IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0013/106/004
Case No: 2042380

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, **Frimley**, **Camberley**, **Surrey, GU16 7SR**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Famvir 750 mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/06/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Famvir 750 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is famciclovir.
Each tablet contains famciclovir 750 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, oval film-coated tablet, biconvex, bevelled edges, debossed with “FAMVIR 750” on one side and plain on the reverse side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

‘Famvir’ is indicated for the treatment of herpes zoster (shingles) infection.

4.2 Posology and method of administration

Dosage:

Adults:
Oral administration, one 750 mg tablet once a day for seven days. The tablets should be taken at approximately the same time each day. Treatment should be initiated as early as possible in the course of the disease, promptly after diagnosis.

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

Renally impaired:
As reduced clearance of penciclovir is related to reduced function, as measured by creatinine clearance, special attention should be given to dosages in patients with impaired renal function. (See section 4.9) The following modifications in dosage are recommended.

For the treatment of herpes zoster infections:

Creatinine clearance (ml/min/1.73m2)	**Dosage**
30	750 mg O.D. or 250mg T.I.D.
10-29	250 mg O.D. or 125mg T.I.D.

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

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

[140 – age in years] x weight (kg) x ***either*** *88.5 (for males)* ***or*** *75.2 (for females)* *72 x serum creatinine (micromol/l)*

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

Hepatically impaired*:*
Dosage modification is not required.

Children:
There are currently insufficient data on the safety and efficacy of 'Famvir' in children.

Administration:
Oral.

4.3 Contraindications

'Famvir' is contra-indicated in patients with known hypersensitivity to famciclovir or other constituents of 'Famvir'. It is also contra-indicated in those patients who have shown hypersensitivity to penciclovir.

4.4 Special warnings and precautions for use

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

4.6 Pregnancy and lactation

Pregnancy:

Although animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir, the safety of Famvir in human pregnancy has not been established. Famvir should, therefore, not be used during pregnancy or in nursing mothers unless the potential benefits of treatment outweigh any possible risk.

Lactation:

Studies in rats show that penciclovir is excreted in the breast milk of lactating females given oral famciclovir. There is no information on excretion in human milk.

4.7 Effects on ability to drive and use machines

There is no evidence that famciclovir (Famvir) 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 Famvir should refrain from driving or operating machinery.

4.8 Undesirable effects

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

The following table specifies the estimated frequency of adverse reaction based on all the spontaneous reports and literature cases that have been reported for Famvir 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), including isolated reports.

Table 1

Blood and lymphatic system disorders Very rare:	 Thrombocytopenia.
Psychiatric disorders Rare: Very rare:	 Confusion (predominantly in the elderly). Hallucinations.
Nervous system disorders Rare: Very rare:	 Headache. Dizziness, somnolence (predominantly in the elderly).
Gastrointestinal disorders Rare: Very rare:	 Nausea. Vomiting.
Hepatobiliary disorders Very rare:	 Jaundice.
Skin and subcutaneous tissue disorders Very rare:	 Rash, pruritus, urticaria, serious skin reactions (e.g. erythema multiforme).

Famciclovir has also been well tolerated in immunocompromised patients. Undesirable effects reported from clinical studies were similar to those reported in the immunocompetent population.

4.9 Overdose

Overdosage 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, symptomatic and supportive therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir (Famvir) dosage has not been appropriately reduced for the level of renal function. Penciclovir is dialysable and plasma concentrations are reduced by approximatel 75% following four hours' haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral antiviral agent (ATC code: JO5A B09).

Famciclovir is the oral form of penciclovir, converted in the body to this active antiviral moiety. Famciclovir is rapidly converted *in vivo* into penciclovir, which has demonstrable *in vivo* activity against *Herpes simplex* viruses (type 1 and 2) and the *Varicella zoster* virus. 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 and efficiently converted into the triphosphate (mediated via virus-induced thymidine kinase). Penciclovir triphosphate persists in infected cells for more than 12 hours where it inhibits replication of the viral DNA. 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.

5.2 Pharmacokinetic properties

General characteristics
Following oral administration, famciclovir is rapidly and extensively absorbed and rapidly converted to the active compound, penciclovir. Bioavailability of penciclovir after oral Famvir is 77%. Mean peak plasma concentration of penciclovir, following a 750 mg oral dose of famciclovir, was 4.9 micrograms/ml and occurred at a median time of 50 minutes post-dose. Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d.) dosing.

The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir is approximately 2.0 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 is excreted in urine unchanged. ‘Famvir’ has not been 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 pharmacokinetics of penciclovir measured after oral administration of ‘Famvir’.

5.3 Preclinical safety data

Carcinogenicity
In 2 year studies there were no changes seen at 200 mg/kg/d. At the maximally tolerated dose of 600 mg/kg/d in female rats there was an increased incidence of mammary adenocardinoma, a common tumour in this strain of rats used in the studies. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

Genotoxicity
Additionally 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 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*.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hydroxypropyl Cellulose
Magnesium Stearate (E572)

Sodium Starch Glycollate

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

White, opaque, PVC/PVdC/Aluminium foil blister packs containing 1 or 7 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley, Camberley
Surrey, GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 13/106/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 1996

Date of last renewal: 30 June 2009

10 DATE OF REVISION OF THE TEXT

July 2009