LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Ganciclovir Oresund Pharma
# (ganciclovir sodium)

# SE/H/2213/01/DC

**This module reflects the scientific discussion for the approval of Ganciclovir Oresund Pharma. The procedure was finalised on 2022-10-13. 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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Ganciclovir Oresund Pharma, 500 mg, Powder for concentrate for solution for infusion.

The active substance is ganciclovir sodium, ganciclovir. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Ganciclovir Oresund Pharma, 500 mg, Powder for concentrate for solution for infusion, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cymevene, 500 mg, Powder for concentrate for solution for infusion authorised in Sweden since 1989, with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

**Potential similarity with orphan medicinal products**

According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/16/1644; EU/3/13/1133; EU/3/12/999; EU/3/11/849; EU/3/07/591.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should update the report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. The detailed RMS assessment of similarity was presented in the RMS Similarity AR circulated at day 70.

**Conclusion**

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Ganciclovir Oresund Pharma is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to PREVYMIS. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for PREVYMIS in *prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)*, does not prevent the granting of the marketing authorisation of Ganciclovir Oresund Pharma. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

# 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

Pharmacodynamic, pharmacokinetic and toxicological properties of ganciclovir are well known. As ganciclovir is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate. Considering the potent toxicological properties of ganciclovir, a short overview of the main toxicological aspects is provided below.

*Genotoxicity*
Ganciclovir can be considered a genotoxicant. It increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50-500 and 250-2000µg/ml, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500mg/kg (IV) (2.8-10x human exposure based on AUC) but not 50mg/kg (exposure approximately comparable to the human based on AUC. Ganciclovir was not mutagenic in the Ames test at concentrations of 500-5000µg/ml. Ganciclovir was found to be positive in the GADD45a-GFP (GreenScreen HC) reporter assay detects genotoxic damage in the human lymphoblastoid TK6 cell line.

*Carcinogenicity*
Ganciclovir is considered a potent carcinogen in mice. It was carcinogenic in mouse at oral doses of 20 and 1000 mg/kg/day (roughly 0.1x and 1.4x, respectively, the mean drug exposure in humans at the recommended IV dose of 5mg/kg, based on AUC). At the dose of 1000mg/kg/day there was a significant increase in the incidence of tumours of the preputial gland in males, forestomach (non-glandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland, and vagina) and liver in females. At the dose of 20mg/kg/day, a slightly increased incidence of tumours was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated at 0.01x the human dose). Except for histocytic sarcoma of the liver, ganciclovir-induced tumours were generally of epithelial or vascular origin. Although the

preputial and clitoral glands, forestomach and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans.

*DART*
Ganciclovir caused decreased mating behaviour, and decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90mg/kg/day (approximately 1.7x the human dose of 5mg/kg, based on AUC). The drug is embryotoxic in both mice and rabbits, causing foetal resorption in at least 85% of animals exposed to 2x the human dose based on AUC (high dose, HD). Month-old male offspring of female mice administered 1.7x HD before and during gestation and during lactation had hypoplastic testes and seminal vesicles and pathologic changes in the non-glandular region of the stomach. In pregnant rabbits given doses 2x HD, foetal effects included growth restriction and teratogenicity (cleft palate, anophthalmia / microphthalmia, aplastic kidneys and pancreas, hydrocephaly and brachygnathia). Moreover, inhibition of spermatogenesis has been observed in mice and dogs. Adult rats exposed in utero to 300mg/kg on Gd10 exhibited Sertoli cell-only tubules intermingled with seminiferous tubules that displayed a normal size and normal cell counts, alterations that resemble focal Sertoli cell-only syndrome in humans.

Overall, ganciclovir is considered genotoxic (proven clastogenic), carcinogenic, teratogenic and a male and female reproductive toxicant. These aspects have been represented in the proposed SmPC texts (SmPC 4.6 and 5.3).

**Environmental Risk Assessment (ERA)**
Since Ganciclovir Oresund Pharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

***Conclusion***
There are no objections to approval of Ganciclovir Oresund Pharma from a non-clinical point of view.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
No bioequivalence study has been submitted in support of this application.

Pharmacokinetic properties of the active substance
When administered intravenously ganciclovir exhibits linear pharmacokinetics over the dosage range 1.6-5.0 mg/kg. The half-life is approximately 3-4 hours.

Biowaiver
The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) since the product is an aqueous parenteral solution for intravenous administration.

Discussion and overall conclusion
The applied product is to be administered as an aqueous intravenous solution containing the same active substance and the same excipients as the currently authorised product. None of the excipients are known to interact with the drug substance. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1). Thus, the absence of bioequivalence studies is acceptable.

**Pharmacodynamics/Clinical efficacy/Clinical safety**
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted, which is acceptable.

**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 Ganciclovir Oresund Pharma.

Safety specification

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • None |
| Missing information | • None |

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

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

Summary of the RMP

The submitted Risk Management Plan, version 0.1 signed 28 October 2021 is considered acceptable.

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.

# V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Ganciclovir Adoh 500 mg, powder for concentrate for solution for infusion, NL/H/2828/001/DC and Alunbrig 30 mg, 90 mg, 180 mg film-coated tablets, EMEA/H/C/004248/0000.

The bridging report submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Ganciclovir Oresund Pharma is found adequate. There are no objections to approval of Ganciclovir Oresund Pharma, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

# VII. APPROVAL

The decentralised procedure for Ganciclovir Oresund Pharma, 500 mg, Powder for concentrate for solution for infusion was positively finalised on 2022-10-13.

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SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | 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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se