Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Famlov 750 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 750mg of famciclovir.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.
White, capsule-shaped, coated tablet with 'FC 750" on one side and '>' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of herpes zoster (shingles) infections.

4.2 Posology and method of administration

Adults:

Herpes zoster (shingles) infections:

One 750 mg tablet once daily for seven days.

The tablets should be taken at approximately the same time each day.

Initiation of treatment is recommended as soon as possible after the onset of rash.

Elderly:
Dosage modification is not required unless renal function is impaired.

Children and adolescents (less than 18 years of age):
Famciclovir is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

Renally impaired:
As reduced renal function results in reduced clearance of penciclovir, special attention should be given to dosage in patients with impaired renal function (see section 4.9). The following dosage is recommended in renally impaired patients (for doses not realisable/practical with this medicinal product other strengths are available).

For the treatment of herpes zoster infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30-59	250 mg twice daily
10-29	250 mg once daily

When only serum creatinine is available, a nomogram or the following formula (Cockcroft and Gault) should be used to estimate creatinine clearance.

Formula to estimate creatinine clearance (ml/min/1.73 m^2):

$$\frac{[140 - \text{age in years}] \times \text{weight (kg)} \times \textbf{either } 88.5 \text{ (for males) } \textbf{or } 75.2 \text{ (for females)}}{72 \times \text{serum creatinine (µmol/l)}}$$

Renally impaired patients on haemodialysis:
A dose interval of 48 hours is recommended for haemodialysis patients for periods between dialysis. Since a four hour haemodialysis results in a 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis.

The recommended dose is one standard dose for first episode or recurrent genital herpes infections and for herpes zoster patients.

Hepatic Impairment:
Dosage modification is not required for patients with well compensated chronic liver disease. There is no information on patients with overtly decompensated chronic liver disease; accordingly no precise dose recommendations can be made for this group of patients.

Method of administration:
For oral administration.
Famciclovir can be administered with or without food.
The tablets should be taken with a sufficient amount of liquid.
Parenteral treatment is recommended for severely ill patients.

4.3 Contraindications

- Hypersensitivity to famciclovir, or any of the excipients.
- Hypersensitivity to penciclovir

4.4 Special warnings and precautions for use

Special attention should be paid to patients with impaired renal function as dosage adjustment may be necessary (see sections 4.2 and 4.9). No special precautions are required for hepatically impaired or elderly patients with normal renal function.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified. Probenecid and other drugs that affect renal physiology could affect plasma levels of penciclovir. Account must be taken of the possibility of interactions with substances eliminated by active tubular excretion such as acetylsalicylic acid and ibuprofen.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450. In a Phase I study, no interactions were observed after co-administration of zidovudine and famciclovir.

4.6 Pregnancy and lactation

Pregnancy
There is no adequate data from the use of famciclovir/penciclovir in pregnant women. Studies in animals have not shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Famciclovir should not be used during pregnancy unless the potential benefits of treatment for the mother outweigh any possible risk for the child.

Lactation
It is unknown whether famciclovir/penciclovir is excreted in human breast milk. Animal studies have shown excretion of famciclovir/penciclovir in breast milk. Famciclovir should not be used during breast-feeding.

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.

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

The following adverse effects can occur during treatment with famciclovir, classified in the following categories

Very common (≥1/10)
Common (≥ 1/100, <1/10)
Uncommon (≥ 1/1000, <1/100)
Rare (≥ 1/10000, <1/1000)
Very rare (< 1/10000).

Blood and lymphatic system disorders
Very rare: thrombocytopenia

Psychiatric disorders
Very rare: hallucinations

Nervous system disorders
Rare: headache, confusion (predominantly in the elderly)
Very rare: dizziness, somnolence (predominantly in the elderly)

Gastrointestinal disorders
Rare: nausea, diarrhoea, abdominal pain
Very rare: vomiting, dyspepsia

Hepato-biliary disorders
Rare: increased bilirubin and liver enzymes
Very rare: jaundice

Skin and subcutaneous tissue disorders
Very rare: serious skin reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme; pruritus, urticaria

Musculoskeletal, connective tissue and bone disorders
Very rare: myalgia, athralgia

Renal and urinary disorders
Rare: elevated serum calcium, changes in creatinine clearance
Very rare: a single report of haemolytic uraemic syndrome at high doses of famciclovir has been made in an immuno-compromised patient.

General disorders and administration site conditions
Rare: fatigue

4.9 Overdose

Overdose experience with famciclovir is limited. A report of accidental acute overdosage (10.5 g) was asymptomatic. In a report of chronic use (10 g/day for two years), famciclovir was well tolerated. 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 is dialysable and plasma concentrations are reduced by approximately 75% following four hours' haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Nucleosides and nucleotides excl. reverse transcriptaseinhibitors
ATC code: J05A B09

Famciclovir is a prodrug. After absorption, famciclovir is rapidly converted to penciclovir, which has demonstrable in vitro activity against herpes simplex (HSV) (types 1 and 2) and varicella zoster (VZV) viruses.

The antiviral effect of orally administered famciclovir has been demonstrated in several animal models, including various studies in HSV-infected mice. This effect is due to in vivo conversion to penciclovir. Penciclovir targets virus-infected cells, where it is rapidly and efficiently converted into the triphosphate by viral thymidine kinase (TK).

Penciclovir triphosphate persists in infected cells for more than 12 hours where it inhibits replication of viral DNA and has a half-life of 9, 10 and 20 hours in cells infected with varicella zoster, herpes simplex virus type 1 and herpes simplex virus type 2 respectively. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Accordingly, uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

The most common form of resistance encountered with aciclovir among HSV strains is a deficiency in the production of the TK enzyme. Such TK-deficient strains would be expected to be cross-resistant to both penciclovir and aciclovir.

Results from penciclovir and famciclovir clinical trials, including studies in which patients were treated with famciclovir for up to four months, 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 during or after treatment with famciclovir or penciclovir.

As has been found with all other antiretroviral agents, it can be anticipated that resistance will develop in some patients receiving long-term treatment. However, the frequency at which this occurs has not yet been established.

The effects of famciclovir on directly virus-related parameters such as virus spread and skin lesions have been demonstrated in clinical trials.

5.2 Pharmacokinetic properties

Following oral administration, famciclovir is rapidly absorbed and extensively converted, penciclovir. The bioavailability of penciclovir after oral administration of famciclovir is 77%.

Mean peak plasma concentrations of penciclovir, following 125 mg, 250 mg and 500 mg oral doses of famciclovir, were 0.8 micrograms/ml, 1.6 micrograms/ml and 3.3 micrograms/ml, respectively, and occurred at a mean time of 45 minutes post-dose. Slight passage of the metabolites across the blood-brain barrier was observed in rats. Penciclovir clearance is reduced in patients with renal impairment. The bioavailability of penciclovir is unaffected by hepatic impairment, but the mean peak plasma level is diminished. Ingestion with food leads to lower mean peak penciclovir concentrations, without effect on its bioavailability.

Plasma concentration-time curves of penciclovir are similar following single and repeat (two or three times daily) dosing. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir is approximately 2 hours. There is no accumulation of penciclovir on repeated dosing with famciclovir. Penciclovir and its 6-deoxy precursor are poorly (<20%) bound to plasma proteins.

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

Characteristics in patients
Uncomplicated herpes zoster infection does not significantly alter the pharmacokinetic parameters of penciclovir measured after oral administration of famciclovir.

5.3 Preclinical safety data

Carcinogenicity
In 2-year studies in female rats receiving the maximum tolerated dose (600 mg/kg/day), an increased incidence of mammary adenocarcinoma was observed, a common tumour in the strain of rats used in these studies.

No effect on tumour incidence was found with a dose 3 times lower (200 mg/kg/day), which corresponds to 3 times the exposure achieved in humans receiving a therapeutic dose (250 mg twice daily).

There was no effect on the incidence of neoplasia in male rats or in mice of either sex.
Although the relevance of these findings to humans is unknown, the safety margin is very narrow. Furthermore, the long-term use of famciclovir is not recommended.

Genotoxicity
Famciclovir was not found to be genotoxic in a comprehensive battery of in vivo and in vitro tests.
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.

Reproductive toxicity
Famciclovir is well tolerated in laboratory animals. In common with other substances of this class, degenerative changes of the testicular epithelium were noted.

In animal studies, impaired fertility was observed in male rats receiving 500 mg/kg. There were no significant effects on fertility in female rats given famciclovir. Famciclovir has been shown not to have any significant effects on sperm count, morphology or motility in man.

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 1 and 7 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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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8 MARKETING AUTHORISATION NUMBER

PA1130/13/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th October 2008

10 DATE OF REVISION OF THE TEXT