New Zealand Data Sheet

APOHEALTH FAMCICLOVIR ONCE

1. PRODUCT NAME

APO-FAMCICLOVIR (125mg, 250mg and 500mg film- coated tablets)

APOHEALTH FAMCICLOVIR ONCE (500mg film- coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

APOHEALTH FAMCICLOVIR ONCE Tablets contain famciclovir 500mg

Excipient(s) with known effect

None

APOHEALTH FAMCICLOVIR ONCE tablets are gluten free and lactose free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

APOHEALTH FAMCICLOVIR ONCE 500mg are white, oval, biconvex film-coated tablets engraved "APO" on one side and "FAM500" on the other side. Each tablet typically weighs 549mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APOHEALTH FAMCICLOVIR ONCE 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

Dose

Recurrent herpes labialis (cold sores)

1500mg as a single dose for one day. Initiation of treatment is recommended at the earliest sign or symptom of a cold sore (e.g. tingling, itching or burning).

Dosage in renally impaired patients

Famciclovir should only be used in patients with or who are at-risk of renal impairment under medical advice. Because reduced clearance of penciclovir, the antivirally active metabolite of famciclovir (see section 5.2 Pharmacokinetic properties), is related to reduced renal function, as measured by creatinine clearance, special attention should be given to dosages in patients with impaired renal function.

Patients who are at higher risk of renal impairment include those who:

- are over 50 years of age
- are smokers
- have diabetes mellitus, hypertension or established cardiovascular disease
- are obese
- have a family history of chronic kidney disease
- are of Aboriginal or Torres Strait Islander origin
- are taking medication that may impair renal function

Such at risk patients should be referred to a medical practitioner for a kidney health check, which usually consists of a simple urine test (dipstick analysis for protein), blood test (measurement of eGFR or kidney function) and blood pressure measurement.

The following modifications in dosage are recommended and which should be managed by a medical practitioner:

- **Recurrent herpes labialis (cold sores)**

Creatinine Clearance (mL/min/1.73m^2)	Dosage
≥60	No dose adjustment necessary (1500mg single dose)
40-59	750mg single dose
20-39	500mg single dose
10-20	250mg single dose
For patients on haemodialysis	250mg single dose

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/1.73^2.

Renally impaired patients on haemodialysis

Since 4 hour haemodialysis results in approximately 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. For patients with herpes zoster, the recommended dose is 250mg after each dialysis. For patients with recurrent genital herpes, famciclovir should be administered either in a single dose of 250mg following dialysis (single-day regimen), or 125mg following each dialysis (multiple-day regimen).

For patients with recurrent herpes labialis (cold sores), famciclovir should be administered in a single dose of 250mg following dialysis (single-day regimen).

Hepatically impaired patients

No dosage adjustment is required in patients with well-compensated hepatic impairment. No data are available for patients with severe uncompensated hepatic impairment (see section 5.2 Pharmacokinetic properties). Conversion of famciclovir to the active metabolite penciclvoir may be impaired in these patients, resulting in lower penciclovir plasma concentrations and thus possibly a decrease of efficacy of famciclovir (see section 5.2 Pharmacokinetic properties).

Elderly

Dosage modification is not required unless renal function is impaired.

Paediatric population

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

Black patients

A placebo-controlled study in immunocompetent Black patients with recurrent genital herpes showed no difference in efficacy between patients receiving famciclovir 1000mg twice daily for one day and placebo. There were no unexpected or new safety findings in this trial in Black patients.

This lack of efficacy in the one-day treatment regimen cannot be extrapolated to the five-day treatment regimen for recurrent genital herpes (125mg twice daily for five days) or other indications in Black patients (see section 5.1 Pharmacodynamic properties and section 5.2 Pharmacokinetic properties).

Mode of administration

Because the systemic availability (AUC) of penciclovir was not altered when famciclovir was administered with food, it appears that famciclovir can be taken without regard to meals (see section 5.2 Pharmacokinetic properties).

For some patients i.v penciclovir may be more appropriate than famciclovir, the oral prodrug of penciclovir. While the decision on the best patient management and mode of administration should rest with the physician, in severely ill patients initiation of therapy with i.v penciclovir should be considered.

