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APPLICATION NUMBER:

209347Orig1s000

SUMMARY REVIEW

Summary Review
NDA 209347 for Ganciclovir Injection
Jeffrey Murray M.D., M.P.H., Deputy Director
January 27, 2017

Summary Review

Date	Feb 8, 2017
From	Jeffrey Murray, M.D., M.P.H.
Subject	Summary Review (Division Director)
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	Proprietary Name Under Review/Ganciclovir injection
Dosage forms / Strength	2.0 mg/mL (500 mg/250 mL)
Proposed Indication(s)	<ol style="list-style-type: none">1. Treatment of CMV retinitis in immunocompromised patients, including patients with AIDS2. Prevention of CMV disease in transplant recipients at risk for CMV disease
Recommended:	<i>Approval</i>

Summary Review

1. Introduction

Please refer to the cross discipline team leader (CDTL) review prepared by Mary Singer and the Medical Officer review prepared by Andreas Pikis for additional details regarding this NDA. NDA 209347 is a 505(b)2 application submitted for Ganciclovir Injection, 2.0 mg/mL (500 mg/250 mL). This 505(b)2 NDA relies on FDA's findings of clinical safety and efficacy from the reference listed drug (RLD), (ganciclovir sodium for injection), approved in 1989. Indications for Cytovene®-IV include: 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. The approval of this application relies primarily on product quality review as stated below and also review of product labeling. No new clinical trials or bioequivalence studies were conducted.

2. CMC/Device

All Product Quality 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. Both DMFs were previously reviewed for ANDAs and were adequate.

Drug Product

Dr. Milton Sloan performed the Drug Product Quality review and recommends approval. 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. The formulation for Exela's Ganciclovir Injection has the same active ingredient, route of administration as Genentech, Inc., CYTOVENE® –IV (ganciclovir sodium for injection), the RLD. CYTOVENE® –IV (ganciclovir sodium for injection) is a lyophilized powder for injection that is reconstituted in 10 mL of sterile water to yield a solution with a ganciclovir concentration of 50 mg/mL and a pH of 11. Based on patient's weight, the appropriate volume of the reconstituted solution is removed from the vial and added to an appropriate intravenous solution. In contrast, Exela's Ganciclovir Injection formulation is a ready to use injection and requires no dilution prior to intravenous administration.

Manufacturing Process

Dr. Sung Kim performed the manufacturing process review and recommends approval.

Microbiology

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Dr. Bernard Marasda in his Microbiology reviewed the application for sterility assurance and recommended approval.

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.

3. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

No pharmacologic data were included in this NDA submission. The Applicant requested a waiver for the requirement for a clinical 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 RLD. 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.

4. 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.

5. 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.

6. Advisory Committee Meeting

No advisory committee meeting was held to discuss this application.

7. Pediatrics

This application for a new formulation of ganciclovir for injection triggers PREA requirements. However, the 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 successfully treated with combination 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. The number of pediatric patients requiring use of intravenous ganciclovir for prevention of CMV disease would be too small to make a study feasible.

8. 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 review of related patents and exclusivity with regard to this 505(b)2 application was assessed by the 505(b)2 committee. No existing exclusivity for related products precludes the approval of this application. At this time, there are no other outstanding regulatory issues regarding this application. Please see the memorandum written by the Nisha Shah on behalf of the Exclusivity Board.

9. 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 package insert, which is not in the PLR/PLLR format. However the product labeling for Exela's product complies with the current PLR/PLLR formatting requirements.

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See Dr. Andreas Pikis' review for description of the major labeling changes for this product. No Patient Labeling or Medication Guide is required for this product because Cytovene-IV[®] labeling does not include one.

The proposed proprietary name, (b) (4) and alternate name, (b) (4) are currently under review by OSE. The proposed proprietary name came in an amendment during the review cycle and a decision will not be ready at the time of approval.

10. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action: *Approval***
- **Risk Benefit Assessment**

As stated in Dr. Singer's CDTL memorandum, 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. Exela's product is somewhat different than Cytovene-IV[®]. 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.

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/s/

JEFFREY S MURRAY
02/16/2017