DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20,363
IND 34,928

Novartis Pharmaceuticals Corporation
Attention: Sheila A. Mathias, Ph.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Mathias:

Reference is made to your correspondence dated September 15, 2006 and October 6, 2006 requesting changes to FDA's Written Request for pediatric studies for famciclovir. Reference is also made to your correspondence dated November 2, 2006. We have reviewed your questions and we are amending the Written Request to:

- modify the sections 'Types of studies" and **"**Age groups in which studies will be performed and the number of patients to be studied" by eliminating the adolescent cohort from Study 1.
- clarify the section "Indication to be studied."
- modify the pharmacokinetic study endpoints.
- clarify when single-dose or multiple-dose data are needed.

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

Types of studies:

Study #1: A multiple-dose safety study with a single-dose pharmacokinetic substudy in pediatric patients ages 1 to 12 years who have herpes simplex virus (HSV) or varicella zoster virus (VZV) infection.

Study #2: A single-dose pharmacokinetic and safety study in infants ages 1 month to <1 year who have: a current HSV infection, or who may have a potential recurrence of HSV infection, or immunocompromised patients at risk for development of HSV infection.

Age-appropriate safety data should be collected for Studies 1 and 2. The pharmacokinetic substudy from Study 1 must be performed prior to conducting Study 2 in order to assess appropriate dosing. The information from the pharmacokinetic substudy must be reviewed by the Division of Antiviral products prior to the initiation of Study 2.

Age groups in which studies will be performed and the number of patients to be studied:

Study 1: The minimum number of patients by age group to be enrolled in the pharmacokinetic substudy in children ages 1 to 12 years with HSV or VZV infection is as follows:

Cohort 1: 1 year to < 2 years: 6 patients
Cohort 2: 2 years to < 6 years: 12 patients
Cohort 3: 6 years to < 12 years: 8 patients

Enrolled patients for the pharmacokinetic substudy must be approximately evenly distributed for disease (HSV or VZV infection) and age across each cohort studied.

After a dosing regimen has been selected for the HSV and VZV infections, based on the results of the pharmacokinetic substudy, enrollment in Study 1 will continue until a total of 100 patients have been enrolled at the chosen dose(s) for HSV and VZV infections. The number of patients with HSV- or VZV-infections must be approximately evenly distributed for disease (HSV- or VZV-infection) and across the age range studied.

Study 2: The minimum number of patients by age group to be enrolled in the single-dose pharmacokinetic study in children ages 1 month to < 1 year with a current HSV infection, or who may have a potential recurrence of HSV infection, or immunocompromised patients at risk for development of HSV infection is as follows:

Cohort 1: 1 month to < 3 months: 6 patients
Cohort 2: 3 months to < 6 months: 6 patients
Cohort 3: 6 months to < 1 year: 6 patients

The number of patients in Study 2 must be distributed approximately evenly within cohort age ranges.

Both studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability.

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Indication to be studied:

Study 1: treatment of HSV or VZV infection.

Study 2: treatment of current HSV infection or suppression of a potential recurrence of HSV infection, or prophylaxis in immunocompromised patients at risk for development of HSV infection.

Drug Information:

Dosage form: Age appropriate-formulation.

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

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Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address, including neutropenia, renal toxicity, CNS toxicity, hepatic toxicity, gastrointestinal toxicity, and any other parameters pertinent to use in this population.

Safety of famciclovir must be studied in an adequate number of pediatric patients to characterize adverse events across the age range studied. Approximately 100 patients, ages 1-12 years with HSV- or VZV-infections, with multiple-dose safety data at the recommended dose(s) are required. The number of patients with HSV- or VZV-infections must be approximately evenly distributed for disease (HSV- or VZV-infection) and across the age range studied.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of single-dose pharmacokinetic and multiple-dose safety data in HSV- or VZV-infected pediatric patients ages 1 year to 12 years and descriptive analyses of single-dose pharmacokinetic and safety data in HSV-infected pediatric patients 1 month to <1 year of age. A minimum number of pediatric patients (as stated above) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max}, $T_{max,}$ and AUC.

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 June 30, 2009. 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. 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 new drug application or as a supplement to your approved NDA 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.

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, 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.

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 in the pediatric population.

If you have any questions, please contact Paras M. Patel, R.Ph., Regulatory Project Manager, at (301) 796-0783.

Sincerely,

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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