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: Roxanne Tavakkol
Senior Regulatory Project Manager
Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Tavakkol:

Reference is made to our initial Pediatric Written Request dated September 10, 2001 for famciclovir (NDA 20-363). We are amending this Pediatric Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the initial Written Request dated September 10, 2001.

Type of studies:

Study #1: A multiple-dose safety study with a pharmacokinetic substudy in infants and children ages 1 to 12 years who have Herpes Simplex Virus infection.

Study #2: A multiple-dose safety study with a pharmacokinetic substudy in infants and children ages 1 to 12 years who have Varicella Zoster Virus infection.

Study #3: A single-dose pharmacokinetic and safety study in infants and children ages 1 month to less than 1 year who have a current Herpes Simplex Virus infection or who may have a potential recurrence, or immunocompromised infants and children who are at risk for development of Herpes Simplex Virus infection.

Age-appropriate safety data should be collected for Studies 1, 2, and 3. The pharmacokinetic substudies from Study #1 and Study #2 will be performed prior to conducting Study #3 in order to assess appropriate dosing. The information from the pharmacokinetic substudies must be reviewed by the Division of Antiviral Drug Products prior to the initiation of Study #3.

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

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

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

After a dosing regimen has been selected based upon the results from the pharmacokinetic substudy, enrollment in Study #1 will continue until a total of 50 subjects have been enrolled at the chosen dose for HSV infection.

Study#2: The approximate number of patients by age group to be enrolled in the pharmacokinetic substudy in children ages 1 to 12 years with VZV infection is as follows:

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

After a dosing regimen has been selected based upon the results from the pharmacokinetic substudy, enrollment in Study #2 will continue until a total of 50 subjects have been enrolled at the chosen dose for VZV infection.

Study#3:

Cohort 1: 1 month to <3 months: approximately 6 subjects
Cohort 2: 3 months to <6 months: approximately 6 subjects
Cohort 3: 6 months to <1 year: approximately 6 subjects

For Studies #1, #2, and #3 the number of patients should be uniformly distributed across the age ranges studied.

Study Endpoints for Studies # 1, 2, 3:
Pharmacokinetic parameters such as Cmax, Cmin, Tmax, t½, AUC and Cl/F. Safety is to be assessed in all studies.

Drug Information:

1. **Dosage form:** The studies described above will use an age-appropriate formulation of famciclovir. The relative bioavailability of the age-appropriate formulation will need to be determined and compared with the marketed formulation of famciclovir. Full reports of any relative bioavailability studies will be submitted to the Agency. If a marketable age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful will need to be submitted. Under these circumstances other formulations can be used if they are standardized, palatable, and shown to be of

acceptable relative bioavailability compared with the marketed product. In addition, the standardized formulation that you develop must be stable for at least the anticipated duration of dosing usually prescribed for HSV infection and VZV infection.

2. **Route of administration:** oral

3. **Regimen:** To be determined by development program. Once the appropriate dosing regimens are selected for Herpes Simplex Virus infection and Varicella Zoster Virus infection, additional patients will be enrolled in Studies #1 and #2 in order to obtain safety data at the chosen doses.

Drug specific safety concerns:
Neutropenia, renal toxicity, CNS toxicity, nausea, vomiting, diarrhea and elevated transaminases.

Statistical information, including power of study and statistical assessments
Studies #1, 2, and 3:

- Descriptive analyses of pharmacokinetic data in HSV-infected pediatric patients and VZV-infected pediatric patients and immunocompromised infants and children who are at risk for development of HSV infection.
- Descriptive analyses of reported adverse events.
- Descriptive analyses of patient's response to therapy.

Labeling that may result from these studies:
Information regarding the pharmacokinetics and safety of famciclovir in the pediatric population.

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. Please include other information as appropriate.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before December 31, 2006. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in responses to this Written Request.

Please submit protocols for the above studies to IND 34,928 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. 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.

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. We will notify you in writing if we agree to any changes to this Written Request.

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, please call Donald W. Reese, PharmD, MBA, Regulatory Project Manager, at (301)-827-2361.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., M.P.H.
Director (Acting)
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/

Edward Cox

12/12/03 07:54:20 PM