NDA 20-357

DEC 2 9 1994

Lipha Pharmaceuticals Inc.
Attention: Gerard L. Daniel, M.D.
Chairman, President & Chief Executive Officer
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Dr. Daniel:

Please refer to your September 29, 1993, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glucophage (metformin hydrochloride tablets) 500 and 850 mg Tablets.

We acknowledge receipt of your amendments dated September 29, November 12, 16, 18, 19, and 23, and December 1, 6, 13, and 15, 1993; and January 11 (2), February 2, 3, 4, 7, 11, 15, and 23, March 4, 7, 11, and 12 (2), May 12, 13, 19, 20, and 27, June 15 and 22, August 19, 30, and 31, October 19 and 28, November 8, 11, 21, 22, and 29, and December 28 and 29 (2), 1994. Your major amendment of August 19, 1994, extended the Goal Date for this NDA to December 29, 1994.

This new drug application provides for the use of Glucophage as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II diabetes), whose hyperglycemia cannot be satisfactorily managed on diet alone.

We have completed the review of this application as amended, including the submitted draft labeling, 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 draft labeling submitted September 29, 1993 (bottle labels), November 11 (blister packaging), and December 29, 1994 (package insert). Accordingly, the application is approved, effective on the date of this letter.

Please submit 15 copies of the final printed labeling (FPL) as soon as available, in no case more than 30 days after it is printed. The FPL must be identical to the draft labeling submitted September 29, 1993 (bottle labels), November 11 (blister packaging), and December 29, 1994 (package insert). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. Please individually mount 10 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-357. Approval of this labeling by FDA is not required before it is used.

We refer to your communication dated December 28, 1994, proposing a patient package insert (PPI). Although we have not completed our review of the PPI, we will do so in the near future. We also refer to your communication of December 29, 1994, in which you committed not to market Glucophage without an accompanying PPI containing mutually agreeable language. You also stated in the latter submission that each bottle of 100 tablets will include a

copy of the approved PPI, and if larger bulk containers are proposed in the future, an appropriate mechanism for distributing the PPI to each patient will be developed in consultation with FDA.

In addition, please submit three copies of the introductory promotional material 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 the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please include the MedWatch telephone number in all your advertising and promotional materials (1-800-FDA-~~0178~~ 1088). Not corrected in original letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Your communications of May 27 and August 31, 1994, commit to performing Phase 4 studies as follows:

1) Your May 27 submission contains a draft of a dose-ranging protocol (No. 94-02-6023) entitled "Dose-Response Study of Various Dose Levels of Metformin v. Placebo in Non-Insulin-Dependent Diabetic Outpatients." A final protocol should be submitted to your IND to conduct this study.

2) Your August 31 submission includes a draft proposal (in response to our letter dated June 29, 1994) for a prospective, randomized, controlled clinical trial involving 10,000 patients with NIDDM to focus on detection, confirmation, and evaluation of the incidence of lactic acidosis while taking Glucophage. Further, you have submitted a detailed protocol to IND on December 8, 1994. We will now solicit a written review of the protocol by several consultants. Their comments will be provided to you so that you can refine the protocol and submit a final version to the IND prior to initiation of the study.

Prominently identify all communications regarding these Phase 4 studies as such.

Your communication of August 31 also provides an overview of the type of medical education program to be conducted by Bristol-Myers Squibb for various health professionals. You indicate that it will primarily emphasize preventing the occurrence of lactic acidosis with proper Glucophage usage.

Please note that we will very likely convene an Endocrinologic and Metabolic Drugs Advisory Committee meeting after Glucophage has been marketed for one year to assess the implementation of the Phase 4 commitment in regard to the large cohort study and the completion of the Phase 4 commitment of the dose-response study.

Regarding the carton and blister-pack labels used for Glucophage Tablets, the "tablet" designation should appear as part of the established name, i.e., "metformin hydrochloride tablets" rather than "metformin hydrochloride." This change can be made some time after introduction of the drug and reported in the first annual report.

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

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

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, please contact:

Mr. John R. Short
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

12/29/94

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research