DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 16, 2017

TO: Ganciclovir injection 500mg/250ml (NDA 209347) File
Valganciclovir Hydrochloride (HCl) (NDAs 22257 and 21304) File

FROM: CDER Exclusivity Board

SUBJECT: Whether the 3-year exclusivity for Valcyte (valganciclovir HCl, NDAs 22257 and 21304) blocks the approval of Ganciclovir injection 500mg/250ml (NDA 209347)

This memorandum addresses whether the unexpired 3-year exclusivity recognized by the Food and Drug Administration (FDA or the Agency) for Valcyte (valganciclovir HCl, new drug applications (NDAs) 22257 (for oral solution) and 21304 (tablets)) (Valcyte) blocks the approval of ganciclovir injection 500mg/250ml (NDA 209347) (Exela Pharma Sciences, LLC's (Exela's) Ganciclovir). For the reasons discussed below, the Exclusivity Board (Board) within the Center for Drug Evaluation and Research (CDER), in consultation with the Division of Antiviral Products (DAVP or Division), has determined that Exela's 505(b)(2) application for Ganciclovir should not be blocked by any unexpired 3-year exclusivity for Valcyte.

I. Factual Background

A. Valcyte

Valcyte contains a single active ingredient, valganciclovir HCl, and a single active moiety, ganciclovir.[1] Valcyte, which was first approved in 2001, has indications for both adult and pediatric populations. In adults, it is indicated for: (1) the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS), and (2) prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk (donor CMV

[1] Valganciclovir HCl is "a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diastereomers." See Valcyte Labeling, Section 11.

seropositive/recipient CMV seronegative). In pediatric populations, it is indicated for the prevention of CMV disease in kidney and heart transplant patients at high risk.[2]

On April 23, 2015, FDA approved supplement 11 to NDA 21304 and supplement 5 to NDA 22257. The supplements "expand the Indications and Usage to include heart transplant patients from 1 month to 4 months of age and . . . extend the duration of dosing regimen from 100 days to 200 days post-transplantation for the prevention of CMV disease in pediatric kidney transplant patients 4 months to 16 years of age."[3] FDA previously determined that the supplements qualified Valcyte for 3-year exclusivity, which expires on April 23, 2018. The 3-year exclusivity is denoted in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) by two exclusivity codes: (1) D-148 ("extended the duration of the dosing regimen from 100 days to 200 days post-transplantation for the prevention of CMV disease in pediatric kidney transplant"), and (2) NPP, new patient population. The D-148 exclusivity code relates to the extension of the dosing regimen from 100 days to 200 days post-transplantation for the prevention of CMV diseases in pediatric kidney transplant patients aged 4 months to 16 years. The NPP exclusivity code relates to the expansion of the heart transplant indication for pediatric patients 1 month to 4 months of age.

B. Ganciclovir

On April 16, 2016, Exela submitted a 505(b)(2) NDA for ganciclovir injection. The Prescription Drug User Fee Act (PDUFA) goal date is February 19, 2017. The applicant is seeking approval for its ganciclovir injection product for the treatment of CMV retinitis in immunocompromised adult patients, including patients with AIDS, and prevention of CMV disease in adult transplant recipients at risk for CMV disease. The product contains ganciclovir as its single active ingredient and ganciclovir as its single active moiety.

II. Legal and Regulatory Overview

The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For original NDAs, section 505(c)(3)(E)(iii) of the Federal Food, Drug & Cosmetic (FD&C) Act states:

> *If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted*

[2] See Valcyte Labeling, Section 1.

[3] Letter from FDA to Roche Palo Alto, LLC, available on drugs@fda at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021304Orig1s011,022257Orig1s005ltr.pdf.

> *or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[4]

The first clause (italicized) in section 505(c)(3)(E)(iii), often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. In the 5-year new chemical entity (NCE) exclusivity context, FDA has interpreted the term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety "that has been approved in another application") are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA's implementing regulations further interpret certain aspects of the statutory language regarding eligibility for 3-year exclusivity.[5]

The second clause in section 505(c)(3)(E)(iii) (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency's interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) generally involves two aspects. One aspect of the scope inquiry focuses on the drug at issue. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. The "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug which includes a previously approved active moiety. FDA interprets this cross reference to mean that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.[6] Another aspect of the scope inquiry focuses on the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant informs the "conditions of approval" relevant to 3-year exclusivity.

