SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Famciclovir 250mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250mg of famciclovir.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.

White, round, coated tablet with 'FC' over "250" on one side and '>' 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

Posology

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	500 mg three times daily for 7 days
	40 to 59	500 mg twice daily for 7 days
	20 to 39	500 mg once daily for 7 days
	< 20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis during 7 days
Herpes zoster in immunocompromised adults		
500 mg three times daily for 10 days	≥ 60	500 mg three times daily for 10 days
	40 to 59	500 mg twice daily for 10 days
	20 to 39	500 mg once daily for 10 days
	< 20	250 mg once daily for 10 days
	Haemodialysis patients	250 mg following each dialysis during 10 days
Genital herpes in immunocompetent adults – first episode of genital herpes		
250 mg three times daily for 5 days	≥ 40	250 mg three times daily for 5 days
	20 to 39	250 mg twice daily for 5 days
	< 20	250 mg once daily for 5 days
	Haemodialysis patients	250 mg following each dialysis during 5 days
Genital herpes in immunocompetent adults – episodic treatment of recurrent genital herpes		
125 mg twice daily for 5 days	≥ 20	125 mg twice daily for 5 days
	< 20	125 mg once daily for 5 days
	Haemodialysis patients	125 mg following each dialysis during 5 days
Genital herpes in immunocompromised adults- episodic treatment of recurrent genital herpes		
500 mg twice daily for 7 days	≥40	500 mg twice daily for 7 days
	20 to 39	500 mg once daily for 7 days
	< 20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis during 7 days
Suppression of recurrent genital herpes in immunocompetent adults		
250 mg twice daily	≥40	250 mg twice daily

	20 to 39	125 mg twice daily
	< 20	125 mg once daily
	Haemodialysis patients	125 mg following each dialysis
Suppression of recurrent genital herpes in immunocompromised adults		
500 mg twice daily	≥40	500 mg twice daily
	20 to 39	500 mg once daily
	< 20	250 mg once daily
	Haemodialysis patients	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.

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.

Black patients
A placebo-controlled study in immunocompetent black patients with recurrent genital herpes showed no difference in efficacy between patients receiving famciclovir 1000 mg twice daily for one day and placebo. There were no unexpected or new safety finding 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 (125 mg twice daily for five days) or other indications in Black patients.

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 listed in section 6.1.
- 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. Raloxifen 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 raloxifen is co-administered with famciclovir the clinical efficacy of the antiviral therapy should be monitored.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
There are no data supporting any special recommendations in women of child-bearing potential.

Patients with genital herpes should be advised to avoid intercourse when symptoms are present even if treatment has been initiated. It is recommended that patients use safer sex practice (see section 4.4).

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 foetal 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.

Breast feeding
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 Tablets 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 postmarketing.

The pooled global placebo or active controlled clinical trials (n=2326 for Famciclovir arm) were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. 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 2) are ranked under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available data).

Table 2 Adverse reactions from clinical trials and post-marketing spontaneous reports

Blood and lymphatic system disorders	
Rare:	Thrombocytopenia.
Psychiatric disorders	
Uncommon:	Confusional state (predominantly in the elderly).
Rare:	Hallucinations.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
Uncommon:	Somnolence (predominantly in the elderly).
Not known:	Seizure*.
Cardiac disorders	
Rare:	Palpitations.
Gastrointestinal disorders	
Common:	Nausea, vomiting, abdominal pain, diarrhoea.
Hepatobiliary disorders	
Common:	Abnormal liver function tests.
Rare:	Cholestatic jaundice.
Immune system disorders	
Not known:	Anaphylactic shock*, anaphylactic reaction*.
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus.
Uncommon:	Angioedema (e.g. face oedema, eyelid oedema, periorbital oedema, pharyngeal oedema), urticaria.
Not known:	Serious skin reactions* (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis), Hypersensitivity vasculitis*.

*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”.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 dialyzable; and 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. Penciclovir triphosphate has an intracellular half-life of 10 hours in HSV-1-, 20 hours in HSV-2- and 7 hours in VZV-infected cells grown in culture. 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, penciclovir resistance is associated with mutations principally in the thymidine kinase (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
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 and safety
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. None 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.

Biotransformation 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.

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).

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 a 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.

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 mutations/chromosomal aberrations in human lymphocytes and in the L5178Y mouse lymphoma assay at concentrations at least 25-fold to 100-fold, respectively higher than the maximum concentration reached in human plasma after a single oral

famciclovir dose of 1500 mg. Penciclovir was negative in the bacterial Ames test and there was 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 corresponding to ≥ 810 times the maximum human dose based on body surface area conversion).

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 treated at doses up to 240 mg/kg/day (corresponding to a 38.4 mg/kg human equivalent dose or 1.3-fold of the highest recommended total daily dose of 1500 mg famciclovir or a patient of 50 kg body weight) or in mice of either sex at doses up to 600 mg/kg/day (corresponding to a 48 mg/kg human equivalent dose or 1.6-fold of the highest recommended total daily dose).

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 after 10 weeks of dosing at 500 mg/kg/day (corresponding to a 80 mg/kg human equivalent dose or 2.7-fold of the highest recommended total daily dose). Furthermore, testicular toxicity was 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 at doses up to 1000 mg/kg/day (corresponding to a 160 mg/kg human equivalent dose or 5.3-fold of the highest recommended total daily dose).

Embryofetal development studies showed no evidence of adverse effects at oral doses of famciclovir and intravenous doses of penciclovir corresponding to 0.7- to 5.3- fold of the highest recommended total daily dose of famciclovir.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sodium starch glycollate (Type A)

Microcrystalline cellulose

Hydroxypropylcellulose

Magnesium stearate

Tablet coat

Polyvinyl alcohol
Titanium dioxide (E-171)

Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/aluminium foil blisters containing 15, 21, 30 and 56 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

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