Public Assessment Report

Scientific discussion

Famciclovir "Sandoz"
125 mg and 500 mg film-coated tablets

Famciclovir

DK/H/1678/001-002/DC

This module reflects the scientific discussion for the approval of Famciclovir "Sandoz". The procedure was finalised on 13 May 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Famciclovir "Sandoz" 125 mg and 500 mg film-coated tablets, from Sandoz B.V. The product was authorised in Denmark on 12 August 2009. The product is indicated for:

- Treatment of genital herpes infections (initial and recurrent epidoses) 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.

Famciclovir is a well-known antiviral for systemic use. It is a prodrug of penciclovir, which is an inhibitor of viral DNA polymerase being a specific inhibitor of the herpes viruses.
According to the indication in question the posology varies in dose and duration.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Famvir 125 mg and 500 mg film-coated tablets marketed in Denmark by Novartis Healthcare and registered since 1995 and 1997, respectively. The reference products used for the BE study is Oravir 500 mg film-coated tablets from Novartis Pharma S.A.S. (France) from the French market.

The marketing authorisation is granted based on article 10.1 (generic application) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each 125 mg and 500 mg tablet contains 125 mg and 500 mg of famciclovir, respectively.

The 125 mg tablets are white, round, biconvex, film-coated tablets with diameter of 7.6 mm approximately.
The 500 mg tablets are white, oval, film-coated tablets, scored on both sides with dimensions of 18.2 x 8.6 mm approximately.
The 500 mg film-coated tablets can be divided into equal halves.

The tablets are provided in blister packs (PVC/PE/PVDC / Aluminium blisters) in various pack sizes.

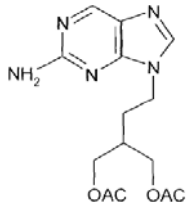
The excipients in the tablet core are: Starch pregelatinised; sodium laurilsulfate; cellulose, microcrystalline; croscarmellose sodium; silica colloidal anhydrous and stearic acid.
The film-coating consists of: Hypromellose (E464); titanium dioxide (E171); macrogol 4000 and macrogol 6000.

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type 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.

II.2 Drug Substance

INN: Famciclovir
Chemical name: 9-[4-acetoxy-3-(acetoxymethy1)but- 1 -yl]-2- aminopurine
Chemical abstract name: 2-[2-(2-Amino-9H-purin-9-yl)ethyl]- 1,3-propanediol diacetate
Molecular formula: $C_{14}H_{19}N_5O_4$
Molecular mass: 321.33 g/mol

Molecular structure:



Famciclovir is an offwhite to pale yellow crystalline powder. It is soluble in water, methanol and chloroform, slightly soluble in ethyl acetate and insoluble in ether.
Famciclovir exhibits polymorphism. Three forms (I, II, III) are reported in the literature references.

The documentation on the active substance famciclovir is presented as a European Drug Master File/Active Substance Master File (DMF). The chemical-pharmaceutical documentation in relation to famciclovir is of sufficient quality in view of the present European regulatory requirements. A detailed description of the synthesis, from simple starting materials, is provided and an evaluation on possible impurities is presented.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Based on the data submitted an appropriate retest period has been set.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up.
A shelf-life of 24 months with the storage precaution “do not store above 30°C” for the drug product is accepted. The additional storage statement “store in original package in order to protect from moisture” is also applied.

III. NON-CLINICAL ASPECTS

This product is a version 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

For this generic application, the MAH has submitted one bioequivalence study (single-dose, 2-way crossover, under fasting conditions) in which the pharmacokinetic profile of the test product Famciclovir "Sandoz" 500 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Oravir 500 mg film-coated tablets from the French market.
Biowaiver for the 125 mg strength has been adequately justified.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 500 mg was administered in each period.
Blood samples were collected pre-dosing and at various time points post administration of a single-dose 500 mg film-coated tablet with 240 ml of water for the analyses of penciclovir.

28 healthy Caucasian subjects (one American Hispanic, 18 females and 10 males, 20-53 years) participated in the study. 26 subjects completed the study.

The pharmacokinetic parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, Residual area, t_{max}, K_{el} and $t_{½\ el}$. Primary variables were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

90% confidence intervals of the ratio (test/reference) of least-squares means for ln-transformed AUC_{0-t} and C_{max} should be within 80% and 125% in order to conclude bioequivalence.

Results

SUMMARY OF RESULTS
PENCICLOVIR
N = 26

Pharmacokinetic Parameters

Parameters		Test (Famciclovir (A)) Mean	SD	CV (%)	Reference (Oravir (B)) Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	10515.49	2157.95	20.52	10379.38	2167.52	20.88
AUC_{0-inf}	(ng·h/mL)	10772.21	2197.69	20.40	10636.06	2200.87	20.69
C_{max}	(ng/mL)	3609.33	992.14	27.49	3745.10	1153.52	30.80
Residual Area	(%)	2.41	0.96	39.86	2.45	0.94	38.35
T_{max}	(h)	1.02	0.42	40.67	0.956	0.418	43.71
T_{max}^{*}	(h)	0.833	0.479	-	0.833	0.333	-
K_{el}	(h^{-1})	0.3422	0.0554	16.18	0.3303	0.0446	13.51
$T_{½ el}$	(h)	2.08	0.33	15.96	2.14	0.29	13.65

*Medians and interquartile ranges are also presented.

Famciclovir (A) vs Oravir (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.36%	101.32%	97.77%
90 % Geometric C.I.[2]	98.91 % to 103.88 %	98.95 % to 103.75 %	89.38 % to 106.95 %
Intra-Subject CV	5.15 %	4.99 %	19.02 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Famciclovir (A) - Oravir (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data

Bioequivalence between the test and reference product was demonstrated since the 90% confidence intervals for the log-transformed AUC_{0-t} and C_{max} were within the acceptance range of 80-125% (98.91-103.88% and 89.38-106.95%, respectively).

The results of the study with the 500 mg formulation can be extrapolated to the other strength 125 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

The RMS 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).

IV.2 Risk management plan & Pharmacovigilance system

Famciclovir was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of famciclovir can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet
The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Famvir marketed by Novartis Healthcare.

The applicants has made a commitment to submit a post-approval type II variation to harmonise the SmPC and package leaflet of the procedure according to the originator's texts, which are currently under an Article 30 Referral procedure, once this is completed.

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 language used for the purpose of user testing the package leaflet was English. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Famciclovir "Sandoz" 125 mg and 500 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a version of Famvir. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other famciclovir containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Famciclovir "Sandoz" with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 13 May 2009. Famciclovir "Sandoz" was authorised in Denmark on 12 August 2009.

A European harmonised birth date has been allocated (1993-12-10) and subsequently the first data lock point for famciclovir is 2009-12. The first PSUR be submitted with a DLP of 2009-12, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 13 May 2014.

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

Drug Substance
- The ASM commits to monitor the first 10 batches during commercial production for genotoxic impurities and will update the authorities with the results.
- Subsequently, one batch every year will be analyzed for genotoxic impurities.

- The ASM commits to continue the studies as per protocol and also add one batch every year. Updating will be sent to authorities on yearly basis or as and when required.

Drug product

- The stability studies of the production scale batches will be continued as stated in the stability protocol, as presented in section 3.2.P.8.1. In addition, at least one production batch of each strength per year will be placed on long-term stability, as per GMP guidelines.

- The applicant will submit 24 months of stability data when available.

SPC and package leaflet

- The applicants has made a commitment to submit a post-approval type II variation to harmonise the SPC and PL of the procedures according to the originator's texts, which are currently under an Article 30 Referral procedure, once this is completed.