DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT

IND 25,082/ NDA 19-661 (ganciclovir)
IND 48,106/ NDA 21-304 (valganciclovir)

Hoffman-La Roche Inc.
Attention: Wendy Corbett, Ph.D., MBA
Senior Program Manager, Pharma Development Regulatory
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Corbett:

Please refer to your correspondences dated March 29, 2007 and May 7, 2007, requesting changes to FDA's Written Request for pediatric studies for ganciclovir and valganciclovir.

We have reviewed your questions and we are amending the Written Request to:

- extend the timeframe for submitting reports of the studies
- modify the pharmacokinetic study endpoints in Studies 2 and 3, respectively
- change the title of Study 2

For clarity, the full text of the Written Request, as amended, follows. This Written Request supersedes all previous versions.

Study #1

- *Type of study:* An open label, dose escalation pharmacokinetic and safety study of valganciclovir in pediatric renal transplant recipients.

- *Study objectives:* 1) To determine the once daily dose of oral valganciclovir that will achieve a ganciclovir 24-hour AUC equivalent to that achieved with standard dosage regimens of intravenous (I.V.) ganciclovir; and (2) to determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir liquid and I.V. administration of ganciclovir

- *Indication to be studied:* Prevention of CMV disease.

- *Age group in which study will be performed*: A minimum of approximately 13 patients with at least five from the age group ≤ 6 years and at least eight from the age group > 6 years to puberty.
- *Study endpoints:* Pharmacokinetic parameters such as: CL, Vss, AUC_{0-24}, C_{max}, and t1/2.

- *Dosage form:* Ganciclovir for I.V. infusion; age-appropriate formulation of valganciclovir.

- *Route of administration:* I.V. (ganciclovir), oral (valganciclovir)

- *Drug specific safety concerns*: Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1) Descriptive analysis of pharmacokinetic data; and 2) descriptive analysis of safety data.

Study #2

- *Type of study:* An open label, comparative pharmacokinetic and safety study in pediatric liver transplant recipients.

- *Study objectives:* 1) To determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir; and 2) to collect safety data in a population of pediatric liver transplant recipients.

- *Indication to be studied:* Prevention of CMV disease

- *Age group in which study will be performed*: A minimum of approximately 20 liver transplant recipients from 3 months to 16 years of age with at least 4 patients in each of 3 age groups: ≤ 2 years; 2 to 6 years; and > 6 years.

- *Study endpoints:* 1) Pharmacokinetic parameters such as: total clearance, Vss, $AUC_{0\text{-}24}$, C_{max}, and t1/2; and 2) incidence of CMV disease.

- *Dosage form:* Ganciclovir for IV infusion; age-appropriate formulation of valganciclovir.

- *Route of administration:* I.V. (ganciclovir), oral (valganciclovir)

- *Drug specific safety concerns*: Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1) Descriptive analysis of safety data; and 2) descriptive analysis of pharmacokinetic data.

Study #3

- *Type of study:* Multi-center, open label, non-comparative safety and pharmacokinetic study in pediatric patients with solid organ transplants.

- *Study objectives:* 1) To determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir; and 2) to collect safety data in a population of pediatric solid organ transplant recipients.

- *Indication to be studied:* Prevention of CMV disease

- *Age group in which study will be performed*: A minimum of approximately 60 patients with solid organ transplants at risk for CMV disease with at least 10 patients ≤ 2 years of age, and at least 15 patients in the age group of 2 years-puberty.

- *Study endpoints:* 1) Pharmacokinetic parameters such as: total clearance, Vss, AUC_{0-24}, C_{max}, and t1/2; and 2) incidence of CMV disease.

- *Dosage form:* Age-appropriate formulation of valganciclovir

- *Route of administration:* Oral

- *Drug specific safety concerns*: Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1) Descriptive analysis of safety data; and 2) descriptive analysis of pharmacokinetic data.

Study #4

- *Type of study*: Single-dose and multiple-dose pharmacokinetic and tolerability study of valganciclovir liquid formulation in a neonatal population with congenital CMV disease

- *Study objectives:* The determination of appropriate dosing of valganciclovir and collection of safety data in a neonatal population.

- *Indication to be studied:* Treatment of congenital CMV disease.

- *Age group:* Birth to approximately 3 months (number of patients adequate to determine dose).

- *Study endpoints:* 1) Pharmacokinetic parameters such as CL/F, V/F, AUC, Cmax and t1/2; 2) plasma CMV virologic measurements; and 3) collection of long-term safety data following administration of valganciclovir to neonates with congenital CMV infection.

- *Dosage form:* Liquid

- *Route of administration:* Oral

- *Drug specific safety concerns:* Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1) Descriptive analysis of safety data; and 2) descriptive analysis of pharmacokinetic data.

Labeling that may result from the studies:
Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies.

Format of reports to be submitted:
You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations

for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or not Hispanic/ Latino.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before March 31, 2008. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:
As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency of your intent to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a **new drug application (NDA) or as a supplement to an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e., approval, approvable, not approvable); or
4. The exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC**

STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at 301-796-0669.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Acting Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Edward Cox
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