It appears that famciclovir can be taken without regard to meals (see section 5.2 Pharmacokinetic properties).

Maximum Tolerated Daily Dose

Herpes zoster patients receiving 750mg three times daily for seven days tolerated the famciclovir therapy well.

Genital herpes patients receiving up to 750mg three times daily for 5 days, and up to 500mg three times daily for 10 days also tolerated the product well.

Good tolerance was also seen in two reported 12 month studies, in which genital herpes patients received doses of up to 250mg three times daily. Similar tolerance was experienced in immunocompromised herpes zoster patients receiving up to 500mg three times daily for 10 days and herpes simplex patients receiving up to 500mg twice daily for 7 days and 500mg twice daily for 8 weeks.

4.3 Contraindications

APOHEALTH FAMCICLOVIR ONCE is contraindicated in patients with known hypersensitivity to famciclovir or other constituents of APOHEALTH FAMCICLOVIR ONCE. It is also contraindicated in those patients who have shown hypersensitivity to penciclovir, the active metabolite of famciclovir.

APOHEALTH FAMCICLOVIR ONCE 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

Refer the patient to a medical practitioner if they have symptoms and signs of an infection other than the cold sore

Impaired renal function

Special attention should be paid to patients with impaired renal function and dosage adjustment is necessary (see section 4.2 Dose and method of administration and section 4.9 Overdose).

Elderly patients

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

Severe 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 section 5.2 Pharmacokinetic properties).

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetics Interactions

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 Section 5.2 Pharmacokinetic properties).

Other drugs that affect renal physiology:

could affect plasma levels of penciclovir (the active metabolite of famciclovir, see section 5.1 Pharmacodynamic properties, Mechanism of Actions).

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 co-administration of zidovudine and famciclovir.

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 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.

Pharmacodynamic Interactions

Because the systemic availability (AUC) of penciclovir was not altered when famciclovir was administered with food, it appears that famciclovir can be taken without regard to meals (see section 5.2 Pharmacokinetic properties).

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1

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 (80 mg/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 safety of famciclovir in human pregnancy has not been established. Famciclovir should therefore not be used during pregnancy unless the potential benefits are considered to outweigh the potential risks associated with treatment.

Breast-feeding

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. Famciclovir should not be used in breastfeeding mothers unless the potential benefits are considered to outweigh the potential risks associated with treatment.

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).

4.7 Effects on ability to drive and use machines

APOHEALTH FAMCICLOVIR ONCE is presumed to be safe or unlikely to produce and effect on the ability to drive or use machinery.

There is no evidence that famciclovir will affect the ability of a patient to drive or to use machines. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking APOHEALTH FAMCICLOVIR ONCE should refrain from driving or operating machinery.

4.8 Undesirable effects

Famciclovir has been well tolerated in human studies. Headache and nausea were reported in clinical trials. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment.

Confusion, predominately in the elderly has been reported rarely.

The following table specifies the estimated frequency of adverse reactions based on all the spontaneous reports and literature cases that have been reported for famciclovir since its introduction to the market.

Adverse reactions (Table 1) are ranked under headings of frequency, using the following convention: *very common (1/10); common (1/100, < 1/10); uncommon (1/1,000, < 1/100); rare (1/10,000, < 1/1,000); very rare (<1/10,000), not known (cannot be estimated from available data)*.

Table 1

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)
Cardiac disorders		
	Rare:	Palpitations
Gastrointestinal disorders		
	Common:	Vomiting, nausea, abdominal pain, diarrhoea
Hepatobiliary disorders		

Common:	Abnormal liver function tests
Rare:	jaundice cholestatic
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria
Not known:	Serious skin reactions*(e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) leukocytoclastic vasculitis.
Muscular skeletal disorders	
Very Rare:	Arthralgia, myalgia

*Adverse drug reactions reported from post-marketing experience with famciclovir via spontaneous case reports and literature cases which have not been reported in clinical trials. Because these adverse drug reactions have been reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency. Frequency is therefore listed as "not known"

Post-marketing Experience

See table above

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdose experience with famciclovir is limited. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dosage has not been appropriately reduced for the level of renal function. Penciclovir, the active metabolite, is dialysable; plasma concentrations are reduced by approximately 75% following 4 hour haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

