
- children and adolescents under 18 years of age

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir maybe impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Use in renal impairment

As reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, patients who have or at risk of renal impairment should be referred to their medical practitioner for screening for renal impairment and any subsequent dosage adjustment if necessary. Appropriate dosage adjustments for renally impaired patients are provided (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). Therefore, use of EZOVIR COLD SORE RELIEF in patients with renal impairment should only be under medical advice.

Use in the elderly

No special precautions are required for elderly patients with normal renal function and patients with mild or moderate hepatic impairment.

Paediatric use

Safety and efficacy of famciclovir in the treatment of herpes labialis in children and adolescents under 18 years of age has not been established. Therefore, use of EZOVIR COLD SORE RELIEF in this age group is not recommended.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 section 5 PHARMACOLOGICAL PROPERTIES).

Other drugs that affect renal physiology

Could affect plasma levels of penciclovir (the active metabolite of famciclovir, see section 5 PHARMACOLOGICAL PROPERTIES). 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-deoxypenciclovir 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 500 mg/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 250 mg famciclovir b.i.d. for 18 weeks. Famciclovir had no effect on fertility in female rats at doses of up to 1000 mg/kg/day, approximately 4 to 27 times the human systemic exposure (AUC).

Use in Pregnancy (Category B1)

Famciclovir was tested for effects on embryofoetal development in rats and rabbits at oral doses up to 1000 mg/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 360 mg/kg/day in rats (1.9 to 12 times the human dose based on body surface area (BSA) comparisons) or 120 mg/kg/day in rabbits (1.2 to 7.1 times the human dose (BSA)). No adverse effects were observed on embryofoetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.4 to 2.6 times the human dose (BSA)) or rabbits (60 mg/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.

EZOVIR COLD SORE RELIEF should therefore not be used during pregnancy unless the potential benefits are considered to outweigh the potential risks associated with treatment.

Use in Lactation

EZOVIR COLD SORE RELIEF 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking EZOVIR COLD SORE RELIEF should refrain from driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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. See Table 1 below.

Table 1: Adverse events (related, possibly related, unassessable or unknown) report by ≥1% of immunocompetent subjects during clinical trials in herpes labiallis.

Adverse event	Famciclovir 1,500 mg q.d (N = 227) N (%)	Famciclovir 750 mg b.i.d (N = 220) N (%)	Placebo (N = 254) N (%)
Patients with AE(s)	63 (27.8)	54 (24.5)	53 (20.9)
AE preferred term			
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)

Postmarketing data

In addition to the adverse events reported in the clinical trials, the following adverse reactions have been reported in postmarketing surveillance. They are ranked under headings of frequency, according to the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.

Adverse events reported by patients receiving famciclovir during postmarketing

Table 2: Adverse Events reported by patients receiving Famciclovir

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia
Psychiatric disorders	
Uncommon: Rare:	Confusional state (predominantly in the elderly) Hallucinations
Nervous system disorders	
Very common: Common: Uncommon: Not known:	Headache Dizziness Somnolence (predominantly in the elderly) Seizure
Cardiac disorders	
Rare:	Palpitations
Gastrointestinal disorders	
Common:	Vomiting, nausea, abdominal pain, diarrhoea
Hepatobiliary disorders	
Common: Rare:	Liver function test abnormal Jaundice cholestatic
Immune system disorders	
Not known:	Anaphylactic shock, anaphylactic reaction
Skin and subcutaneous tissue disorders	
Common: Uncommon: Very rare: Not known:	Rash, pruritus Angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria Serious skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) Hypersensitivity vasculitis
Musculoskeletal disorders	
Very rare:	arthralgia, myalgia

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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 hours of haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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).

Clinical Trials

In one large placebo-controlled trial, 701 immunocompetent adults with recurrent herpes labialis were treated with famciclovir 1500 mg once (n = 227), famciclovir 750 mg 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 breastfeeding 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 1500 mg single dose treated patients was 4.4 days compared to 4.0 days in famciclovir 750 mg 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 1500 mg 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 750 mg b.i.d. (median time 2.1 days).

5.2 PHARMACOKINETIC PROPERTIES

Famciclovir is the oral prodrug of penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to the antivirally active compound penciclovir. The bioavailability of penciclovir after oral famciclovir administration is 77%. Mean peak plasma concentrations (Cmax) of penciclovir occurred at a median time of 45 minutes following administration of single oral doses of famciclovir (as shown in Table 3). No data is available on the pharmacokinetics of 1500 mg famciclovir as a single dose.

Table 3: Mean peak plasma concentration (Cmax) of penciclovir after administration of single oral doses of famciclovir

Famciclovir single oral dose (mg)	Cmax (mcg/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-deoxyprecursor are poorly (< 20%) bound to plasma proteins. Famciclovir is eliminated principally as penciclovir and its 6-deoxyprecursor, 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

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 section 4.2 DOSE AND METHOD OF 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 500 mg famciclovir. No dose adjustment is recommended for patients with well compensated hepatic impairment (see section 4.2 DOSE AND METHOD OF ADMINISTRATION - HEPATIC IMPAIRMENT and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 bodyweight 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 maybe 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 4.2 Dose and Method of Administration).

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.

5.3 PRECLINICAL SAFETY DATA

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 125 mg b.i.d. for acute recurrent genital herpes, and a penciclovir AUC of 27 microgram.h/mL at 500 mg 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 section 5.2 PHARMACOKINETIC PROPERTIES). 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.

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.

Carcinogenicity

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 600 mg/kg/day. No increases in tumour incidences were reported for male rats treated at doses of up to 240 mg/kg/day or in mice of either sex at doses of up to 600 mg/kg/day. At the no effect levels of 240 and 200 mg/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 500 mg t.i.d or 125 mg 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).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

EZOVIR COLD SORE RELIEF tablets contain copovidone, crospovidone, microcrystalline cellulose, OPADRY II complete film coating system YS- 22-18096 White, silicon dioxide, sodium stearylfumarate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

EZOVIR COLD SORE RELIEF 500 mg: PVC/Al blister pack of 3 tablets

Australian Register of Therapeutic Goods (ARTG)

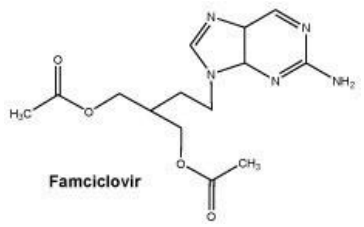
AUST R 351702 – EZOVIR COLD SORE RELIEF 500 mg

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name:9-(4-acetoxy-3-acetoxymethylbut-1-yl)- 2-aminopurine.

Molecular formula: $C_{14}H_{19}N_5O_4$

Molecular weight: 321.3

CAS Number

104227-87-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

7 December 2020

10 DATE OF REVISION

21 March 2023

Summary Table of Changes

Section Changed	Summary of New Information
3, 4, 5 & 6	Minor editorial changes.
8	Updated sponsor details.

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