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APPLICATION NUMBER:

209347Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL Review
NDA 209347 for Ganciclovir Injection
Mary Singer, MD, PhD.
January 27, 2017

Cross-Discipline Team Leader Review

Date	January 27, 2017
From	Mary Singer, MD., PhD.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 209347
Supplement#	S-000
Applicant	Excelsa Pharma Sciences, LLC
Date of Submission	4/19/16
PDUFA Goal Date	2/19/17
Proprietary Name / Established (USAN) names	(b) (4) (proposed)/Ganciclovir injection
Dosage forms / Strength	2.0 mg/mL (500 mg/250 mL)
Proposed Indication(s)	1. Treatment of CMV retinitis in immunocompromised patients, including patients with AIDS 2. Prevention of CMV disease in transplant recipients at risk for CMV disease
Recommended:	<i>Approval</i>

Cross Discipline Team Leader Review

1. Introduction

NDA 209347 is a 505(b)2 application submitted for Ganciclovir Injection, 2.0 mg/mL (500 mg/250 mL). The proposed drug product differs from the reference listed drug, Cytovene®-IV (ganciclovir sodium for injection), approved under NDA 019661 in 1989 for treatment of CMV retinitis in immunocompromised patients and prevention of CMV in transplant patients at risk for CMV disease. The Applicant's proposed drug product has the same active ingredient, route of administration and indications as Cytovene®-IV, but differs with respect to active ingredient concentration, dosage form, and excipients in the formulation. No new clinical studies have been performed, and the Applicant is relying on FDA's findings of safety and effectiveness for Cytovene®-IV. The review of this application has focused on chemistry, manufacturing and controls (CMC) and biopharmaceutics issues, as well as product labeling.

2. Background

Ganciclovir injection is currently available as Cytovene®-IV (NDA 019661), and as 3 generic ganciclovir versions (ANDA 090658, ANDA 202624, and ANDA 204950), each as 500 mg ganciclovir base/vial. Oral ganciclovir is currently not available in the US.

Pre-IND 117705 was submitted on February 4, 2013, to discuss the Applicant's plans for submission of this 505(b)2 NDA. The Applicant's questions concerned the appropriate reference listed drug (RLD), their proposed reliance data on the FDA's findings of safety and efficacy for the RLD, the proposed biowaiver for the drug product, and the proposed method for sterilization of the drug product. The Division of Antiviral Products (DAVP) responded in writing on March 13, 2013, and agreed with the use of Cytovene®-IV as RLD, the proposed 505(b)2 pathway (i.e., reliance on FDA's previous findings of safety and effectiveness for Cytovene®-IV), and provided advice regarding the Applicant's proposed request for a biowaiver and regarding product sterilization. The DAVP also recommended that an extractable and leachable study be performed.

3. CMC/Device

The following section briefly summarizes the findings for each of the Product Quality reviews. Each of the Office of Product Quality (OPQ) reviewers recommended approval of Exela's Ganciclovir Injection.

Drug Substance

As summarized in the Drug Substance review by Dr. Haripada Sarker, the drug substance information is cross-referenced to two Type II DMFs (DMF 15567 (by Exela Pharma), and DMF [REDACTED] (b) (4)).

[REDACTED] The subsequent amendments for both DMFs were found to be adequate by Dr. Sarker for NDA 209347.

Drug Product

As summarized in the Drug Product Quality review by Dr. Milton Sloan, Ganciclovir Injection 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. Exela's Ganciclovir Injection is an (b) (4) preservative free solution. Ganciclovir Injection is intended for direct intravenous injection only and without further dilution. Exela's formulation contains sodium chloride, USP, as a (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, (b) (4)

Ganciclovir Injection is packaged in a 250 mL (b) (4) from (b) (4) sealed with a Twist-off port from Technoflex, and oversealed in aluminum pouches. The bag is fabricated from (b) (4) layer film designed for (b) (4) medical use (complies with FDA, 21 CFR 177.1810 (b) (3) and USP class VI).

The formulation for Exela's Ganciclovir Injection has the same active ingredient, route of administration, and indications as Genentech, Inc., CYTOVENE® –IV (ganciclovir sodium for injection), the Reference Listed Drug (RLD). As per the package insert, CYTOVENE®–IV (ganciclovir sodium for injection) is a lyophilized powder for injection and each vial contains the equivalent of 500 mg ganciclovir as the sodium salt (46 mg sodium). Reconstitution of the lyophilized powder for injection with 10 mL of Sterile Water for Injection, USP, yields a reconstituted solution with pH 11 and a ganciclovir concentration of 50 mg/mL. Based on patient's weight, the appropriate volume of the reconstituted solution is removed from the vial and added to an appropriate intravenous solution (typically 100 mL) for infusion over an hour. Appropriate infusion fluids include 0.9% sodium chloride, 5% dextrose, Ringer's Injection, or Lactated Ringer's Injection, USP. Exela's Ganciclovir Injection is a ready to use injection and requires no dilution prior to intravenous administration.

The following table compares Exela's Ganciclovir Injection with Cytovene®-IV.

Table 1. Comparison of Exela’s Ganciclovir Injection Formulation with the RLD, Cytovene®-IV Formulation

Exela’s Formulation		Roche/Genentech, Inc, CYTOVENE® –IV (ganciclovir sodium for injection)	
Ingredients	Composition	Ingredients	Composition
Ganciclovir, USP	2.0 mg/mL 500 mg/250 mL	Ganciclovir (present as sodium salt)	500 mg/vial
Sodium Chloride, USP	8.0 mg/mL (b) (4)	Sodium Chloride, USP	Absent
Sodium Hydroxide, NF (if required)	q.s. to pH 7.5 (b) (4)	Sodium Hydroxide, NF	(b) (4)
Hydrochloric Acid, NF (if	q.s. to pH 7.5 (b) (4)	Hydrochloric Acid, NF	Absent
Water for Injection, USP	q.s.	Water for Injection, USP	Absent

¹Information regarding Roche/Genentech, Inc, CYTOVENE® –IV (ganciclovir sodium for injection) formulation was obtained from the current package insert, vial label, and carton.

With regard to stability testing, Dr. Sloan summarized the findings as follows: The drug product is a ready mixture in 0.8% sodium chloride diluent. Compatibility of the excipients with the drug substance and vehicle is shown with the stability data. No significant changes were observed throughout stability testing of the drug product at accelerated and real-time storage testing.

The control of excipients was considered acceptable. There were no leachables detected during long-term storage of ganciclovir drug product that may originate from components used in the container closure system.

Manufacturing Process

As summarized by Dr. Sung Kim in the process review, the manufacturing process consists of (b) (4)

[Redacted text block]

A recommendation for approval was made from the process perspective.

Microbiology

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As summarized by Dr. Bernard Marasda in his Microbiology review from a product quality perspective, the sterilization methods include (b) (4)

The submission was recommended for approval on the basis of sterility assurance.

Facilities

As summarized by Dr. Cassandra Abellard, a review of the application and inspectional documents of the facilities responsible for manufacturing Ganciclovir Injection per NDA 209347 has determined that there are no significant outstanding risks for these facilities. All facilities were found to be acceptable with no pre-approval inspections required.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology studies were submitted with this application. See Dr. John Dubinion's Pharmacology/Toxicology review for further details.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

No clinical pharmacology data were included in this NDA submission, as the Applicant requested a waiver for the requirement for in vivo relative bioavailability study. See Dr. Islam Younis' review for further details.

Biopharmaceutics

As summarized by Dr. Mei Ou, the Biopharmaceutical reviewer, the Applicant requested a waiver of the requirement to conduct an in vivo bioavailability/bioequivalence study for their proposed drug product. The Applicant provided supportive information demonstrating that the physicochemical characteristics (pH and osmolality), of the infusion solution of the proposed drug product, are comparable to those of the reconstituted diluted infusion solution of the reference listed drug product, and the differences in concentration of the active ingredient, administered volume, and infusion rate between the proposed drug product and the RLD product do not affect the in vivo bioavailability and bioequivalence. The Biopharmaceutical reviewer determined that a bridge between the proposed drug product and the RLD product has been established in accordance with 21 CFR 320.24(b)(6), and recommended approval of the proposed product.

