DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-496

Aventis Pharmaceuticals
Attention: Kimberly Davis, Senior Regulatory Analyst
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807-2854

Dear Ms. Davis:

Reference is made to your Proposed Pediatric Study Request, dated January 17, 2001, submitted to your new drug application (NDA) for Amaryl® (glimepiride) Tablets.

To obtain needed pediatric information on glimepiride, 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:

TYPE OF STUDY:

Study 1: A single-dose pharmacokinetic study or, alternatively, a population pharmacokinetic study in pediatric patients with type 2 diabetes.

Study 2: A clinical trial of 24-weeks' duration comparing glimepiride monotherapy versus metformin monotherapy in pediatric patients with type 2 diabetes.

INDICATION TO BE STUDIED (OBJECTIVE/RATIONALE):

Treatment of hyperglycemia in pediatric patients with type 2 diabetes whose hyperglycemia is not adequately controlled on a regimen of diet and exercise alone.

STUDY DESIGN:

Study 1: A single-dose pharmacokinetic study in which a 1.0 mg dose of glimepiride will be administered with breakfast. Alternatively, a population pharmacokinetic study with sparse sampling approach may be conducted in a subset(s) of patients in Study 2 during glimepiride monotherapy. For a population pharmacokinetic study, four blood samples should be obtained from each of the patients. It is recommended that blood samples be collected using an optimal sampling scheme over a 24-hour dosing period at the final steady-state dose level. Fixed sampling times should be avoided.

Study 2: A randomized, active-controlled clinical trial of 24-weeks' duration (post-randomization) in pediatric patients with type 2 diabetes not adequately controlled on diet and exercise alone. Patients will be blinded to their treatment. Investigators will not be blinded. Glimepiride should be titrated every four weeks for the first 12 weeks as necessary to achieve a target fasting plasma glucose (FPG) < 140 mg/dL. No dose increases will be allowed after Week 12. Back titration because of hypoglycemia (defined as glucose $\leq$ 36 mg/dL or third party intervention) is allowed. A sequential, escalating dose titration schedule of 1, 2, 4, or 8 mg once per day for glimepiride is recommended. The dosing schedule for metformin will be 500 mg twice-daily initially, and 1000 mg twice-daily from

Week 12 to Week 24. At your discretion, a third arm of glimepiride plus metformin can be added. No other antidiabetic medications will be allowed other than study medications.

AGE GROUP IN WHICH STUDY WILL BE PERFORMED:

Study 1: Approximately equal numbers of patients less than 12 years of age and 12 to 17 years of age. Approximately equal numbers of patients of each gender in each age group should be included.

Study 2: Patients will be under 18 years of age at randomization with at least 25% of patients under 12 years of age in all treatment groups.

NUMBER OF PATIENTS TO BE STUDIED:

Study 1: For a single dose pharmacokinetic study, at least 24 patients (preferably at least 12 males and at least 12 females) will be studied. If the study design is a population pharmacokinetic study, a subset of at least 40 patients from the glimepiride arm of Study 2 will be studied.

Study 2: At least 75 patients per arm must complete 24 weeks of on-study follow-up.

ENTRY CRITERIA (STUDIES 1 AND 2):

Patients must have a clinical diagnosis of type 2 diabetes with HbA1c values between 7.1 and 12% after 3 months of diet and exercise management.

Patients must have post-sustacal C-peptide levels ≥ 1.5 ng/dL.

GAD (glutamic acid decarboxylase) and ICA (islet cell antigen) autoantibodies must be shown to be negative to exclude a diagnosis of type 1 diabetes.

Patients must have a serum creatinine <1.0 dL/mL or be shown to have a normal creatinine clearance.

Patients must be recruited from those who have not previously received an oral hypoglycemic agent. At least 50% of the study population must consist of patients who are African-American, Native American, or Latino/Hispanic.

Pregnancy testing: Females of childbearing potential should have a negative pregnancy test at screening and prior to randomization. Urine pregnancy testing should be performed at approximately Week 6 and at end of study.

STUDY ENDPOINTS AND TIMING OF ASSESSMENTS, INCLUDING PRIMARY EFFICACY ENDPOINTS:

Study 1: Pharmacokinetic parameters will include AUC, Cmax, Tmax, CL/F, Vss/F and $t_{1/2}$. If possible, the effect of demographic covariates (e.g., age, gender, and body weight) on pharmacokinetic parameters will be assessed.

Study 2: The primary efficacy endpoint will be the change from baseline in HbA1c at Week 24. Secondary efficacy endpoints will include FPG, fasting plasma lipids (total cholesterol, LDL, HDL, and triglycerides), and percent completers. Study medication pill counts will be taken as a measure of compliance.

Safety assessments will include vital signs, adverse events, body weight, height, and episodes of hypoglycemia (defined as glucose ≤ 36mg/dl or requiring third party intervention). In girls, menstrual patterns should be assessed. Assessments will take place at patient screening and at approximately Week 24 or exit. The dose and type of antidiabetic therapy at Week 24 or exit will be reported.

DRUG INFORMATION:

Dosage form: Tablets
Route of administration: Oral
Formulation: Same as marketed

REGIMEN:

Study 1: A single-dose pharmacokinetic study in which a 1.0 mg dose of glimepiride will be administered with breakfast.

Study 2: A sequential, escalating dose titration schedule of 1, 2, 4, or 8 mg once per day for glimepiride is recommended. The dosing schedule for metformin is 500 mg twice-daily initially, and 1000 mg twice-daily from approximately Week 12 to Week 24.

DRUG SPECIFIC SAFETY CONCERNS:

Concerns include changes in body weight and episodes of hypoglycemia.

STATISTICAL INFORMATION, INCLUDING:

Study 1: Descriptive summary of pharmacokinetic parameters.

Study 2: Treatment group comparisons for change from baseline in HbA1c will be made using an analysis of covariance (ANCOVA) model with baseline as covariate. The treatment difference in mean change from baseline in HbA1c will be assessed by a one-sided 97.5% confidence interval for the difference using adjusted means and the associated standard error from the ANCOVA model. To assess non-inferiority of the test drug compared to control, a non-inferiority margin of –0.3% in HbA1c should be applied. Analyses of data from both the intent-to-treat (ITT) population and the completers will be performed to ascertain if dropouts biased the ITT results. The ITT population will include all randomized patients who have baseline data and any post-baseline data.

LABELING THAT MAY RESULT FROM THE STUDIES:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

FORMAT OF REPORTS TO BE SUBMITTED:

Full study reports or analyses not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation, and with accompanying computer-based clinical and safety data listings.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES:

Reports of the above studies must be submitted to the Agency on or before **March 1, 2004.** Please keep in mind that pediatric exclusivity only attaches 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.

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. 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 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 you 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.

If you wish to discuss any amendments to the 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.

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, contact James Cross, Regulatory Project Manager, at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Jenkins

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