

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Famciclovir Teva 250 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of famciclovir.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round, film-coated tablets, engraved 8118 on one side and 93 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Varicella zoster virus (VZV) infections – herpes zoster

Famciclovir is indicated for

- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults (see section 4.4)
- the treatment of herpes zoster in immunocompromised adults (see section 4.4).

Herpes simplex virus (HSV) infections – genital herpes

Famciclovir is indicated for

- the treatment of first and recurrent episodes of genital herpes in immunocompetent adults
- the treatment of recurrent episodes of genital herpes in immunocompromised adults
- the suppression of recurrent genital herpes in immunocompetent and immunocompromised adults.

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV infection (see section 5.1).

4.2 Posology and method of administration

Herpes zoster in immunocompetent adults

500 mg three times daily for seven days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Herpes zoster in immunocompromised adults

500 mg three times daily for ten days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Genital herpes in immunocompetent adults

First episode of genital herpes: 250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after a diagnosis of first episode of genital herpes.

Episodic treatment of recurrent genital herpes: 125 mg twice daily for five days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (*e.g.* tingling, itching, burning, pain) or lesions.

Recurrent genital herpes in immunocompromised adults

Episodic treatment of recurrent genital herpes: 500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (*e.g.* tingling, itching, burning, pain) or lesions.

Suppression of recurrent genital herpes in immunocompetent adults

250 mg twice daily. Suppressive therapy should be discontinued after a maximum of 12 months of continuous antiviral therapy to reassess recurrence frequency and severity. The minimum period of reassessment should include two recurrences. Patients who continue to have significant disease may restart suppressive therapy.

Suppression of recurrent genital herpes in immunocompromised adults

500 mg twice daily.

Patients with renal impairment

Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to doses in patients with impaired renal function. Dose recommendations for adult patients with renal impairment are provided in Table 1.

Table 1 Dose recommendations for adult patients with renal impairment

Indication and nominal dose regimen	Creatinine clearance [ml/min]	Adjusted dose regimen
Herpes zoster in immunocompetent adults 500 mg three times daily for 7 days	≥60 40 to 59 20 to 39 <20 Haemodialysis patients	500 mg three times daily for 7 days 500 mg twice daily for 7 days 500 mg once daily for 7 days 250 mg once daily for 7 days 250 mg following each dialysis for 7 days
Herpes zoster in immunocompromised adults 500 mg three times daily for 10 days	≥60 40 to 59 20 to 39 <20 Haemodialysis patients	500 mg three times daily for 10 days 500 mg twice daily for 10 days 500 mg once daily for 10 days 250 mg once daily for 10 days 250 mg following each dialysis for 10 days
Genital herpes in immunocompetent adults – first episode of genital herpes 250 mg three times daily for 5 days	≥40 20 to 39 <20 Haemodialysis patients	250 mg three times daily for 5 days 250 mg twice daily for 5 days 250 mg once daily for 5 days 250 mg following each dialysis for 5 days
Genital herpes in immunocompetent adults – episodic treatment of recurrent		

genital herpes 125 mg twice daily for 5 days	≥20 <20 Haemodialysis patients	125 mg twice daily for 5 days 125 mg once daily for 5 days 125 mg following each dialysis for 5 days
Genital herpes in immunocompromised patients episodic treatment of recurrent genital herpes 500 mg twice daily for 7 days	≥40 20 to 39 <20 Haemodialysis patients	500 mg twice daily for 7 days 500 mg once daily for 7 days 250 mg once daily for 7 days 250 mg following each dialysis for 7 days
Suppression of recurrent genital herpes in immunocompetent adults 250 mg twice daily	≥40 20 to 39 <20 Haemodialysis patients	250 mg twice daily 125 mg twice daily 125 mg once daily 125 mg following each dialysis
Suppression of recurrent genital herpes in immunocompromised adults 500 mg twice daily	≥40 20 to 39 <20 Haemodialysis patients	500 mg twice daily 500 mg once daily 250 mg once daily 250 mg following each dialysis

Patients with renal impairment on haemodialysis

Since 4-h haemodialysis resulted in up to 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. The recommended dose regimens for haemodialysis patients are included in Table 1.

Patients with hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see sections 4.4 and 5.2).

Elderly patients (≥65 years)

Dose modification is not required unless renal function is impaired.