6. Clinical Microbiology

No new virology data (clinical or preclinical) were submitted with this application. See Dr. Takashi Komatsu's Virology review for additional information.

7. Clinical/Statistical-Efficacy

No clinical data were submitted with this NDA and the Applicant is relying on FDA's findings of safety and effectiveness for the reference listed drug, Cytovene®-IV (ganciclovir sodium). See Dr. Andreas Piki's clinical review for additional information.

8. Safety

No clinical data were submitted with this NDA and the Applicant is relying on FDA's findings of safety and effectiveness for the reference listed drug, Cytovene®-IV (ganciclovir sodium). See Dr. Andreas Piki's clinical review for additional information.

9. Advisory Committee Meeting

No advisory committee meeting was held to discuss this application.

10. Pediatrics

Because this is an application for a new formulation of ganciclovir for injection, PREA requirements were triggered. Cytovene®-IV had orphan drug status at the time of approval, and thus, pediatric studies were not required at that time. This Applicant requested a full waiver for pediatric studies, and the DAVP and the Pediatric Review Committee agreed that a waiver should be granted for pediatric study requirements because such studies would be 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.

11. Other Relevant Regulatory Issues

A preliminary exclusivity review performed by Garrette Martin-Yeboah, Pharm D., Regulatory Project Manager for this application, concluded that the Applicant is not eligible for any 3- or 5-year exclusivity because no new clinical studies were submitted with the application. Additionally, no financial disclosures were required with the application because no clinical studies were conducted. A final review of related patents and exclusivity with regard to this 505(b)2 application is pending by the 505(b)2 committee. At this time, there are no other outstanding regulatory issues regarding this application

12. 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. Except for some minor modifications which are currently under review by the Applicant, the proposed revisions to the label have been discussed with and agreed upon by the Applicant. The major changes in the modified label involve the following sections:

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 11 Description

See Dr. Andreas Pikis' review for description of the major labeling changes for this product. A Medication Guide or other patient labeling is not required for this product because Cytovene-IV® labeling does not include any patient labeling, and because the product is for designed use under a Healthcare provider's direction predominantly in the hospital or clinic setting.

Revised carton and container labeling are currently under review by the OPQ.

The proposed proprietary name, (b) (4) and alternate name, (b) (4) are currently under review by the Office of Surveillance and Epidemiology (OSE).

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** *Approval, as recommended by the review team.*
- **Risk Benefit Assessment**

Intravenous ganciclovir is an important drug for treatment and prevention of CMV disease in at-risk populations, including hematopoietic stem cell and solid-organ transplant recipients, and in patients with CMV retinitis, including those with HIV/AIDS. The risks of ganciclovir, including hematologic toxicity, fetal toxicity, impairment of fertility, mutagenesis and carcinogenesis are prominently displayed in a Boxed Warning in the Ganciclovir Injection Package Insert. Other labeled Warnings for Ganciclovir injection include renal impairment and precautions regarding intravenous infusion of ganciclovir.

Exela's product may provide some advantages over Cytovene-IV[®]. Because of its more neutral pH, infusion site reactions such as phlebitis, may be fewer with the Exela product. In addition, because it is supplied as a premixed solution without the requirement for dilution, less pharmacy preparation and handling is necessary, which may lower the risk of pharmacy personnel exposure to ganciclovir, which requires special precautions for handling and disposal as outlined in the Cytovene-IV[®] package insert.

Overall, the risk/benefit assessment for Ganciclovir injection is favorable.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies:** No postmarketing REMS are recommended.
- **Recommendation for other Postmarketing Requirements and Commitments:** No postmarketing requirements or commitments are recommended.
- **Recommended Comments to Applicant:** There are no additional comments for the Applicant.

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/s/

MARY E SINGER
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