CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209347Orig1s000

CLINICAL REVIEW(S)

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUGS AND PRODUCTS

DATE: February 8, 2017

FROM: Andreas Pikis, Medical Officer, DAVP

SUBJECT: Financial disclosure

NDA: 209-347

APPLICANT: Exela Pharma Sciences

This submission is a 505(b)(2) New Drug Application for GANCICLOVIR INJECTION 2.0 mg/mL (500 mg/250 mL). The Applicant submitted information describing the Chemistry, Manufacturing and Controls for GANCICLOVIR INJECTION, 500 mg/250 mL. The reference listed drug (RLD) for this application is CYTOVENE®-IV, which was approved under NDA 19,661 on June 23, 1989 (held by Roche). . Under the applicable regulations, an applicant is required to submit to FDA a list of all clinical investigators who conducted covered clinical studies and to identify those who are full-time or part-time employees of the sponsor of the each covered study (21 CFR 54.4). This application did not include any Clinical studies; thus, no financial disclosure information was required for this New Drug Application.

Andreas Pikis, M.D.,
Medical Officer, DAVP

Concurrences:
Mary Singer, M.D., Ph.D.,
Medical Team Leader, DAVP

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/s/

ANDREAS PIKIS
02/10/2017

MARY E SINGER
02/10/2017
I concur with Dr. Pikis' assessment.

Medical Officer's Review

Date	January 8, 2017
From	Andreas Pikis, M.D.
Medical Team Leader	Mary Singer, M.D., Ph.D.
Subject	Medical Officer's review
NDA #	209-347
Applicant	Exela Pharma Sciences
Date of Submission	April 18, 2016
PDUFA Goal Date	February 19, 2017
Proprietary Name / Established (USAN) names	[redacted] (b) (4) Ganciclovir Injection
Dosage forms / Strength	500 mg/250 mL
Proposed Indication(s)	1. Treatment of cytomegalovirus (CMV) retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS) 2. Prevention of CMV disease in adult transplant recipients at risk for CMV disease
Recommended:	Approval

This submission is a 505(b)(2) New Drug Application for GANCICLOVIR INJECTION 2.0 mg/mL (500 mg/250 mL). The Applicant submitted information describing the Chemistry, Manufacturing and Controls for GANCICLOVIR INJECTION, 500 mg/250 mL. The reference listed drug (RLD) for this application is CYTOVENE®-IV, which was approved under NDA 19,661 on June 23, 1989 (held by Roche). The proposed drug product is a sterile, colorless solution with a concentration of 2.0 mg/mL ganciclovir in a 250 mL single-dose bags for intravenous use. Each intravenous bag contains 500 mg of ganciclovir, USP in 0.8% sodium chloride. GANCICLOVIR INJECTION is intended for direct intravenous injection only and without further dilution. Exela's formulation contains sodium chloride, USP as a [redacted] (b) (4) and sodium hydroxide, NF and/or hydrochloric acid, NF to adjust the drug product solution to a target pH of 7.5 (7.0 – 8.0). Exela's formulation contains no preservatives, [redacted] (b) (4).

GANCICLOVIR INJECTION is packaged in a 250 mL [redacted] (b) (4) bag from [redacted] (b) (4), sealed with a Twist off port from Technoflex, and oversealed in aluminum pouches. The bag is fabricated from [redacted] (b) (4) layer film designed for [redacted] (b) (4) medical use (complies with FDA, 21 CFR 177.1810 (b) (3) and USP class VI). The submitted information for Chemistry, Manufacturing and Controls for GANCICLOVIR INJECTION was reviewed by Dr. Milton Sloan, the Chemistry reviewer, who recommended approval of the proposed drug product (please refer to Dr. Sloan's review for further details).

The application included a request for the waiver of the requirement to conduct in vivo bioavailability/bioequivalence studies for their proposed drug product based on 21CFR§320.22(b) regulation, and this request was reviewed by Dr. Mei Ou, the Biopharmaceutical reviewer. Dr. Ou determined that the Applicant provided the supportive information demonstrating that (1) the differences in concentration of the active ingredient, administered volume, and infusion rate between the proposed drug and the RLD will not cause difference in the in vivo performance; (2) the physicochemical characteristics (i.e., pH, osmolality) of the proposed drug and the RLD are comparable. Therefore, a bridge between the proposed drug product and the RLD product has been established and bioavailability/ bioequivalence studies are not needed (for further details please see the review by Dr. Ou).

