DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-304/S-008
NDA 22-257/S-003

SUPPLEMENT APPROVAL

Hoffmann-La Roche Inc.
Matthew Brammer, Pharm.D., M.S.
Program Manager
Pharma Development Regulatory
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Brammer:

Please refer to your Supplemental New Drug Application (sNDA) dated October 2, 2009, received October 7, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Valcyte (valganciclovir hydrochloride) 450 mg Tablets.

Please refer to your sNDA dated July 29, 2010, received August 2, 2010, submitted under 505(b) of the FDCA for Valcyte (valganciclovir hydrochloride) for oral solution.

We acknowledge receipt of your submissions to NDA 21-304/S-008 dated October 12, 2009, December 17, 2009, January 29, 2010, February 3, 2010, March 19, 2010, March 22, 2010, April 13, 2010, April 22, 2010, May 7, 2010, May 13, 2010, May 21, 2010, June 1, 2010, June 11, 2010, July 29, 2010, and July 30, 2010.

These Prior Approval supplemental new drug applications propose the following:

- To extend the current dosing regimen to 900 mg (two 450 mg tablets) once a day within 10 days of transplantation until 200 days post-transplantation for the prevention of cytomegalovirus (CMV) disease in adult kidney transplant patients at high risk (donor CMV seropositive/recipient CMV seronegative);

- To add an upper limit to the creatinine clearance calculated using the Schwartz formula used for determination of pediatric doses; and

- To revise the Patient Package Insert to include more patient friendly language.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert,) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for these NDAs, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed container labels that are identical to the enclosed immediate container labels submitted on July 29, 2010, as soon as they are available, but not more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submission in Electronic Format-Human Pharmaceutical Product Applications and Related Submissions Using eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies mounted on heavy-weight paper or, similar material. For administrative purposes, designate this submission **"Product Correspondence-Final Printed Catron and Container Labels for approved NDA 21-304/S-008 and NDA 22-257/S-003."** Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 months to less than 4 months because very few patients in this age group undergo kidney transplantation and, therefore, necessary studies are highly impracticable.

We are deferring submission of your pediatric study for ages 4 months to 16 years of age until August 31, 2013, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1670-1 Tolerability study of up to 200 days of valganciclovir for oral solution or tablets in pediatric kidney transplant recipients.

Final Protocol Submission:	August 31, 2010
Study Completion:	June 30, 2013
Final Report Submission:	August 31, 2013

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Valcyte (valganciclovir hydrochloride) Tablets were approved on March 29, 2001, and Valcyte (valganciclovir hydrochloride) for Oral Solution was approved on August 28, 2009, we are aware of widespread use of Valcyte (valganciclovir hydrochloride) and ganciclovir for the treatment or prevention of CMV infections, which has increased the serious risk of drug resistance leading to treatment failure. Therefore, analyses of Valcyte (valganciclovir hydrochloride)-resistant CMV isolates from patients not responding to treatment are necessary to help physicians determine appropriate use of Valcyte (valganciclovir hydrochloride). Moreover, understanding the levels of resistance conferred by specific mutations is important in selection and design of alternative therapies. Because the reported incidence of CMV resistance to ganciclovir is rising, we consider this to be "new safety information" as defined in FDAAA.

Since approval of both NDAs, we have also become aware of data from Study NT18435, related to the treatment and prevention of CMV disease, regarding potential effect on spermatogenesis in humans. Since approval, Valcyte (valganciclovir hydrochloride) has carried a boxed warning regarding potential effects on spermatogenesis based on preclinical study data. Data submitted with this application support increasing the dosing duration of Valcyte (valganciclovir hydrochloride) for CMV prevention in kidney transplant patients from 100 days to 200 days, thereby potentially increasing the serious risk for adverse effects of Valcyte (valganciclovir

hydrochloride) on spermatogenesis. This potential effect has not been evaluated in any clinical trial, including Study NT18435, used to support extending treatment from 100 days to 200 days. Therefore, we consider this information to also be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of the potential serious risks of impaired spermatogenesis in humans and drug resistance leading to treatment failure.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1670-2: Characterization of the following amino acid substitutions in the pUL54 DNA polymerase. Cross-resistance to cidofovir and foscarnet should be evaluated in pUL54 amino acid substitutions.

Prioritization of Uncharacterized Amino Acid Substitutions in the pUL54 DNA Polymerase:

High Priority	**Medium Priority**	**Low Priority**
E235G, D277N, N345S, V476G, V482G, Q578H/L, A619T, S660G/N, F718L/S, I726V/T, E793V, Q795P/R, V902M/G, M959T	F357L, T437M, A505V, S612N, S649P, V654G, G822D, M828V, P859A, E903G	Q229K, D247N, D262N, T271A, V284E, D288N, Y380C, F396L, L424V, F460l, A543S, R581H, G667N, A692G, K947E, I960V

Protocol Submission:	COMPLETED
Study Start:	COMPLETED
Final Report Submission-High Priority:	March 31, 2011
Final Report Submission-Medium Priority:	September 30, 2011
Final Report Submission- Low Priority:	June 30, 2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of the potential serious risk of impaired spermatogenesis in humans.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1670-3: Testicular toxicity trial to investigate the effects of ganciclovir on spermatogenesis in humans.

Final Protocol Submission:	December 31, 2010
Trial Completion:	June 30, 2014
Final Report Submission:	December 31, 2014

Submit the protocol to your IND 48,106, with a cross-reference letter to these NDAs. Submit all final reports to these NDAs. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you that there are PMRs and PMCs listed in the September 12, 2003, and August 28, 2009, approval letters that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314(b)(3)(i)]. From FDA 2253 is available at http:/www.fda.gov/opacp/morechoices/fdafroms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials refer to the Division of Drug Marketing, advertising and Communications (DDMAC), see http:www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22257	SUPPL-3	ROCHE PALO ALTO LLC	VALCYTE
NDA-21304	SUPPL-8	ROCHE PALO ALTO LLC	VALCYTE(VALGANCICLOVIR HYDROCHLORIDE)450

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
08/05/2010

DEBRA B BIRNKRANT
08/05/2010