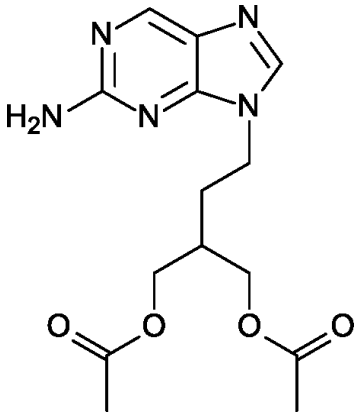
Pharmacotherapeutic group

Oral antiviral agent

ATC code

JO5A B09

Chemical Structure



It is a synthetic acyclic guanine derivative

Chemical name

2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediol diacetate

Molecular formula

$C_{14}H_{19}N_5O_4$

Molecular weight

321.3.

Mechanism of action

Famciclovir is the oral prodrug of penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has demonstrable *in vitro* activity against herpes simplex viruses (HSV types 1 and 2), varicella zoster virus (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 acyclovir 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 acyclovir. 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 efficacy and safety

Adults

In a reported study in suppression of recurrent genital herpes in which immunocompetent patients were treated with famciclovir for 4 months, there was no evidence of resistance to the active metabolite penciclovir when isolates from 71 patients were analysed.

Reported results from penciclovir and famciclovir patient studies, including studies of up to four months treatment with famciclovir, have shown a small overall frequency of penciclovir resistant isolates: 0.3% in the 981 total isolates tested to date and 0.19% in the 529 virus isolates from immunocompromised patients. The resistant isolates were found at the start of treatment or in a placebo group, with no resistance occurring on or after treatment with famciclovir or penciclovir.

In reported placebo-controlled and active-controlled studies, both in immunocompetent and immunocompromised patients with herpes zoster, famciclovir was effective in the resolution of lesions. A placebo controlled study has demonstrated that famciclovir significantly reduces the duration of post-herpetic neuralgia when administered to patients with herpes zoster. In a large clinical study, famciclovir was shown to be effective and well tolerated in the treatment of ophthalmic zoster.

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 b.i.d and 6.2 days in placebo-treated patients. This translates to treatment effects of 1.8 (CI95% 0.9, 2.7) and 2.2 (CI95% 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).

Three placebo-controlled studies in immunocompetent patients showed that famciclovir administered either as 125mg twice daily for five days (two studies) or 1000mg twice daily for one day (one study) was effective in the treatment of recurrent genital herpes. In an active-controlled study in immunocompetent patients with recurrent genital herpes, famciclovir 1000mg twice daily for one day was non-inferior to valaciclovir 500mg twice daily for three days. A placebo-controlled study in immunocompetent Black patients with recurrent genital herpes showed no difference in efficacy between patients receiving famciclovir 1000mg twice daily for one day or placebo. There were no unexpected or new safety findings in this trial in Black patients.

An active-controlled study in HIV-infected patients showed that famciclovir 500mg twice daily for seven days was effective and well tolerated in the episodic treatment of HSV infections. Placebo-controlled and uncontrolled studies showed that famciclovir 500mg twice daily was effective and well tolerated in the suppression of recurrent genital herpes in HIV-infected patients; the placebo-controlled study showed that famciclovir significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

Paediatric population

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

The available data are insufficient to support the use of famciclovir for the treatment of chickenpox or infections due to herpes simplex virus in this patient population (see section 4.2 Dose and method of administration). No efficacy studies have been conducted in paediatric patients and there are no efficacy data in adults with diseases similar to the ones evaluated in the safety and pharmacokinetics paediatric studies (i.e. chickenpox or gingivostomatitis).

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

5.2 Pharmacokinetic properties

Absorption

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir is 77%. Mean peak plasma concentration of penciclovir, following a 125mg, 250mg, 500mg, 750mg and 1000mg oral dose of famciclovir, was 0.8microgram/mL, 1.6micrograms/mL, 3.3micrograms/mL, 5.1micrograms/mL and 6.6micrograms/mL respectively, and occurred at a median time of 45 minutes post-dose. No data is available on the pharmacokinetics of 1500mg famciclovir as a single dose. The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

Distribution

Famciclovir is the oral prodrug of the antivirally active compound penciclovir. There is no accumulation of penciclovir on repeated dosing with famciclovir. Penciclovir and its 6-deoxy precursor are poorly (< 20%) bound to plasma proteins.

