COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Wirnazir 450 mg film-coated tablets

(valganciclovir hydrochloride)

NL/H/4444/001/DC

Date: 29 July 2019

This module reflects the scientific discussion for the approval of Wirnazir 450 mg film-coated tablets. The procedure was finalised on 23 May 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Wirnazir 450 mg film-coated tablets from Vocate Pharmaceuticals SA.

The product is indicated for:

- The induction and maintenance treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS).
- The prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Valcyte 450 mg film-coated tablets (NL License RVG 25992) which has been registered in the Netherlands by Roche Nederland B.V. since 20 September 2001. Following this national authorisation Valcyte was registered in all EU Member States through MRP and repeat use procedures (NL/H/323/001).

The concerned member state (CMS) involved in this procedure was Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

Wirnazir is a pink, oval, biconvex film-coated tablet debossed with 'J' on one side and '156' on the other side. Each film-coated tablet contains 496.3 mg valganciclovir hydrochloride equivalent to 450 mg of valganciclovir (as free base).

The film-coated tablets are packed in Aluminium/Aluminium blisters or High Density Polyethylene (HDPE) bottles filled with purified cotton with child-resistant polypropylene screw cap with pulp liner (made of backing, wax, foil, PET and heat seal).

The excipients are:
Tablet core – microcrystalline cellulose, crospovidone type A, povidone (K-30) and stearic acid (50).
Film-coating - hypromellose 3 cP, hypromellose 6 cP, titanium dioxide (E171), macrogol 400, red iron oxide (E172) and polysorbate 80.

II.2 Drug Substance

The active substance is valganciclovir hydrochloride, an established substance described in the United States Pharmacopoeia (USP), but not in the European Pharmacopeia (Ph.Eur.). It is a pro-drug for ganciclovir. The drug substance is a white to off-white powder and slightly hygroscopic. It is freely soluble in water and sparingly soluble in methanol. The drug substance exhibits polymorphism. The manufacturer of the active substance (ASM) produces the crystalline form. The drug substance has three chiral carbon atoms. The drug substance corresponds to the L-isomer. A test for enantiomeric purity is included in the drug substance specification.

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 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/EMA 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.

Manufacturing process

Valganciclovir hydrochloride is manufactured in an eight step process: six chemical synthesis steps, one purification step and one physical alteration step. The manufacturing process is described in sufficient detail. The declared starting materials as well as their specifications are justified. The active substance was sufficiently characterised with regard to chemical structure and polymorphic form. Sufficient information is provided on impurities.

Quality control of drug substance

The drug substance specification has been established in-house, based on the specifications of the manufacturer The drug substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for nine batches.

Stability of drug substance

No data have been provided by the applicant on the stability of the drug substance. It is confirmed that the same re-test period and storage conditions are used as are defined in the ASMF (36 months without any specific storage condition).

II.3 Medicinal Product

Pharmaceutical development

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

justified and their functions explained. The development focussed on the optimisation of the amounts of the individual excipients and particle size.
A bioequivalence study has been performed between the proposed product and the German reference product. Dissolution profiles of the tablets are compared with the reference product in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. All profiles show dissolution of more than 85% after 15 minutes.

Manufacturing process

The manufacturing process consists of weighing, sifting, dry mixing, granulation, drying, sifting and milling of granules, pre-lubrication, lubrication, compression, coating and packaging. It is considered to be a standard process. The manufacturing process was described in sufficient detail.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

Excipients of the tablets are tested according to the Ph.Eur., except the Opadry film-coating solution. An acceptable in-house specification is presented for this colourant. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for description, identification, average weight, water content, dissolution, uniformity of dosage units, related compounds, assay, microbiological examination and identification of colourants. The test for microbiological examination is not routinely performed. The drug product specification is mainly based on the USP monograph for valganciclovir tablets.
The proposed limit for dissolution is acceptable in view of the dissolution profile of the bioequivalence study test batch in the QC medium, as per the 'Reflection paper on the Dissolution specification for generic oral immediate release products'.
Analytical methods were adequately described. Batch analytical data showing compliance with the proposed release specification are provided.

Stability of drug product

Stability data on the product was provided for three production batches. Batches are tested at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in the proposed packaging. A photostability study has been performed. No changes are observed in the currently available stability data. The photostability data demonstrate that the drug product is not sensitive to light. Polymorphic form is demonstrated to remain stable upon storage. The proposed shelf-life of 2 years without special storage conditions can be accepted. The results of a 60 day in-use stability study are provided. The in-use period is suitable for the intended posology after first opening of the HDPE containers.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Wirnazir 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 Wirnazir 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 Valcyte 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Valganciclovir hydrochloride 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 member states agreed 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 Wirnazir 450 mg, film-coated tablets (Vocate Pharmaceuticals SA, Greece) is compared with the pharmacokinetic profile of the reference product Valcyte 450 mg film-coated tablets (Roche Pharma A.G., Germany).

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

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 28 (including 2 standbys) healthy male subjects, aged 19-40 years. Each subject received a single dose (450 mg) of one of the 2 valganciclovir formulations. The tablet was orally administered with 240 ml water after a standardised high fat, high caloric vegetarian breakfast which was served maximal 30 minutes prior to dosing. There were 2 dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4.0, 4.5, 5.0, 6, 7, 8 and 10 hours after administration of the products.

A single dose, crossover study under fed conditions to assess bioequivalence is considered adequate. Whenever possible, the tablets should be taken with food. When valganciclovir was given with food at the recommended dose of 900 mg, higher values were seen in both mean ganciclovir AUC (approximately 30%) and mean ganciclovir Cmax values (approximately 14%) than in fasting state. Also, the inter-individual variation in exposure of ganciclovir decreases when valganciclovir is taken with food. Valganciclovir has only been administered with food in clinical studies. Therefore, administration with food is recommended. The bioequivalence study under fed conditions is acceptable.

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

At dosing none of the subjects withdrew and the 2 standbys were not dosed. All subjects completed the study and as such, 26 subjects were eligible for pharmacokinetic analysis

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

Treatment N=26	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	316 ± 61	320 ± 61	155 ± 53	1.75 (1.0 – 3.0)	0.89 ± 0.17
Reference	297 ± 56	301 ± 56	161 ± 53	1.75 (0.67 – 3.5)	0.89 ± 0.13
***Ratio (90% CI)**	1.06 (1.03 – 1.09)	1.06 (1.03 – 1.09)	0.95 (0.85 - 1.05)	--	--
CV (%)	6.0	6.0	22.3	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

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 Wirnazir 450 mg, film-coated tablets is considered bioequivalent with Valcyte 450 mg film-coated tablets.

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 Wirnazir.

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

Important identified risks	-
Important potential risks	-
Missing information	-

The member states agreed that, as for the reference product Valcyte, no safety concerns are specified in the RMP. Routine pharmacovigilance activities and routine risk minimisation measures are sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Valcyte. 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 this 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 the innovator product Valcyte 450 mg film-coated tablets. 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

Wirnazir 450 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Valcyte 450 mg film-coated tablets. Valcyte 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Wirnazir with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 May 2019.

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