This application did not include any Clinical Pharmacology, Pharmacology/Toxicology, Virology, or Clinical data; thus, no detailed reviews from these disciplines were necessary.

Recommended Regulatory Action

Approval

Recommendations for Postmarketing Requirements and Commitments

The current 505(b)(2) NDA triggers PREA for the approved indications. However, the Division of Antiviral Products and the Pediatric Review Committee determined that a waiver should be granted for pediatric assessment requirements because studies in children are highly impractical for the approved indications. Specific justification for waiver for each indication is as follows:

Treatment of CMV retinitis: Because adult and pediatric patients with HIV infection are now generally treated with highly active antiretroviral therapy as soon as HIV is diagnosed, the incidence of opportunistic infections, including CMV retinitis, has decreased significantly, and the number of pediatric patients with CMV retinitis would be too small to make a study feasible.

Prevention of CMV disease in transplant patients: Although intravenous ganciclovir was the first antiviral drug approved (1989) for the prevention of CMV disease in transplant recipients, it was replaced in clinical practice initially by oral ganciclovir (1994) and most recently by oral valganciclovir (2003). The long-term use of intravenous ganciclovir (indicated for up to 100 days to 120 days post-transplantation) is generally impractical due to the requirement of an indwelling catheter to deliver the drug, which also places the patient at increased risk of acquiring potentially life-threatening catheter-related infections. Thus, the number of pediatric patients requiring use of intravenous ganciclovir for prevention of CMV disease would be too small to make a study feasible.

Labeling

Because this NDA relies on FDA's previous findings of safety and efficacy for the RLD, Cytovene®-IV, the proposed product labeling is based on that of CYTOVENE®-IV. Of note, the current approved CYTOVENE®-IV package insert is not in the PLR/PLLR format; whereas the proposed product labeling complies with the current PLR/PLLR formatting requirements.

The proposed label submitted with this NDA has been reviewed by all disciplines. Modifications of the proposed label have been discussed with and agreed upon by the Applicant. The major changes in the modified label involve the following sections:

USE IN SPECIFIC POPULATIONS

The subsections of Pregnancy, Lactation, and Females and Males of Reproductive Potential have been modified to comply with the Pregnancy and Lactation Labeling Rule (PLLR). These subsections read as follows:

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

Pregnancy Testing

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)]*.

DESCRIPTION

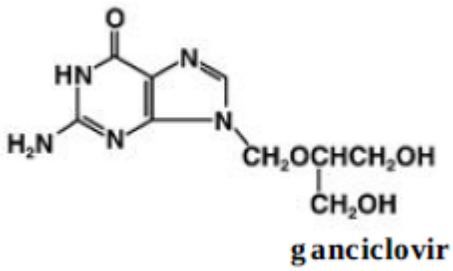
This section was changed to provide information for the new drug product. This section reads as follows:

11 DESCRIPTION

GANCICLOVIR INJECTION, 500 mg is a sterile, unpreserved solution 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.

Ganciclovir, an antiviral agent, is a synthetic guanine derivative, 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine. Ganciclovir is a white to off-white crystalline powder with a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255.23. Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/mL in water at 25°C and an n-octanol/water partition coefficient of 0.022. The pK_as for ganciclovir are 2.2 and 9.4.

The chemical structure of ganciclovir is:



ganciclovir

The plastic container is fabricated from a multilayer film designed for medical use. The solution is in contact with the inner polypropylene layer of the container. No components of the plastic container material were found to migrate into the solution.

Andreas Pikis, M.D.
Medical Reviewer, DAVP

Concurrences
Mary Singer, M.D., Ph.D.
Medical Team Leader, DAVP

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/s/

ANDREAS PIKIS
01/12/2017

MARY E SINGER
01/12/2017
I concur with Dr. Pikis' Clinical review and recommendation.