APPLICATION NUMBER:

209347Orig1s000

NON-CLINICAL REVIEW(S)
PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 209347
Supporting document/s:
Applicant's letter date: April 19, 2016
CDER stamp date: April 19, 2016
Product: (b)(4) (Ganciclovir Injection)
Indication: CMV in HIV/Transplant Patients
Applicant: Exela Pharma Sciences, LLC
Review Division: DAVP
Reviewer: John Dubinion, Ph.D.
Supervisor/Team Leader: Hanan Ghantous, Ph.D., D.A.B.T.
Division Director: Debra Birnkrant, M.D.
Project Manager: Garrette Martin-Yeboah, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209347 are owned by Exela Pharma Sciences, LLC or Exela has obtained a written right of reference. Any information or data necessary for approval of NDA 209347 that Exela Pharma Sciences, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug’s approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209347.
# TABLE OF CONTENTS

1 EXECUTIVE SUMMARY ........................................................................................................... 5  
   1.1 INTRODUCTION ............................................................................................................. 5  
   1.2 RECOMMENDATIONS .................................................................................................... 5  

2 DRUG INFORMATION ............................................................................................................. 9  
   2.1 DRUG ............................................................................................................................ 9  
   2.2 RELEVANT INDs, NDAs, BLAs AND DMFs ................................................................. 9  
   2.3 DRUG FORMULATION .................................................................................................. 9  
   2.4 COMMENTS ON NOVEL EXCIPIENTS ...................................................................... 9  
   2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN ............................. 9  
   2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN .......................... 10  
   2.7 REGULATORY BACKGROUND .................................................................................... 10  

3 STUDIES SUBMITTED .......................................................................................................... 10
1 Executive Summary

1.1 Introduction

The sponsor submitted a 505 b2 marketing application for Ganciclovir Injection claiming that the active ingredient is the same as that of Cytovene® - IV (NDA 019661) which the FDA has made a finding of safety and effectiveness for Cytomegalovirus disease. The reference listed drug has a label that has not been converted to PLR (Physician Labeling Rule) or PLLR (Pregnancy and Lactation Labeling Rule), so the sponsor has proposed label changes to the nonclinical sections in order to reflect label updates as required by the PLLR.

All external references referred to in the sponsor’s draft label were reviewed for accuracy, and the sponsor agrees with the proposed edited label.

1.2 Recommendations

1.2.1 Approvability

It is recommended that Ganciclovir Injection and the proposed label changes be approved.

1.2.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.2.3 Labeling (under review)

5 WARNINGS AND PRECAUTIONS

5.3 Impairment of Fertility

Based on animal data, GANCICLOVIR INJECTION at the recommended human dose (RHD) may cause temporary or permanent inhibition of spermatogenesis in males, and may cause suppression of fertility in females. Advise patients that fertility may be impaired with use of GANCICLOVIR INJECTION [see Use in Specific Population (8.1), Nonclinical Toxicology (13.1)].

5.4 Fetal Toxicity

GANCICLOVIR INJECTION may cause fetal toxicity when administered to pregnant women based on findings in animal studies. Systemic exposure of ganciclovir in animals at approximately 2 times the RHD caused fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes in animals included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with GANCICLOVIR INJECTION. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with
GANCICLOVIR INJECTION [see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)].

5.5 Mutagenesis and Carcinogenesis

Animal data indicate that ganciclovir is mutagenic and carcinogenic. GANCICLOVIR INJECTION should therefore be considered a potential carcinogen in humans [see Dosage and Administration (2.6), Nonclinical Toxicology (13.1)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary

In animal studies, ganciclovir caused maternal and fetal toxicity and embryo-fetal mortality in pregnant mice and rabbits as well as teratogenicity in rabbits at exposures two times the exposure at the recommended human dose (RHD) [see Data]. Although placental transfer of ganciclovir has been shown to occur based on ex vivo experiments with human placenta and on at least one case report in a pregnant woman, no adequate human data are available to establish whether GANCICLOVIR INJECTION poses a risk to pregnancy outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2-4% and 15–20%, respectively.

Clinical considerations

Disease-associated maternal and/or fetal risk

Most maternal CMV infections are subclinical or they may be associated with a mononucleosis-like syndrome. However, in immunocompromised patients, CMV infections are often symptomatic and are associated with significant morbidity and mortality. The transmission of CMV to the fetus is a result of maternal viremia and transplacental infection. CMV infection can also occur perinatally from mother to infant by exposure to CMV in cervicovaginal secretions. Approximately 10% of infected newborns are symptomatic at birth. Mortality in symptomatic infants is about 10%, and approximately 50 to 90% of survivors experience significant problems, including sensorineural hearing loss, mental retardation, and other neurologic deficits. The risk and severity of congenital CMV infection appear to be higher in infants born to mothers with primary CMV infection than in those born to mothers with reactivation of CMV infection.

