DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 25,082/ NDA 19-661; 20-460 (ganciclovir)
IND 48,106/ NDA 21-304 (valganciclovir)

Hoffman-La Roche Inc.
Attention: Melanie Bishop
Program Director
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Bishop:

Reference is made to our initial Pediatric Written Request dated June 1, 2001 for ganciclovir (NDAs 19-661; 20-460) and for valganciclovir (NDA 21-304), and to your general correspondence submission dated July 25, 2000. In addition, please refer to the teleconference held with Hoffman-La Roche and members of this Division on September 14, 2001. This amended Pediatric Written Request supercedes the initial Written Request dated June 1, 2001.

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}, Cmax, 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.

- *Labeling that may result from the study:* Appropriate sections of the labels may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before December 31, 2004. Please remember that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Study #2

- *Type of study:* An open label, non-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_{0-12}, AUC_{0-24}, Cmax, 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.

- *Labeling that may result from the study*: Appropriate sections of the labels may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before December 31, 2004. Please remember that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

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_{0-12}, AUC_{0-24}, Cmax, 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.

- *Labeling that may result from the study*: Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before December 31, 2004. Please remember that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

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 study:* Appropriate sections of the label may incorporate dosing information for neonates.

- *Format of reports to be submitted:* Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study: Reports of the above studies must be submitted to the Agency on or before December 31, 2004. Please remember that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Reports of the studies that meet the terms of the Written Request dated 1 June 2001, as amended by this letter must be submitted to the Agency on or before December 31, 2004, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Please submit protocols for the above studies to an investigational new drug applications 25,082 and 48,106 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. Please 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 supplement to your approved NDAs 21-304 and 19-661/20-460 with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please 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. Please also 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.

If you wish to discuss any further amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

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, contact Leslie Stephens, Regulatory Project Manager, at 301-827-2335

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D.
Acting Director
Office of Drug Evaluation IV
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/

Mark Goldberger
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