CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Famciclovir 125 PCH, film-coated tablets, 125 mg
Famciclovir 250 PCH, film-coated tablets, 250 mg
Famciclovir 500 PCH, film-coated tablets, 500 mg
Pharmachemie B.V., the Netherlands

famciclovir

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/868/01-03/DC
Registration number in the Netherlands: RVG 34066, 34067, 34068

Date of first publication: 4 August 2008
Date of last revision: 23 September 2010

Pharmacotherapeutic group:	direct acting antivirals, nucleosided and nucleotides excluding reverse transcriptase inhibitors.
ATC code:	J05A B09
Route of administration:	oral
Therapeutic indication:	treatment and suppression of genital herpes infections in immunocompetent patients, treatment of herpes zoster infections in immunocompetent patients, and treatment of herpes zoster and herpes simplex in immunocompomised patients.
Prescription status:	prescription only
Date of authorisation in NL:	11 July 2008
Concerned Member States:	AT, EE, IT, LT, LV, UK (all strengths); ES, IE (not for 500 mg); CZ, SK, PT (not for 125 mg).
Withdrawals:	All strengths in ES (10-7-2009), LV (22-12-2008), LT (6-8-2009) 250 mg and 500 mg in CZ (17-2-2010) and PT (9-2-2007)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Famciclovir 125 PCH, 125 mg film-coated tablets, Famciclovir 250 PCH, 250 mg film-coated tablets and Famciclovir 500 PCH, 500 mg film-coated tablets from Pharmachemie B.V., the Netherlands. The first date of authorisation was on 11 July 2008 in the Netherlands.

The product is indicated for:
- Treatment of genital herpes infections (initial and recurrent episodes) in immunocompetent patients.
- Suppression of recurrent genital herpes infections 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.

A comprehensive description of the indications and posology is given in the SPC.

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. Penciclovir is phosphorylated to the triphosphate form by viral and host kinases and inhibit viral DNA polymerase by competing with deoxyguanosine triphosphate. In addition, they are incorporated into the nascent viral DNA chain and cause chain termination. Penciclovir triphosphate persists in infected cells for more than 12 hours where it inhibits viral DNA synthesis and, therefore, replication of viral DNA. It 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.

This application concerns a generic application claiming essential similarity with the innovator products Famvir® (NL License RVG 18397, 16989 and 19072), containing 125 mg, 250 mg and 500 mg famciclovir respectively, which have been registered in the Netherlands by Novartis since 1995. In addition, reference is made to Famvir authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the British reference product Famvir, registered in the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance famciclovir, is an established active substance and a white to pale yellow powder. Famciclovir is not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Quality control of drug substance
The active substance is based on in-house specifications and includes tests for appearance, identification, heavy metals, sulphated ash, loss on drying, water content, assay, related substances, residual solvents, particle size and bulk density. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 9 production batches. The MAH committed that process validation of the active substance will be completed prior to product launch.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 24 months. Based on the data submitted, a retest period was granted of 30 months when stored below 25°C.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Famciclovir 125 PCH film-coated tablets contain as active substance 125 mg famciclovir and are white to off-white, round, film-coated tablets, engraved 8117 on one side and 93 on the other side.
Famciclovir 250 PCH film-coated tablets contain as active substance 250 mg famciclovir and are white to off-white, round, film-coated tablets, engraved 8118 on one side and 93 on the other side.
Famciclovir 500 PCH film-coated tablets contain as active substance 500 mg famciclovir and are white capsule shaped film-coated tablets, engraved 93 on one side and 8119 on the other side.

The tablets are packed in white opaque PVC/PE/Aclar – Aluminium blisters packs.

The excipients are
Core - microcrystalline cellulose E460, colloidal anhydrous silica E551, sodium starch glycolate (Type A), low-substituted hydroxypropylcellulose, croscarmellose sodium, sodium stearyl fumarate.
Film coating - titanium dioxide E171, polydextrose E1200, hypromellose E464, triacetin E1518, macrogol 8000.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Excipients
The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for low-substituted hydroxypropylcellulose for which reference is made to the Pharmacopoeia in the United States (USP) and for microcrystalline cellulose E460, colloidal anhydrous silica E551 and polydextrose E1200 for which reference is made to in-house specifications.

Manufacturing process and quality control of the medicinal product
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation. The MAH committed to perform full-scale validation of the drug product production process on the first three batches of each strength.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on Ph.Eur. and in-house specifications and includes tests for appearance, hardness, friability, disintegration time, identification, assay, dissolution rate, uniformity of dosage units, microbiological purity and related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 6 pilot-scale batches from the proposed production site(s) has been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 2 pilot-scale batches of the 125 mg tablet, and 1 pilot-scale batch of both the 250 and 500 mg tablet in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. The labelled storage conditions are: *"Keep blister in the outer carton in order to protect from light"*. The MAH committed to perform drug product stability studies on three commercial scale batches of each strength. The MAH committed to conduct stability studies on one batch of 125 mg at room temperature up to 6 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

These products are generic formulations of Famvir, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of famciclovir released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Famciclovir is a well known active substance with established efficacy and tolerability.