Biotransformation

Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir, is approximately 2 hours.

Elimination

Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted in urine and no unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir.

Characteristics in special populations

Patients with herpes zoster

Uncomplicated herpes zoster does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration 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.

Subjects with renal impairment

The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal insufficiency and should be managed by a medical practitioner (see section 4.2 Dose and method of administration).

Patients who are at higher risk of renal impairment include those who:

- are over 50 years of age
- are smokers
- have diabetes mellitus, hypertension or established cardiovascular disease
- are obese
- have a family history of chronic kidney disease
- are of Aboriginal or Torres Strait Islander origin
- are taking medication that may impair renal function

Such at risk patients should be referred to a medical practitioner for a kidney health check which usually consists of a simple urine test (dipstick analysis for protein), blood test (measurement of eGFR or kidney function) and blood pressure measurement.

Therefore use of famciclovir in patients who have or are at-risk of renal impairment should only be under medical advice.

Subjects with 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) or penciclovir following a single dose of 500 mg famciclovir. No dose adjustment is recommended for patients with mild to moderate hepatic impairment (see section 4.2 Dose and method of administration and section 4.4 Special warnings and precautions for use). The pharmacokinetics of penciclovir have not been evaluated in patients with severe uncompensated hepatic impairment. Conversion of famciclovir to the active metabolite

penciclvoir may be impaired in these patients, resulting in lower penciclovir plasma concentrations and thus possibly a decrease of efficacy of famciclovir.

Elderly subjects

Based on cross-study comparisons, the mean penciclovir AUC was about 40% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Some of this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see section 4.2 Dose and method of administration).

Gender

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

Paediatric patients

In the paediatric studies described in section “Clinical studies”, the famciclovir doses were based on the patient’s body weight and were selected to provide systemic exposures similar to the penciclovir systemic exposure observed in adults after administration of 500mg famciclovir. Based on the pharmacokinetic data observed with these doses in children, a new weight-based dosing algorithm was designed and used in the multiple-dose safety studies in patients 1 to ≤12 years of age. Pharmacokinetic data were not obtained with the revised weight-based dosing algorithm.

Race

A retrospective evaluation was performed to compare the pharmacokinetic parameters obtained in Black and Caucasian subjects after single and repeat once-daily, twice-daily, or three times-daily administration of famciclovir 500mg. Data from a study in healthy volunteers (single dose), a study in subjects with varying degrees of renal impairment (single and repeat dose) and a study in subjects with hepatic impairment (single dose) did not indicate any relevant difference in the pharmacokinetics of penciclovir between Black and Caucasian subjects.

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 4.5microgram.h/mL at 125mg b.i.d. for acute recurrent genital herpes, and a penciclovir AUC of 27microgram.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 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.

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 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 29microgram.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 46microgram.h/mL respectively, or approximately 2 to 12 times the human systemic exposure (AUC).

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Poloxamer 407
- Stearic Acid
- Hypromellose (Hydroxypropyl Methylcellulose)
- Macrogol 8000 (Polyethylene Glycol 8000)
- Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 3 years from the date of manufacture

6.4 Special precautions for storage

Store at or below 25°C

Keep out of reach of children

6.5 Nature and contents of container

APOHEALTH FAMCICLOVIR ONCE

Strength	Container	Number of tablets in pack
500mg Tablets	Coldform foil/aluminum foil Blisters	3

Not all strengths, pack types or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

APOHEALTH FAMCICLOVIR ONCE (Pharmacist Only Medicine): Tablets containing 500mg or less for the treatment of recurrent herpes labialis when pack contains up to 3 tablets)

8. SPONSOR

Arrotex Pharmaceuticals (NZ) Limited:

C/o Quigg Partners

Level 7, The Bayleys Building

36 Brandon Street,

Wellington 6011, New Zealand

Phone +64 9 918 5100

9. DATE OF FIRST APPROVAL

04 July 2013

10. DATE OF REVISION OF THE TEXT

03 May 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Update to sponsor's details