NDA 21-036/S-001

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Glaxo Wellcome, Inc.
Attention: Sherman N. Alfors
Project Director, Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Alfors:

Please refer to your supplemental new drug application dated October 25, 1999, received October 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relenza® (zanamivir for inhalation).

We acknowledge receipt of your submissions dated:

October 25, 1999	March 3, 2000	April 3, 2000
February 7, 2000	March 6, 2000	April 11, 2000
February 18, 2000	March 9, 2000	April 17, 2000
February 24, 2000	March 14, 2000	April 21, 2000 (2)
February 25, 2000	March 21, 2000	
March 1, 2000	March 29, 2000	

This supplemental new drug application provides for the use of Relenza® for the treatment of uncomplicated acute illness due to influenza A and B in pediatric patients 7 years and older who have been symptomatic for no more than 2 days.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, patient package insert, and patient instruction leaflet) and submitted draft labeling (package insert, patient package insert, and patient instruction leaflet submitted April 21, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-036/S-001." Approval of this submission by FDA is not required before the labeling is used.

In addition to the Phase 4 commitments agreed upon with the approval of original NDA 21-036, we remind you of your Phase 4 commitments for this supplemental application specified in your submission dated April 21, 2000. These latter commitments, along with any completion dates agreed upon, are listed below.

1. Provide subgroup analyses for efficacy and safety in pediatric age groups from applicable studies with pediatric subgroups.

2. Develop, conduct, and report a study to assess the ability of children and adolescents of various ages to use the zanamivir dry powder inhalation system (Diskhaler) based on patient or parental comprehension of the proposed Instructions for Use. This study will seek to identify potential obstacles to effective use by categories of potential patients arising from characteristics of the Diskhaler and the Instructions for Use. This study will also seek to develop and test improvements in Instructions for Use that may lead to more reliably effective use by pediatric patients in the settings characteristic of the indication (i.e., primary care medical care settings, acutely ill children, need for instructions that will reliably lead to appropriate use beginning with the first dose). This study may be conducted as a substudy on pediatric subjects within a larger study enrolling both pediatric and adult subjects. Submit the draft protocol for review and comment to assure that the design of the study is adequate to address this commitment.

3. Provide a plan to increase information regarding safety and efficacy in racial and ethnic minority patients. This plan should include (a) subgroup analyses of Caucasian versus non-Caucasian patient subgroups for primary safety and efficacy endpoints as part of the final study report for recently completed and ongoing studies; (b) targeted recruitment of non-Caucasian patients in ongoing and future studies, including the labeling comprehension study on use of the Diskhaler with its Instructions for Use; (c) a summary and aggregate analysis of results for different racial/ethnic populations across studies; and (d) a review of Glaxo Wellcome's global postmarketing adverse event database for reports of lactose intolerance in non-Caucasian patients.

4. Provide a progress report (as part of the existing Phase 4 commitment for detection and analysis of influenza resistance to zanamivir) on the work toward improving culture yield and increasing the number of isolates examined from both clinical trials and postmarketing surveillance. Provide the plan for examining zanamivir-resistant clinical isolates of influenza for cross-resistance.

5. Within one month of approval of S-001, provide a proposal for a letter to health care professionals describing safety issues noted with the use of zanamivir and a proposal for dissemination of this letter. This letter will (a) address the safety-related modifications to the package insert (including but not limited to reports of serious respiratory adverse events in patients with and without underlying respiratory disease), (b) remind health care professionals to also consider bacterial etiologies when patients present with influenza-like illnesses, and (c) address the change in pregnancy category. Following the Division's review of this proposal and agreement on content and mode of dissemination, this letter will be distributed within one month (most likely in June or July) and before the drug is promoted for pediatric use.

   A second letter to health care professionals (covering the same safety issues as the first letter and incorporating any needed safety updates) will be drafted and submitted to the Division for review. Following the Division's review and agreement on content and dissemination, this letter will be distributed prior to the next influenza season (i.e., mailing to be completed by end-October 2000).

6. For each postmarketing adverse drug experience with a fatal outcome, Glaxo Wellcome will make diligent efforts to obtain additional information about antecedent and concomitant medical circumstances of the fatality. These diligent efforts will include requesting that each health care professional reporter provide a copy of medical records, results of laboratory or diagnostic tests, and an autopsy report (if an autopsy was performed). Prepare and submit "15-Day Alert Reports - Follow Up" to report such information in accordance with 21 CFR 314.80 (c)(1)(ii).

7. Collect and submit specific postmarketing adverse drug experience information directly to DAVDP as follows:
   a. Submit each serious postmarketing adverse drug experience report (involving one or more of the respiratory system, cardiovascular system, allergic and allergic-like reactions) directly to DAVDP within 15 calendar days of receipt, regardless of whether the adverse drug experience is classified as expected or unexpected.
   b. Submit a report of each fatal postmarketing adverse drug experience directly to DAVDP within 15 calendar days of receipt, regardless of whether the fatality is classified as expected or unexpected, and regardless of which specific organ system is involved.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study,

expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have submitted in this application safety and efficacy information in children 5 years of age and older. However, the totality of the evidence did not adequately support approval for children under age 7 years. Because it is not likely that pediatric patients less than seven years of age will be able to use this formulation of zanamivir with the delivery device during an acute influenza illness, we hereby defer any requirement for further pediatric studies until December 31, 2002. However, in the interim, please submit an update on your development plans regarding pediatric use of the nebulized formulation you have discussed in the past, within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule. As you are aware, determination of pediatric exclusivity for Relenza® is deferred to a later date, when all of the requirements outlined in the Pediatric Written Request letter, dated December 29, 1998, have been fulfilled.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

NDA 21-036/S-001

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

When any letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Virginia Yoerg, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure