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Public Assessment Report

Scientific discussion

Valganciclovir STADA 450 mg Filmtabletten
VALGANCICLOVIR HYDROCHLORIDE

Date of RMS-Transfer: 17.09.2019

AT/H/1056/001
(former NL/H/3019/001/DC)

III Public Assessment Report

Scientific discussion

**Valganciclovir CF 450 mg,
film-coated tablets**

(valganciclovir hydrochloride)

NL/H/3019/001/DC

Date: 21 December 2015

This module reflects the scientific discussion for the approval of Valganciclovir CF 450 mg, film-coated tablets. The procedure was finalised on 30 January 2015. 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 |
| 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 |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| 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 Valganciclovir CF 450 mg, film-coated tablets from Centrafarm B.V.

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.

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7, HHV8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus (HBV).

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 authorization Valcyte was registered in all EU Member States through MRP and repeat use procedures (NL/H/323/001).

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

The concerned member states (CMS) involved in this procedure were Austria, Croatia, France, Germany, Poland and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Valganciclovir CF 450 mg 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 of valganciclovir hydrochloride equivalent to 450 mg of valganciclovir (as free base).

The film-coated tablets are packed in Aluminium/PVC/Aluminium/OPA blisters and HDPE containers with polypropylene screw caps with aluminium pulp liners and cotton enclosed.

The excipients are:

Tablet core - cellulose microcrystalline (PH101), crospovidone (Type A), povidone (K-30), stearic acid

Film-coating – Opadry Pink 15B24005 hypromellose (3 cP), hypromellose (6 cP), titanium dioxide (E171), macrogol 400, iron oxide red (E172), polysorbate 80.

II.2 Drug Substance

The active substance is valganciclovir hydrochloride, an established active substance described in the Pharmacopoeia of the United States (USP). It is a white to off-white powder, which is freely soluble in water and sparingly soluble in methanol. Valganciclovir is the valine monoester of ganciclovir and consists of two diastereomers. Both diastereomers have the (R/S)-configuration at the valine chiral center and an approximately equimolar ratio of (R) and (S) configuration. Valganciclovir hydrochloride

displays polymorphism; the crystalline form is produced by the manufacturer. The active substance is hygroscopic.

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/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

The valganciclovir hydrochloride manufacturing process consists of six stages. Adequate specifications are applied for the starting material, limiting various (potentially) genotoxic impurities.

Quality control of drug substance

For the drug substance specifications are applied either in line or tighter than the requirements of USP monograph on valganciclovir hydrochloride plus a number of additional requirements. The active substance specification is considered adequate to control the quality. Batch analysis results have been provided on nine batches have been provided, demonstrating compliance with this specification.

Stability of drug substance

Three batches have been put on stability at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). All stability results were in accordance with the set drug substance specification and no clear trends can be observed. Based on the provided data, and on view of the USP monograph's storage instruction the proposed storage condition "Preserve in tight, light-resistant containers, store between 15°C and 30°C." is accepted.

II.3 Medicinal Product

Pharmaceutical development

The pharmaceutical development has been adequately described in satisfactory detail. The initial formulation is strongly based on the qualitative composition of the reference product. Numerous optimisation studies have been performed for fine-tuning of the final composition.

The bioequivalence study was conducted between the proposed product and the German reference product. The German reference product is acceptable in view of its registration by MRP NL/H/323/001. Both test- and reference bio-batches show dissolution results > 85% after 15 min in all three pH media supporting the view that the dissolution profiles of both products are comparable. The development of the dissolution method has been adequately described.

Manufacturing process

The manufacturing process comprises the following steps: sifting, preparation of granulating solution, dry mixing, wet granulation, drying, sifting & milling, sifting of extra granular ingredients, pre-lubrication, lubrication, compression, film-coating and packing. Detailed descriptions and a flow-chart have been provided. The manufacturing process is considered a standard process. The proposed in-process controls are considered adequate and acceptable.

Three batches have been validated. The presented validation data are considered acceptable.

Control of excipients

Iron oxide red as component of Opadry Pink 15B24005, complies with Commission Regulation (EU) No. 231/2012, and all other components meet the requirements of Ph. Eur. The specifications are acceptable.

Quality control of drug product

Adequate requirements for the drug product are laid down. The specifications includes tests for description, identification, average weight, water content, dissolution, uniformity of dosage units, related compounds, assay, identification of colourant and microbial examination. The analytical methods have been adequately validated.

Batch analysis results for 3 batches have been provided with results meeting the set requirements.

Stability of drug product

Stability studies on 3 pilot-scale batches have been started, and 24 months normal (25°C/60% RH) and 6 months accelerated (40°C/75% RH) stability data are available. The drug product appears to be stable during the studies. Also the crystalline form remains unchanged. The product is not sensitive to light. Based on the provided stability data the claimed shelf-life of 36 months without specific storage condition in the two packaging configurations can be accepted.

The MAH provided results from an in-use stability study with the 60's count HDPE container. Based on the available two months stability data no significant changes were observed; the in-use shelf-life of two months after first opening is justified.

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. For stearic acid it is stated that the source of stearic acid is based on vegetable raw materials and technical aids of non-animal origin only; consequently no TSE risk is involved.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Valganciclovir CF 450 mg, film-coated tablets 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 by the MAH.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Valganciclovir CF 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 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Valganciclovir CF 450 mg (Centrafarm B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Valcyte 450 mg tablets (Roche, 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 studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 (including two standbys) healthy male subjects, aged 19 - 40 years. Each subject received a single dose (450 mg) of both the test and the reference valganciclovir formulations. A standardized high fat high caloric vegetarian breakfast was served maximal 30 minutes prior to dosing. The tablets were administered in solid form with 240 ml water. For each subject there were 2 dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 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 standby's were not dosed. All subjects completed the study and as such, 26 subjects were included in the analysis.

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

| Treatment N=26 | AUC _{0-t} ng.h/ml | AUC _{0-∞} 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) | 0.96 (1.03 – 1.09) | 0.96 (1.03 – 1.09) | 0.95 (0.85 - 1.05) | -- | -- |
| CV (%) | 6.0 | 6.0 | 22.3 | -- | -- |
| AUC_{0-∞} 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 | | | | | |

*In-transformed values

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Valganciclovir CF 450 mg 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 CF.

- Summary table of safety concerns as approved in RMP

| | |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Important identified risks (s) | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • Patients with severe uncontrolled diarrhoea 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, 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

Valganciclovir CF 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 CF 450 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 January 2015.

IV STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------|------------------------------|------------------------|----------------------------|
| Renewal | NL/H/3019/001/R/001 | 17.11.2018 | 17.12.2018 | approval | n |
| Update of ASMF | NL/H/3019/001/II/006 | 29.04.2019 | 28.06.2019 | approval | n |
| RMS-Transfer | Transfer to AT/H/1056/001 | - | - | - | - |
| Valganciclovir Hydrochloride ASMF has now been updated from VG series Version AP-19, May-2018 to VR series AP-23, March 2020 from Hetero Labs Limited, Unit IX and a variation to include this updated version of the ASMF is herewith submitted. -The company code has been changed from VGN to VGR . | AT/H/1056/001/II/007 | 18.09.2020 | 09.04.2021 | approval | n |
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