Data

Animal Data
Daily intravenous doses of ganciclovir were administered to pregnant mice (108 mg/kg/day) and rabbits (60 mg/kg/day), and also to female mice (90 mg/kg) prior to mating, during gestation, and during lactation. Fetal resorptions were present in at least 85% of rabbits and mice. Additional effects observed in rabbits included fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In pre/postnatal development studies in mice, there were maternal/fetal toxicity and embryolethality which included fetal effects of hypoplasia of the testes and seminal vesicles in the male offspring, as well as pathologic changes in the nonglandular region of the stomach. The systemic exposure (AUC) of ganciclovir during these studies was approximately 2-times (pregnant mice and rabbits) and 1.7-times (pre/postnatal mice) the exposure in humans at the RHD [see Nonclinical Toxicology (13.1)].

8.2 Lactation

Risk Summary

No data are available regarding the presence of ganciclovir in human milk, the effects on the breastfed infant, or the effects on milk production. When ganciclovir was administered to lactating rats, ganciclovir was present in milk [see Data]. Advise nursing mothers that breastfeeding is not recommended during treatment with GANCICLOVIR INJECTION because of the potential for serious adverse reactions in nursing infants. Furthermore, the Centers for Disease Control and Prevention recommends that HIV-infected mothers not breastfeed their infants to avoid potential postnatal transmission of HIV [see Warnings and Precautions (5.1, 5.3, 5.5), Nonclinical Toxicology (13.1)].

Data

Animal Data

Ganciclovir administered intravenously (at 0.13 mg/h) to lactating rats (on lactation day 15) resulted in passive transfer into milk. The milk-to-serum ratio for ganciclovir at steady state was 1.6 ± 0.33.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential should undergo pregnancy testing before initiation of GANCICLOVIR INJECTION [see Dosage and Administration (2.2), Use in Specific Populations (8.1)].

Contraception

Females
Because of the mutagenic and teratogenic potential of ganciclovir, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with GANCICLOVIR INJECTION [see Warnings and Precautions (5.3, 5.4), Nonclinical Toxicology (13.1)].

Males

Because of its mutagenic potential, males should be advised to practice barrier contraception during and for at least 90 days following, treatment with GANCICLOVIR INJECTION [see Warnings and Precautions (5.3, 5.4), Nonclinical Toxicology (13.1)].

Infertility

GANCICLOVIR INJECTION at the recommended doses may cause temporary or permanent female and male infertility [see Warnings and Precautions (5.3, 5.4), Nonclinical Toxicology (13.1)].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, Mutagenesis

Ganciclovir was carcinogenic in mice at the same mean drug exposure in humans as at the RHD (5 mg/kg). At the dose of 1000 mg/kg/day (1.4 times the exposure at the RHD) there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the dose of 20 mg/kg/day (0.1 times the exposure at the RHD), a slightly increased incidence of tumors 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 (exposure estimated as 0.01 times the RHD). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumors 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.

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations of 50 to 500 and 250 to 2000 μg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (2.8 to 10 times the exposure at the RHD) but not at doses of 50 mg/kg (exposure approximately comparable to the RHD). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5000 μg/mL.

Impairment of Fertility
Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following doses of 90 mg/kg/day (exposures approximately 1.7 times the RHD). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1 times the exposure at the RHD.

2 Drug Information

2.1 Drug

Generic Name: Ganciclovir Injection

Chemical Name: 9-[[2-hydroxy-1-(hydroxymethyl)- ethoxy]methyl]guanine

Molecular Formula/Molecular Weight: C₉H₁₃N₅O₄ / 255.23

Structure or Biochemical Description:

Pharmacologic Class: Antiviral Agent; Synthetic Guanine Derivative

2.2 Relevant INDs, NDAs, BLAs and DMFs

Cytovene®- IV; NDA 019661

2.3 Drug Formulation

Ganciclovir Injection is 500 mg of ganciclovir in a sterile, unpreserved 250mL solution single-dose bag for intravenous administration. The appearance of the solution is clear and colorless. Each mL contains 2.0 mg of ganciclovir, 8.0 mg of sodium chloride in water for injection, and may contain sodium hydroxide, and/or hydrochloric acid, as required to adjust the pH to 7.5.

2.4 Comments on Novel Excipients

N/A

2.5 Comments on Impurities/Degradants of Concern

N/A
2.6  Proposed Clinical Population and Dosing Regimen

Treatment of CMV retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome:

Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days.

Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week.

Prevention of CMV disease in transplant recipients:

Induction: 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days.

Maintenance: 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week until 100 to 120 days post-transplantation.

2.7  Regulatory Background

Ganciclovir is an approved drug product under NDA 019661 (Genentech: Cytovene® IV).

3  Studies Submitted

A comprehensive review of the nonclinical studies for ganciclovir has been performed under NDA 019661. A single nonclinical non-GLP study was submitted to qualify potential leachable compounds from the plastic container which was a novel container for the current NDA. No components of the plastic container material were found to migrate into the solution within the expiration period.

16-03713-N1: Determination of the Leachable Amount of Chemical Compounds from Technoflex Intravenous Bag into Gancyclovir Injection (2.0 mg/mL, 500 mg/250 mL)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN H DUBINION
01/12/2017

HANAN N GHANTOUS
01/12/2017