IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0577/109/001
Case No: 2051809

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

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, **Grange Road**, **Dublin 13**, **Ireland**

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

Myclovear 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 **17/07/2009** until **16/07/2014**.

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

Myclovear 750 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Myclovear 750 mg tablet contains 750 mg of famciclovir.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oval, film-coated tablets with dimensions of 20.5 x 9.8 mm approximately.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of genital herpes infections (initial and recurrent epidoses) in immunocompetent patients.
- Treatment of herpes zoster infections of the skin and mucous membranes in immunocompetent patients in whom a severe course of infection is anticipated,including herpes zoster ophthalmicus.
- Treatment of herpes zoster and herpes simplex infections in immunocompromised patients.

4.2 Posology and method of administration

Adults

First-episode genital herpes infections:
250 mg three times daily for 5 days
The first dose should be taken as soon as possible after the onset of the infection.

Recurrent genital herpes infections:
250 mg twice daily for 5 days
Initiation of treatment is recommended during the prodromal period or as soon as possible after the onset of lesions.

Suppression of genital herpes infections in immunocompetent patients:
250 mg twice daily. The duration of treatment depends on the severity of the disease.
Therapy should be interrupted periodically at intervals of 6 to 12 months in order to observe possible changes in the natural history of the disease. The long-term use of famciclovir is not recommended.
A dose of 500 mg twice daily has been shown to be effective in HIV patients (see section 5.1).

Herpes zoster infections, including herpes zoster ophthalmicus in immunocompetent patients:
500 mg three times daily for 7 days or 750 mg twice daily* for 7 days.
Initiation of treatment is generally recommended as soon as possible (within 48 hours) of the onset of rash.

** Only relevant for the 750 mg strength*

Herpes zoster infections in immunocompromised patients:
500 mg three times daily for 10 days
Initiation of treatment is generally recommended as soon as possible (within 48 hours) of the onset of rash.

Herpes simplex infections in immunocompromised patients:
500 mg twice daily for 7 days.
Initiation of treatment is recommended as soon as possible after the onset of lesions.

Elderly

Dosage modification is not required, unless renal function is impaired.

Children

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

Renally impaired patients

Special attention should be given to dosage in patients with impaired renal function, as reduced clearance of penciclovir is related to impaired renal function measured in relation to creatinine clearance (see section 4.9). The following dosage is recommended in renally impaired patients:

Immunocompetent patients

For the treatment of herpes zoster or first-episode genital herpes infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30-59	250 mg once daily
10-29	125 mg once daily

For the treatment of acute recurrent genital herpes infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30-59	250 mg once daily
10-29	125 mg once daily

For the suppression of recurrent genital herpes infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
≥ 30	No adjustment
10-29	125 mg twice daily

Immunocompromised patients

For the treatment of herpes zoster infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30-59	250 mg twice daily
10-29	125 mg once daily

For the treatment of herpes simplex infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30-59	250 mg twice daily
10-29	125 mg twice 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):

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

Renally impaired patients on haemodialysis
A dose interval of 48 hours is recommended for haemodialysis patients for periods between dialysis. Famciclovir must be administered immediately after dialysis, as 4 hours of haemodialysis reduce the plasma penciclovir concentration by approximately 75%.
The recommended dose is one standard dose for first episode or recurrent genital herpes infections and for herpes zoster patients.

Hepatically impaired patients
Dosage modification is not required for patients with well compensated chronic liver disease. No data are available on patients with 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.
Parenteral treatment is recommended for severely ill patients.

4.3 Contraindications

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

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.

Genital herpes is a sexually transmitted disease. Patients should avoid sexual intercourse when symptoms are present even if treatment with an antiviral has been initiated, in order to protect their partners.

During treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still theoretically possible. Patients should therefore take appropriate steps for protected intercourse (i.e. use condoms).

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified. Probenecid and other substances that affect renal physiology could affect the plasma levels of penciclovir. Account must be taken of the possibility of interactions with substances eliminated by active tubular excretion such as acetylsalicylic acid, 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 Myclovear should refrain from driving or operating machinery.

4.8 Undesirable effects

The adverse reactions reported are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Thrombocytopenia	
Nervous system disorders	Headache		Dizziness, fatigue, somnolence (predominantly in the elderly)	
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, abdominal pain, constipation			
Skin and subcutaneous tissue disorders	Increased tendency to sweat, pruritus		Serious skin reactions, e.g. erythema multiforme, Stevens-Johnson’s syndrome, and toxic epidermal necrolysis; rash, urticaria	
General disorders and administration site conditions				Fever
Hepatobiliary disorders			Jaundice, abnormal liver function tests	

Psychiatric disorders		Confusion (predominantly in the elderly)	Hallucinations	

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 4 hours of haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excl. reverse transcriptase inhibitors, 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) and *Epstein-Barr* (EBV) viruses. The drug exhibits only limited activity *in vitro* against *cytomegalovirus*.

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.

A placebo-controlled study in patients with immunodeficiency due to HIV has shown that famciclovir 500 mg twice daily significantly reduced the number of days with both symptomatic and asymptomatic HSV (herpes simplex virus) secretion.

In a large clinical study famciclovir proved to be effective and have good tolerance in the treatment of ophthalmic zoster.

5.2 Pharmacokinetic properties

Following oral administration, famciclovir is rapidly absorbed and extensively converted to 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. No unchanged famciclovir can be detected in urine. Tubular secretion contributes to the renal elimination.

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:
Starch Pregelatinised

Sodium Laurilsulfate
Cellulose, Microcrystalline
Croscarmellose Sodium
Silica Colloidal Anhydrous
Stearic acid

Film-coating:
Hypromellose (E464)
Titanium Dioxide (E171)
Macrogol 4000
Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Tablets are provided in blister packs (PVC/PE/PVDC / Aluminium blisters)

Pack sizes: 7 tablets

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 577/109/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th July 2009

10 DATE OF REVISION OF THE TEXT