



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**WRITTEN REQUEST – AMENDMENT 3**

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 correspondence dated February 19, 2008, requesting changes to FDA's June 21, 2001 Written Request for pediatric studies for ganciclovir and valganciclovir.

We have reviewed your proposed change, requesting an extension of the timeframe for submitting reports of the FDA's Written Request for pediatric studies for ganciclovir and valganciclovir, and are amending the Written Request to extend the timeframe for submitting reports of the studies. All other terms stated in our Written Request issued on June 21, 2001, and as amended on November 6, 2001 and June 1, 2007, remain the same.

**Timeframe for submitting reports of the studies:**

Reports of the pediatric studies must be submitted to the Agency on or before December 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.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated June 21, 2001, as amended by this letter and by previous amendment(s) dated November 6, 2001 and June 1, 2007, must be submitted to the Agency on or before December 31, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies 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 (301-827-5911) 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 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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the studies demonstrate that ganciclovir/valganciclovir is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study reports. These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. 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).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

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

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Sincerely,

*{See appended electronic signature page}*

Edward Cox, M.D., M.P.H.  
Director  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure: Attachment

Attachment

Reference is made to your Proposed Pediatric Study Request submitted on July 25, 2000 to IND 48,106 for valganciclovir. Reference is also made to NDA 19-661 and NDA 20-460 for ganciclovir.

To obtain needed pediatric information on ganciclovir and valganciclovir, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

**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  $\leq 6$  years and at least eight from the age group  $> 6$  years to puberty.
- *Study endpoints:* Pharmacokinetic parameters such as: CL, Vss, AUC<sub>0-24</sub>, C<sub>max</sub>, and t<sub>1/2</sub>.
- *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:  $\leq 2$  years; 2 to 6 years; and  $> 6$  years.
- *Study endpoints:* 1) Pharmacokinetic parameters such as: total clearance,  $V_{ss}$ ,  $AUC_{0-24}$ ,  $C_{max}$ , and  $t_{1/2}$ ; 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  $\leq 2$  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,  $V_{ss}$ ,  $AUC_{0-24}$ ,  $C_{max}$ , and  $t_{1/2}$ ; 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 December 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.

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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.

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/s/

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Edward Cox  
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