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[4] See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv).

[5] See generally, 21 CFR 314.108.

[6] See Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Oct. 5, 2015) (Docket No. FDA-2015-P-2482), aff'd *Otsuka Pharmaceutical Co., Ltd., et al v. FDA*, Case No. 1:15-cv-01688-KBJ (D.D.C. July 28, 2016) (upholding FDA's interpretation of section 505(c)(3)(E)(iii) that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity) (currently pending appeal).

For supplements to approved NDAs, section 505(c)(3)(E)(iv) of the FD&C Act states:

> *If a supplement to an application approved under subsection (b) [of this section] is approved after [September 24, 1984,] and the supplement contains reports of new clinical investigations (other than bioavailabilty [sic] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement,* the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for a **change approved in the supplement** effective before the expiration of three years from the date of the approval of the supplement under subsection (b) [of this section] . . . . [(emphasis added)].

Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA and a supplement to an NDA, FDA has taken a consistent approach to both types of applications in determining eligibility for 3-year exclusivity and scope. The eligibility clause in section 505(c)(3)(E)(iv) (italicized) corresponds to the eligibility clause in section 505(c)(3)(E)(iii) of the FD&C Act, except, among other things, in section 505(c)(3)(E)(iv), the word "supplement" is substituted for the word "application" in section 505(c)(3)(E)(iii). As with an original NDA, a supplement may be eligible for 3-year exclusivity if it contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the supplement that were conducted or sponsored by the applicant submitting the supplement.

The bar clause of section 505(c)(3)(E)(iv) (underlined) describes 3-year exclusivity as blocking approval of a 505(b)(2) application for "a change approved in the supplement." Although this language is not identical to the phrase "conditions of approval of such drug in the approved subsection (b) application" used in section 505(c)(3)(E)(iii), in determining the scope of exclusivity and which applications are barred, there are likewise two aspects of the inquiry. One aspect of the inquiry focuses on the drug at issue. Under FDA's interpretation of section 505(c)(3)(E)(iv) of the FD&C Act, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity. If the 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety) to which exclusivity has attached, then the second aspect of the scope inquiry applies. This aspect of the scope inquiry focuses on the exclusivity-protected change approved in the supplement. FDA examines the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the supplement. If the 505(b)(2) application for a single-entity drug is for the same drug for the same exclusivity-protected change approved in the supplement, it will be blocked. However, 3-year exclusivity does not block a 505(b)(2) application for the same drug that does not seek approval for the exclusivity-protected change approved in the supplement.

III. Discussion and Conclusion

At issue here is whether the 3-year exclusivity for Valcyte blocks the approval of Exela's 505(b)(2) application for Ganciclovir.

Although Valcyte and Exela's Ganciclovir have different active ingredients—valganciclovir HCl and ganciclovir, respectively—the products have the same active moiety, ganciclovir. Because the two products at issue contain the same active moiety, Exela's Ganciclovir could potentially be barred by Valcyte's unexpired 3-year exclusivity.

The Board must therefore consider whether the 505(b)(2) applicant is seeking approval for the exclusivity-protected changes approved in the supplements for Valcyte. The Board concludes that Exela is not seeking approval for the exclusivity-protected changes approved in the supplements. Valcyte's 3-year exclusivity relates to the new pediatric uses approved in the supplements. Exela is seeking approval of Ganciclovir for only adult indications: the treatment of CMV retinitis in immunocompromised adult patients, including patients with AIDS, and prevention of CMV disease in adult transplant recipients at risk for CMV disease. Exela is not seeking approval of Ganciclovir for any pediatric uses, and therefore, the conditions of approval for Ganciclovir are clearly outside the scope of Valcyte's 3-year exclusivity.

The Board recommends that any unexpired 3-year exclusivity for Valcyte should not block the approval of Exela's Ganciclovir injection 500mg/250ml (NDA 209347).

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/s/

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02/16/2017