LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Valganciclovir Cipla
(valganciclovir hydrochloride)

SE/H/1525/01/DC

This module reflects the scientific discussion for the approval of Valganciclovir Cipla. The procedure was finalised on 2016-04-20. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Valganciclovir Cipla, film-coated tablets, 450 mg, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Cipla (EU) Limited applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CZ, DE, DK, ES, FI, FR, HR, HU, IT, NL, NO, PL, RO, SK and UK as concerned member states (CMS).
SI was concerned member states (CMS) during the first round of the DCP, but the application was withdrawn in SI by the applicant during clockstop.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Valcyte, film-coated tablets, 450 mg authorised in the Netherlands since 2001, with Roche Nederland B.V. as marketing authorisation holder.

The reference product used in the bioequivalence study is Valcyte, film-coated tablets, 450 mg from UK with Roche Products Limited as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Valganciclovir is a prodrug of ganciclovir. It is well absorbed in the gastrointestinal tract and is quickly and completely metabolised to ganciclovir. The oral bioavailability of ganciclovir following oral treatment with valganciclovir is approximately 60%. Following an oral dose of valganciclovir maximal plasma concentrations of valganciclovir occur at approximately 1 to 1.5 hours and for ganciclovir 30 minutes later. Dose–proportionality with respect to ganciclovir following administration of valganciclovir in the dose range 450 to 2625 mg was only demonstrated when the product was taken with food. Intake with food resulted in increase in AUC (30%) and c_{max} (14%) compared to the fasted state. The inter-individual variability decreases when valganciclovir is taken with food and in clinical studies valganciclovir was administered with food. Therefore it is recommended that valganciclovir is administered with food if possible. The terminal half-life for ganciclovir from valganciclovir is 4.1 ±0.9 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 50 healthy volunteers, comparing Valganciclovir, 450 mg, film-coated tablets with Valcyte, 450 mg, film-coated tablets under fed conditions (high-fat high-calorie meal). A study under fed conditions is appropriate since the SmPC of the reference product recommends administration with food if possible. A dose of 2x450 mg was used, which is considered acceptable since dose-proportionality has been demonstrated. The study was conducted at Sitec Labs Pvt. Ltd, Navi Mumbai, India between 9th July and 27th August 2014. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of valganciclovir and ganciclovir were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for the parent drug valganciclovir (and also for the active metabolite ganciclovir, which is used as supportive evidence). Thus, bioequivalence with the reference product has been adequately demonstrated.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for valganciclovir, n=50.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**743.07±143.54**	**358.61±94.81**	**1.50 (0.75-3.52)**
Reference	**734.03±163.60**	**404.74±99.03**	**1.50 (0.75-2.75)**
***Ratio (90% CI)**	**101.81 (99.44-104.24)**	**88.41 (82.97-94.19)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Cipla.

Safety specification
Summary table of safety concerns as submitted by the applicant

Important identified risks	• Hematopoietic cytopenias and associated infections and hemorrhage • Hypersensitivity • Seizures associated with co-administration with Imipenem-cilastatin
Important potential risks	• Male infertility • Adverse Pregnancy Outcomes • Carcinogenicity • Potential for overdose in patients with renal impairment • Potential interactions with other drugs that cause myelosuppression • Potential interaction with drugs which are excreted through the kidneys
Missing information	• Safety in patients with severe uncontrolled diarrhea or with evidence of malabsorption • Pediatric patients < 4 months

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

The RMP is approved.

V. USER CONSULTATION

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 PIL was Portuguese .
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

The benefit/risk ratio is considered positive and Valganciclovir Cipla, film-coated tablets, 450 mg, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Valganciclovir Cipla, film-coated tablets, 450 mg, was positively finalised on 2016-04-20.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se