COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Valaciclovir 1000 mg Focus, film-coated tablets (valaciclovir hydrochloride hydrate)

NL License RVG: 125516

Date: 24 February 2022

This module reflects the scientific discussion for the approval of Valaciclovir 1000 mg Focus, film-coated tablets. The marketing authorisation was granted on 16 March 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMV	Cytomegalovirus
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
HSV	Herpes simplex virus
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VZV	Varicella zoster virus

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Valaciclovir 1000 mg Focus, film-coated tablets, from Focus Care Pharmaceuticals B.V.

The product is indicated for:

Varicella zoster virus (VZV) infections – herpes zoster
Valaciclovir Focus is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (see section 4.4 of the SmPC).

Valaciclovir Focus is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression (see section 4.4 of the SmPC).

Herpes simplex virus (HSV) infections
Valaciclovir Focus is indicated for:

- the treatment and suppression of HSV infections of the skin and mucous membranes, including
  - treatment of first-episode of genital herpes in immunocompetent adults and adolescents and in immunocompromised adults.
  - treatment of recurrent genital herpes in immunocompetent adults and adolescents and in immunocompromised adults.
  - suppression of recurrent genital herpes in in immunocompetent adults and adolescents and in immunocompromised adults.
- the treatment and suppression of recurrent ocular HSV infections in immunocompetent adults and adolescents and in immunocompromised adults (see section 4.4 of the SmPC).

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1 of the SmPC).

Cytomegalovirus (CMV) infections
Valaciclovir Focus is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents (see section 4.4 of the SmPC).

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Zelitrex 500 mg, film-coated tablet which has been registered by GlaxoSmithKline B.V. since 11-12-1995 via a mutual recognition procedure (SE/H/1041/002). The reference product used in the bioequivalence study is Valtrex 1000 mg, film coated tablet authorised by GlaxoSmithKline B.V. (SE/H/1041/003).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product is a biconvex, oblong, white, film-coated tablet. The tablet contains as active substance valaciclovir hydrochloride hydrate equivalent to 1000 mg valaciclovir. The film-coated tablets are packed in PVC-PVdC-PVC/Alu blisters.

The excipients are:
Tablet core – povidone (E1201), pregelatinised starch, crospovidone (E1202), colloidal anhydrous silica (E551) and magnesium stearate (E470b).
Film-coating (Opadry YS-1-18043) – titanium dioxide (E171), hypromellose 6cP/3cP, polyethylene glycol 400 (E1521) and polysorbate 80.

The excipients and packaging are common for this type of dosage form.

II.2 Drug Substance

The active substance is valaciclovir hydrochloride hydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white crystalline powder. Valaciclovir hydrochloride is freely soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in acetonitrile. Valaciclovir has two enantiomers for which control is adopted. Polymorphism has been adequately discussed. Valaciclovir hydrochloride manufactured by the active substance manufacturer is the hydrate form.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification and methods are in line with the Ph. Eur. monograph, with additional tests as per CEP and for palladium, microbial contamination and particle size.

The additional methods have been adequately described and validated. Provided batch results show compliance to the specification. The specification is acceptable.

Stability of drug substance

The re-test period of the substance is three years when stored in double polyethylene bags with desiccant bags in between, in a triple laminated bag (polyethylene /aluminium/polyethylene) placed in a polyethylene container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Suitability of the product for the paediatric population has been adequately discussed. Manufacturing development as presented is sufficient.

The MAH performed a bioequivalence study, which will be discussed in section IV on clinical aspects. Complementary to the bioequivalence study, comparative dissolution studies were performed at three pHs. For all three dissolution media the similarity factor was calculated, and did not demonstrate bioequivalence as demonstrated *in vivo*. However, in the event that the results of comparative *in vitro* dissolution of the bio-batches do not reflect bioequivalence as demonstrated *in vivo*, the latter prevails.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The description of the manufacturing process is provided including details and process parameters and a flow chart is provided. Critical steps are identified and adequately controlled. Holding time of bulk tablets and the container closure applied are provided. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

Compliance to the Ph.Eur is stated as relevant, additional information in relation to functional related characteristics is provided. The specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specification includes tests for appearance, identification, water content, average mass and uniformity of mass, resistance to crushing of tablets, dissolution, assay, uniformity of dosage units, related substances and microbiological quality. 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. The stability indicating nature of the method for related substances and assay has been established.

Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the release specification.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Valaciclovir 1000 mg Focus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Valaciclovir 1000 mg Focus, film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zelitrex, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Valaciclovir is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Valaciclovir 1000 mg, film-coated tablet is compared with the pharmacokinetic

profile of the reference product Valtrex 1000 mg, film-coated tablet (Laboratórios Wellcome de Portugal, Lda., Portugal).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, open-label, two way crossover bioequivalence study was carried out under fasted conditions in 46 healthy subjects, aged 18-51 years. Each subject received a single dose (1000 mg) of one of the two valaciclovir formulations. The tablet was orally administered with 240 ml water after an overnight fasting period of ten hours. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected prior to drug administration and at 0.167, 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, and 6.00 hours after administration of the products. The design of the study is acceptable.

Valaciclovir may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of valaciclovir. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All 46 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (AUC_{0-t} and C_{max} (arithmetic means), $AUC_{0-\infty}$ (arithmetic mean), t_{max} (median, range)) of valaciclovir under fasted conditions.

Treatment N=46	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	291.5 (± 69.5)	293.2 (± 69.6)	186.8 (± 73.8)	1.00 (0.30 – 2.5)
Reference	312.52 (± 81.5)	314.3 (± 81.6)	186.6 (± 71.0)	1.33 (0.33 – 2.18)
***Ratio (90% CI)**	0.935 (0.908 - 0.936)	0.935 (0.908 – 0.963)	1.000 (0.932 – 1.074)	-
CV (%)	8.25	8.25	20.4	-

$AUC_{0-\infty}$	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
CI	Confidence interval
CV	Coefficient of variation
t_{max}	time for maximum concentration

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Valaciclovir 1000 mg Focus, film-coated tablet is considered bioequivalent with Valtrex 1000 mg, film-coated tablet.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Valaciclovir 1000 mg Focus.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zelitrex. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zelitrex 500 mg, film-coated tablets (RVG 18065) for design, layout and key safety messages. The bridging report

submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Valaciclovir 1000 mg Focus, film-coated tablet has a proven chemical-pharmaceutical quality and is a generic form of Zelitrex. Zelitrex 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 Board followed the advice of the assessors.

On the basis of the data submitted, the MEB considered that essential similarity has been demonstrated for Valaciclovir 1000 mg Focus, film-coated tablet with the reference product, therefore, have granted a marketing authorisation. The national procedure was finalised with a positive outcome on 16 March 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse