CBG MEB

Public Assessment Report

Scientific discussion

Valganciclovir Accord 450 mg film-coated tablets

(valganciclovir hydrochloride)

NL/H/3314/001/DC

Date: 9 March 2017

This module reflects the scientific discussion for the approval of Valganciclovir Accord 450 mg film-coated tablets. The procedure was finalised on 10 March 2016. 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
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Valganciclovir Accord 450 mg film-coated tablets, from Accord Healthcare Ltd.

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 states (CMS) involved in this procedure were Austria, Cyprus, Czech Republic, Denmark, Estonia, Spain, Finland, France, Ireland, Italy, Lithuania, Latvia, Malta, Norway, Poland, Portugal, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Valganciclovir Accord 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 OPA-Aluminium-PVC/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 8 step process: 6 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 9 batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Storage under long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable throughout the tested period. A retest period of 36 months without any specific storage condition is justified.

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 dry blending, granulation, lubrication of the granules, compression and film-coating of the tablets. 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 3 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 finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, water content, dissolution, uniformity of dosage units, related compounds, assay, microbial examination and identification of colorants. The release and shelf life specifications are identical except for water content 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 3 batches from the proposed production site have been provided, demonstrating compliance with the specification.

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 24 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 packagings. 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 36 months 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 Valganciclovir Accord 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 Valganciclovir Accord 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 450 mg film-coated tablets 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Valganciclovir Accord 450 mg film-coated tablets (Accord Healthcare Ltd., UK) 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
The choice of the German 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.

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 C_{max} 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 Valganciclovir Accord 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 Valganciclovir Accord.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Severe leucopenia, neutropenia, anaemia • Thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia • Male infertility • Hypersensitivity • Seizures associated with co-administration with Imipenem-cilastatin
Important potential risks	• Carcinogenicity, teratogenicity and reproductive toxicity • Potential for overdose in patients with renal impairment • Potential interactions with drugs that cause myelosuppression • Potential interaction with drugs which are excreted through the kidneys
Missing information	• Patients with severe uncontrolled diarrhea or with evidence of malabsorption

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 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

The package leaflet (PL) 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: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questionnaire contained 13 questions addressing the key safety issues and presentation of information. Furthermore, four additional questions were presented to attain the general views about the leaflet from the participant. All questions provide for open answers, are ordered randomly and are not leading. This is acceptable. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Valganciclovir Accord 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 Valganciclovir Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 March 2016.

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 the procedure	Approval/ non approval	Assessment report attached