During the decentralised procedure a discussion was held regarding the proposed indications for Famcicolovir PCH, since the indication *"The suppression of recurrent genital herpes infections"* and was not approved in all member states for the reference product (Famvir). The member states decided to approve the indication "*the suppression of recurrent genital herpes infections*" and to await the final SPC for Famvir. Famvir has been listed for article 30 referral (harmonisation of the SPC). The MAH committed to update the SPC in line with the SPC for Famvir once it has been harmonised.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Famciclovir 250 PCH is compared with the pharmacokinetic profile of the reference product Famvir 250 mg. Both products contain 250 mg famciclovir.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

Bioequivalence study
A single-dose, 2-way cross-over bioequivalence study was carried out under fasted conditions in 32 healthy subjects (13 males and 19 females), aged 18-51 years. For each subject there were 2 dosing periods of one of the 250 mg famciclovir formulations (500 mg; 2x250 mg tablets), separated by a washout period of 7 days. The tablets were orally administered with 240 ml water after an overnight fast for at least 10 hours. In total 18 blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 16 hours after administration of the products.

The bioavailability of the test product Famciclovir 250 PCH film-coated tablets was compared to the British reference product Famvir 250 mg tablets. The MAH used the metabolite penciclovir as analyte for proof of bioequivalence. This is considered acceptable, as famciclovir acts as a pro-drug, and famciclovir plasma concentrations are negligible. After absorption, famciclovir is rapidly converted to penciclovir.

Famciclovir should be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of famciclovir. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results
One subject withdrew from the study due to adverse events. Thirty-one subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of penciclovir under fasted conditions

Treatment N=31	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	10129 ± 1788	10242 ± 1799	3997 ± 1057	0.86 ± 0.41	2.4 ± 0.4
Reference	10158 ± 1724	10271 ± 1727	4046 ± 863	0.77 ± 0.25	2.3 ± 0.4
***Ratio (90% CI)**	1.00 (0.96-1.03)	0.97 (0.96-1.03)	0.97 (0.89-1.06)	---	---
CV (%)	7.8	7.8	20.5	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of penciclovir under fasted conditions, it can be concluded that Famciclovir 250 PCH film-coated tablets and Famvir 250 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The 250 mg tablets are dose proportional with the 125 and 500 mg tablets. The pharmacokinetics of the active substance are linear in the range 125-500 mg. The results of the bioequivalence study performed with the 250 mg tablets therefore apply to the other strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management Plan
Famciclovir was approved for the first time in 1993, i.e. there is more than 10 years post-authorisation experience with this active substance. The safety profile of famciclovir can be considered well established. No product specific pharmacovigilance issues were identified pre- or post authorisation that are not adequately covered by the current SPC. Additional risk minimization activities have not been identified with the reference medicinal product. The applicant has a pharmacovigilance system at its disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not considered necessary for this product.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with in total 20 participants.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Famciclovir 125 PCH film-coated tablets, Famciclovir 250 PCH film-coated tablets and Famciclovir 500 film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Famvir, 125, 250 and 500 mg tablets. Famvir is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is in line with that of the reference product. However, the indication *"Suppression of recurrent genital herpes infections in immunocompetent patients"* has not been approved in all member states. The innovator product Famvir has been listed for article 30 referral (harmonisation of the SPC). The MAH committed to update the SPC in line with the SPC for Famvir once it has been harmonised.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Famciclovir 125 PCH, Famciclovir 250 PCH and Famciclovir 500 PCH were authorised in the Netherlands on 11 July 2008. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Famciclovir 125 PCH, Famciclovir 250 PCH and Famciclovir 500 PCH with the reference products, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

A European harmonised birth date has been allocated (10 December 1993) and subsequently the first data lock point for famciclovir is December 2006. The first PSUR is therefore expected in December 2009, after which a PSUR should be submitted every 3 years.

The date for the first renewal will be 1 September 2010.

The following post-approval commitments have been made during the procedure:

Quality – Active substance
- The MAH committed that process validation of the active substance will be completed prior to product launch.

Quality – Medicinal product
- The MAH committed to perform full-scale validation of the drug product production process on the first three batches of each strength.
- The MAH committed to perform drug product stability studies on three commercial scale batches of each strength.
- The MAH committed to conduct bulk stability studies on one commercial batch of 125 mg at room temperature up to 6 months.

Clinical – Medicinal product
- The MAH committed to update the SPC in line with the SPC for Famvir once it has been harmonised. Famvir has been listed for article 30 referral (harmonisation of the SPC).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of the marketing authorisation holder in AT, EE, IE, LT, and LV.	NL/H/868/ 001-003/ IA/001	IA	14-1-2008	28-1-2008	Approval	N
Change in the name and/or address of the marketing authorisation holder in IT.	NL/H/868/ 001-003/ IA/002	IA	11-3-2008	25-3-2008	Approval	N
Withdrawal of the marketing authorisation in LV.	NL/H/868/ 001-003/ MR	Withdrawal	---	22-12-2008	---	N
Withdrawal of the marketing authorisation in ES.	NL/H/868/ 001-003/ MR	Withdrawal	---	10-7-2009	---	N
Withdrawal of the marketing authorisation in LT.	NL/H/868/ 001-003/ MR	Withdrawal	---	6-8-2009	---	N
Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance. Addition of a new test parameter to the specification of an active substance.	NL/H/868/ 001-003/ IB/003	IB	20-7-2009	19-8-2009	Approval	N
Submission of a new version of the DMF.	NL/H/868/ 001-003/ II/004	II	18-8-2009	1-9-2009	Approval	N
Change in batch size of the active substance or intermediate. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/868/ 002-003/ IA/005	IA	14-9-2009	28-9-2009	Approval	N
Change in batch size of the finished product. Downscaling down to 10-fold.	NL/H/868/ 001/IA/006	IA	14-9-2009	28-9-2009	Approval	N
Withdrawal of the marketing authorisation in CZ.	NL/H/868/ 002/MR	Withdrawal	---	17-2-2010	---	N