Children and adolescents

Famciclovir is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Paediatric population

The safety and efficacy of famciclovir in children and adolescents aged less than 18 years have not been established. Currently available data are described in sections 5.1 and 5.2.

Method of administration

Famciclovir can be taken without regard to meals (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity to penciclovir.

4.4 Special warnings and precautions for use

Use in patients with renal impairment

In patients with impaired renal function dose adjustment is necessary (see sections 4.2 and 4.9).

Use in patients with hepatic impairment

Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of famciclovir may occur.

Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients.

Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, *i.e.* those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, transmission is still possible. Therefore, in addition to therapy with famciclovir, it is recommended that patients use safer sex practices.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on famciclovir

No clinically significant interactions have been identified.

Concurrent use of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir, by competing for elimination. Therefore patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid, should be monitored for toxicity. If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances, a dose reduction of famciclovir to 250 mg three times daily may be considered.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifene has been shown to be a potent inhibitor of this enzyme *in vitro*. Co-administration of raloxifene 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of famciclovir in pregnant women. Based on these limited amounts of information, the cumulative analysis of both prospective and retrospective pregnancy cases did not provide evidence indicating that the product causes any specific fetal defect or congenital anomaly. Animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir). Famciclovir should only be used during pregnancy when the potential benefits of treatment outweigh the potential risks.

Lactation

It is unknown whether famciclovir is excreted in human breast milk. Animal studies have shown excretion of penciclovir in breast milk. If the woman's condition mandates treatment with famciclovir, discontinuation of breast-feeding may be considered.

Fertility

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking famciclovir should refrain from driving or operating machinery.

4.8 Undesirable effects

Headache and nausea have been reported in clinical studies. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment. All other adverse reactions were added during post-marketing.

A total of 1,587 patients have received famciclovir at recommended doses in placebo- (n= 657) and active- (n=930) controlled studies. These clinical studies were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. For adverse reactions which have never been observed in these studies, the upper limit of the 95% confidence interval is not expected to be higher than 3/X (based on the "rule of three"), with X representing the total sample size (n=1,587).

Adverse reactions (Table 2) are ranked under headings of frequency, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

Table 2 Adverse reactions

<u>Blood and lymphatic system disorders</u>	
Rare:	thrombocytopenia
<u>Psychiatric disorders</u>	
Uncommon:	confusion
Rare:	hallucinations
<u>Nervous system disorders</u>	

Very common: headache
Common: dizziness, somnolence

Gastrointestinal disorders

Common: nausea, vomiting

Hepato-biliary disorders

Common: abnormal liver function tests
Rare: cholestatic jaundice

Skin and subcutaneous tissue disorders

Common: rash, pruritus
Uncommon: urticaria, serious skin reactions* (*e.g.* erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)

* Never reported in clinical trials; category is based on the “rule of three”

Overall, adverse reactions reported from clinical studies with immunocompromised patients were similar to those reported in the immunocompetent population. Nausea, vomiting and abnormal liver function tests were reported more frequently, especially at higher doses.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 dose has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4-h haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors
ATC code: J05A B09

Mechanism of action

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

The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir. In virus-infected cells the viral thymidine kinase (TK) phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. This triphosphate persists in infected cells in excess of 12 hours and inhibits viral DNA chain elongation by competitive inhibition with deoxyguanosine triphosphate for incorporation into the growing viral DNA, thus halting virus replication of viral DNA. In uninfected cells treated with penciclovir, concentrations of penciclovir triphosphate are only barely detectable. Hence the probability of toxicity to mammalian host cells is low and uninfected cells are

unlikely to be affected by therapeutic concentrations of penciclovir.

Resistance

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

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

Clinical efficacy

In placebo-controlled and active-controlled studies both in immunocompetent and immunocompromised patients with uncomplicated herpes zoster, famciclovir was effective in the resolution of lesions. In an active-controlled clinical study, famciclovir was shown to be effective in the treatment of ophthalmic zoster in immunocompetent patients.

Efficacy of famciclovir in immunocompetent patients with first episode of genital herpes was shown in three active-controlled studies. Two placebo-controlled studies in immunocompetent patients and one active-controlled study in HIV-infected patients with recurrent genital herpes showed that famciclovir was effective.

Two placebo-controlled 12-month studies in immunocompetent patients with recurrent genital herpes showed that famciclovir-treated patients had a significant reduction of recurrences as compared to placebo-treated patients.

