Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fenilabial 500mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg famciclovir

Excipient with known effect:
Each film-coated tablet contains 107.4 mg of lactose anhydrous.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, oval, film-coated tablet biconvex debossed with ‘FV’ on one side and ‘500’ on the reverse side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Herpes simplex virus (HSV) infections – herpes labialis
Fenilabial is indicated for the treatment of recurrent episodes of herpes labialis in immunocompetent adults. Clinical studies in immunocompromised patients with herpes labialis have not been conducted.

4.2 Posology and method of administration

Posology

For dose recommendations that are not possible with this product, other medicinal products should be used.

Herpes labialis in immunocompetent adults
1500 mg as a single dose for one day for the episodic treatment of recurrent herpes labialis. The minimum time interval between two treatments for acute recurrent herpes labials has not been defined.

Treatment should be initiated at the first sign (erythema) or symptoms (e.g. tingling, itching, burning, pain, or lesion) of a recurrent episode (see section 4.4).

Dosing in special populations:

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 labialis in		

immunocompetent adults		
	≥60	1500 mg single dose
	40 to 59	750 mg single dose
	20 to 39	500 mg single dose
	<20	250 mg single dose
	Haemodialysis patients	250 mg single dose following 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.

Method of administration
Fenilabial can be taken without regard to meals (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance (famciclovir) or to any of the excipients listed in section 6.1. Hypersensitivity to penciclovir (the active metabolite of famciclovir).

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
Fenilabial 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 in recurrent herpes labialis
Clinical efficacy data have not been presented for Fenilabial when administered more than 1 hour after onset of prodromal symptoms.

Transmission of herpes labialis
Fenilabial has not been shown to affect viral shedding or infectiousness in herpes labialis.

Information concerning excipients
Lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances during concurrent use, other treatments should be considered at any next episode of herpes labialis.

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

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). Fenilabial 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. Animal studies have indicated impaired fertility (see Section 5.3) in male rats given 500mg/kg/d. There were no significant effects on fertility in females rats given famciclovir.

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 Fenilabial should refrain from driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
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 Fenilabial 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 Fenilabial since its introduction to the market.

Tabulated summary of adverse reactions
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).

Description of selected adverse reactions

Table 2 Adverse reactions

Blood and lymphatic system disorders		
	Rare:	Thrombocytopenia.
Psychiatric disorders		
	Uncommon:	Confusional state (predominantly in elderly).
	Rare:	Hallucinations.
Nervous system disorders		
	Very common:	Headache.
	Common:	Dizziness.
	Uncommon:	Somnolence (predominantly in elderly).
Cardiac disorders		
	Rare	Palpitations
Gastrointestinal disorders		
	Common:	Nausea, vomiting, abdominal pain, diarrhoea
Hepatobiliary disorders		
	Common:	Abnormal liver function tests.
	Rare:	Cholestatic jaundice.
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)

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 national reporting system details listed below:

HPRA 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

Symptoms

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.

Management

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: JO5AB09

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 (VZV), 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 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 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
In a randomised controlled trial in immunocompetent adults with recurrent herpes labiales (at least 3 prior episodes) in which famciclovir was administered within 1hour of prodromi, one day treatment with a dose of 1500mg shortened the time to healing of herpes labialis lesions from 8.4 to 6.5 days compared to placebo. There was no reduction in the number of aborted lesions.

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

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 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.

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 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 did not induce gene mutation in bacterial or mammalian cell systems, nor was there 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 high 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).

Embyrofetal 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:
Lactose Anhydrous
Hydroxypropylcellulose
Sodium Starch Glycollate, type A
Magnesium Stearate

Tablet coat:
Hypromellose
Titanium Dioxide (E171)
Macrogol 4000
Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Fenilabial is supplied in PVC/PVdC/Aluminium blister packs containing 3 film-coated tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0678/141/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th May 2014

10 DATE OF REVISION OF THE TEXT

August 2016