DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-178

1/31/01

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, Regulatory Science
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Mr. Randolph:

Reference is made to your Proposed Pediatric Study Request for Glucovance (glyburide and metformin HCl tablets) submitted on November 24, 1999, to IND 52,837.

To obtain needed pediatric information on fixed combination glyburide and metformin, 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 studies:

Study 1. A single-dose study of the pharmacokinetics of glyburide and metformin in children and adolescents with type 2 diabetes mellitus following administration of a fixed combination of glyburide and metformin.

Study 2. A 26-week, double-blind, parallel-group clinical trial in children and adolescents with type 2 diabetes mellitus to assess safety and efficacy of a fixed combination of glyburide and metformin as compared to glyburide monotherapy and metformin monotherapy.

The pharmacokinetic study (Study 1) should precede Study 2.

While not required by this Written Request, an open-label extension of the 26-week study is encouraged in which patients not adequately controlled on either glyburide or metformin alone (FBG > 140 mg/dL, HbA1c > 7.0%) are switched to Glucovance and titrated to optimal effect.

Indication to be studied:

Treatment of hyperglycemia in pediatric patients ≥10 and ≤16 years of age with Type 2 diabetes mellitus not adequately controlled with diet and exercise, with or without oral hypoglycemic agent therapy.

Age groups in which studies will be performed:

Studies 1 and 2. Children and adolescents ≥10 and ≤16 years of age.

Study Design:

Study 1. Open-label, single-dose pharmacokinetic study in children and adolescents with type 2 diabetes who are receiving stable insulin therapy. Glyburide and metformin blood levels are to be obtained before and sequentially after administration of a single tablet containing 1.25 mg glyburide and 250 mg metformin administered prior to breakfast.

Study 2. Positive-controlled, randomized, double-blind, parallel-group study for 26 weeks to compare the safety and efficacy of glyburide/metformin fixed combination to metformin monotherapy and glyburide monotherapy in pediatric patients with type 2 diabetes not adequately controlled with diet and exercise, with or without oral hypoglycemic agent therapy, and with FBG ≤ 350 mg/dL. Existing oral hypoglycemic therapy should be discontinued on enrollment. Patients still meeting entry criteria after a washout phase may then be randomized into one of the three treatment arms. All patients must receive diet counseling. The double-blind period of 26 weeks duration should include a titration phase with a goal of FBG ≤ 140mg/dL for all 3 treatment groups followed by at least 12 weeks at the highest titrated dose. The maximun titrated dose for each treatment arm will be:

≤20 mg once a day for the glyburide monotherapy arm
≤1000 mg[1] twice a day for the metformin monotherapy arm
≤5 mg glyburide/1000 mg metformin twice a day for the fixed combination arm

Criteria for the withdrawal of patients with sustained hyperglycemia should be incorporated into the protocol for patient safety.

Number of patients to be studied:

Study 1. At least 24 patients with a reasonable distribution of patients across the specified age range.

Study 2. A minimum of 150 patients with approximately equal randomization to glyburide monotherapy, metformin monotherapy, and fixed combination glyburide/metformin. There should be a reasonable distribution of patients across the specified age range in all treatment groups.

[1]Preliminary pharmacokinetic data in children suggest lower exposures to metformin relative to adults at equivalent nominal doses. As such, extrapolation of dosing recommendations from adults to children may not be justified. We recommend that the optimally effective dose of metformin be determined in children prior to finalizing the dosing recommendation for the 26-week study. If you determine that a dosing regimen different from the one recommended above is preferable, you must submit A PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES requesting the change.

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Entry Criteria:

Study 1. Males and females ≥ 10 years and ≤ 16 years of age with established type 2 diabetes mellitus who are receiving stable insulin therapy. Exclusion criteria should include the following: serum creatinine ≥ 1.0 mg/dL or abnormal creatinine clearance.

Study 2. Males and females ≥ 10 years and ≤ 16 years of age with type 2 diabetes mellitus not adequately controlled with diet and exercise, with or without oral hypoglycemic agent therapy, with FBG ≤ 350 mg/dL. Patients with type 1 diabetes mellitus must be excluded using accepted criteria.

Study Endpoints:

Study 1. Pharmacokinetic parameters such as Cmax, Tmax, AUC, CL/F, VSS/F, and t ½ for glyburide and metformin will be determined.

Study 2. The primary efficacy variable will be change from baseline in HbA1c. Secondary endpoints should include changes in fasting plasma glucose, body weight, and fasting and post-prandial insulin levels.

Drug Information:

Study 1.

- Route of administration: oral
- Regimen: fixed combination glyburide/metformin, 1.25 mg/250 mg, single dose
- Dosage form: tablets
- Formulation: marketed tablet

Study 2.

- Route of administration: oral
- Regimen: fixed combination glyburide/metformin, 1.25 mg/250 mg; glyburide 2.5 mg; or metformin 500 mg once daily initially with titration to glycemic control or maximum dose
- Dosage form: tablets
- Formulation: marketed tablets

Drug Specific Safety Concerns:

Studies 1 and 2. Diarrhea, gastrointestinal discomfort, hypoglycemia.

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Statistical Information:

Study 1. Descriptive summary of PK parameters.

Study 2. Statistical analysis of the 3 treatment groups will be performed using an ANCOVA model, with change in HbA1c at 26 weeks of double-blind treatment or last prior visit as the primary measure of efficacy, with a term for treatment and with the baseline value as the covariate. The primary analysis will be the intent-to-treat (ITT) population. Subjects who are withdrawn from the study due to lack of glycemic control will have their last blinded observation carried forward for the ITT analysis.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of studies 1 and 2.

Format of reports:

Full study reports 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 July 15, 2003. Please keep in mind that pediatric exclusivity only extends patent protection or exclusivity that has not expired or been previously extended 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 supplement to the 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.

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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.

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, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely yours,

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