Placebo-controlled and uncontrolled studies of up to 16 weeks' duration showed that famciclovir was effective 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

Famciclovir experimental oral granules were evaluated in 169 paediatric patients 1 month to ≤ 12 years of age. One hundred of these patients were 1 to ≤ 12 years of age and were treated with famciclovir oral granules (doses ranged from 150 mg to 500 mg) either twice (47 patients with herpes simplex virus infections) or three times (53 patients with chickenpox) daily for 7 days. The remaining 69 patients (18 patients 1 to ≤ 12 months, 51 patients 1 to ≤ 12 years) participated in single-dose pharmacokinetic and safety studies using famciclovir oral granules (doses ranged from 25 mg to 500 mg). Famciclovir weight-based doses were selected to provide penciclovir systemic exposures similar to the penciclovir systemic exposures observed in adults after administration of 500 mg famciclovir. One of these studies comprised a control group; therefore a conclusion on the efficacy of the investigated regimens is not possible. The safety profile was similar to that seen in adults. However, systemic drug exposure in infants < 6 months of age was low, thus precluding any assessment of famciclovir's safety in this age group.

5.2 Pharmacokinetic properties

General characteristics

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 was 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/ml, 1.6 micrograms/ml, 3.3 micrograms/ml and

5.1 micrograms/ml, respectively, and occurred at a median time of 45 minutes post-dose.

Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing, indicating that there is no accumulation of penciclovir on repeated dosing with famciclovir.

The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

Distribution

Penciclovir and its 6-deoxy precursor are poorly (<20%) bound to plasma proteins.

Metabolism and elimination

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

The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir was approximately 2 hours.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

Characteristics in special populations

Patients with herpes zoster infection

Uncomplicated herpes zoster infection 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 dosing 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 impairment (see section 4.2).

Subjects with hepatic impairment

Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral administration of famciclovir. No dose adjustment is recommended for patients with mild and moderate hepatic impairment (see sections 4.2 and 4.4). The pharmacokinetics of penciclovir have not been evaluated 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.

Paediatric population

Repeated oral dosing of famciclovir (250 or 500 mg three times daily) to paediatric patients (6-11 years) infected with hepatitis B did not have notable effect on the pharmacokinetics of penciclovir compared to single dose data. There was no accumulation of penciclovir.

In children (1-12 years) with herpes simplex virus infection or chickenpox given single oral doses of famciclovir (see section 5.1), the apparent clearance of penciclovir increased with body weight in a nonlinear manner. The plasma elimination half-life of penciclovir tended to decrease with decreasing age, from an average of 1.6 hours in the patients aged 6-12 years to 1.2 hours in patients aged 1-<2 years.

Elderly patients (≥65 years)

Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly 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).

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.

5.3 Preclinical safety data

General toxicity

Studies on safety pharmacology and repeated-dose toxicity reveal no special hazard for humans.

Genotoxicity

Famciclovir was not found to be genotoxic in a comprehensive battery of *in vivo* and *in vitro* tests designed to detect gene mutation, chromosomal damage and repairable damage to DNA. Penciclovir, in common with other substances 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*.

Carcinogenicity

At high doses in female rats, there was an increased incidence of mammary adenocarcinoma, a tumour commonly observed in the strain of rats used in the carcinogenicity study. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

Reproductive toxicity

Impaired fertility (including histopathological changes in the testis, altered sperm morphology, reduced sperm concentration and motility, and reduced fertility) was observed in male rats given 500 mg/kg/day. Furthermore, degenerative changes of the testicular epithelium were noted in the general toxicity studies. This finding was reversible and has also been observed with other substances of this class. Animal studies did not indicate any negative effect on female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Microcrystalline cellulose E460
Colloidal anhydrous silica E551
Sodium starch glycolate (Type A)
Low-substituted hydroxypropylcellulose
Croscarmellose sodium
Sodium stearyl fumarate

Film-coat:

Titanium dioxide (E171)
Polydextrose (E1200)
Hypromellose (E464)
Triacetin (E1518)
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Keep blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

White opaque PVC/PE/Aclar – Aluminium blisters packs

1, 12, 14, 15, 20, 21, 30, 56 & 60 film-coated tablets. Hospital packs of 50 (50 x 1) film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/025/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th February 2008

Date of last renewal: 11th September 2010

10 DATE OF REVISION OF THE TEXT

November 2015