

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-357/S019

CORRESPONDENCE

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 27-Nov-2000 10:42am EST
From: Saul Malozowski
MALOZOWSKIS
Dept: HFD-510 PKLN 14B32
Tel No: 301-827-6398 FAX 301-443-9282

TO: David Orloff (ORLOFFD)

CC: Jena Weber (WEBERJ)

CC: Robert Misbin (MISBINR)

Subject: Glucophage S-019 Ped Req

Bob gave me last week a review that I edited. I am waiting for the new version.

Saul

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: December 15, 2000

FROM: David G. Orloff, M.D. */S/ 12-15-00*
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 20-357/S-019
Glucophage (metformin HCl)
Bristol-Myers Squibb
Pediatric studies
Submitted 2-15-00

SUBJECT: sNDA review issues and action

Background

The original Written Request for pediatric studies of Glucophage was issued June 9, 1999, and was subsequently amended September 22, 1999 and February 7, 2000. The WR required two studies in order to meet the requirements for pediatric exclusivity. The first was a 16-week placebo-controlled, DB, randomized efficacy and safety study, with an open-label extension out to 52 weeks. Appropriate escape criteria and rescue treatments were specified in the WR and in the protocol. Patients were to be off previous oral agents for diabetes for at least _____ A minimum of 70 patients, male and female aged from 8 to 16 years, with Type 2 DM, were to be enrolled, with a 1:1 randomization to metformin vs. placebo. The primary endpoint was change from baseline in FPG. The dose of metformin was 500 mg BID increasing to a maximum dose of 1000 mg BID as tolerated. Change in HbA1c, weight, and plasma lipids were secondary endpoints.

The second study was a _____ PK study in at least 24 children and adolescents with Type 2 DM receiving combination insulin and metformin (500 BID) for one week.

Clinical safety and efficacy

Dr. Misbin has reviewed the clinical study (039). This trial enrolled 82 patients (42 metformin, 40 placebo) roughly matched at baseline for measures of glycemic control/diabetes severity. After 16 weeks of double-blind treatment, there was a placebo subtracted mean decrease from baseline in FPG in the metformin group of 64 mg/dL ($p < 0.001$). In addition, there was a mean 1% decrease in HbA1c in the metformin group and no change in the placebo group. There were no meaningful differences in the changes in plasma lipids across the treatment groups seen over this period.

Metformin was well tolerated except for the expected GI side effects, and there was a single report of asymptomatic hypoglycemia in a metformin patient.

NDA # 20-357/S-019
Drug: Glucophage
Proposal: pediatric studies for exclusivity
12/15/00

The efficacy results from the extension study demonstrated conclusively that the differences in baseline glycemia between the two original randomized groups did not impact on the efficacy of metformin. Specifically, placebo patients crossing over to metformin after 16 weeks showed changes after an additional 16 weeks (week 32 from start of study) of follow up commensurate with those seen at 16 weeks in the cohort originally randomized to metformin for the double-blind phase of the study.

No new safety issues were raised by the experience in the extension study. Likewise, the safety update submitted September 1, 2000, including updated information on studies 038 (PK study), 039, and _____ raised no new issues.

Biopharmaceutics

The sponsor was also requested to perform a _____ PK study in children and adolescents with Type 2 DM after one week of therapy with combination NPH insulin and metformin 500 BID. Dr. Wei of OCPB has reviewed the results of this study. In brief, 32 patients were studied, of which 6 were excluded from the data analysis. The significant findings were of AUC and Cmax in the pediatric patients markedly lower than those in adults studied in previous similarly designed trials. The renal clearance of metformin in children in this study was approximately 20% greater than in historic adult controls. The most likely conclusion is that the children enrolled were non-compliant with dosing in the week preceding the study, and that this affected the outcome of the single-dose PK component of the study.

OCPB (with medical concurrence) therefore recommends a repeat single-dose PK study in children and adults dosed in a controlled setting. This has been agreed to by the sponsor as a phase 4 commitment.

Pharmacology/Toxicology

No pharmacology/toxicology issues are raised by the proposed use in pediatric populations.

Chemistry/ Microbiology

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity

No DSI inspection was requested.

Financial disclosure

The financial disclosure information is in order and has been reviewed by the medical officer. There are no concerns related to financial conflicts of interest that impact on the reliability of the data submitted.

Recommendation

This sNDA may be approved with changes to labeling in Clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions, and Dosage and Administration. The recommended maximum dose in children is 2000 mg daily based upon the experience in the clinical trial

NDA # 20-357/S-019

Drug: Glucophage

Proposal: pediatric studies for exclusivity

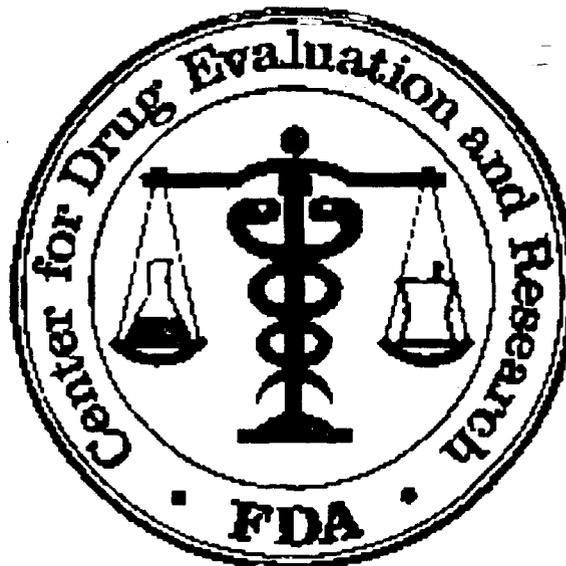
12/15/00

submitted for review. The phase 4 PK commitment for a repeat PK study in children and adults is covered in the action letter.

**APPEARS THIS WAY
ON ORIGINAL**

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: 12/15/00



TO:

FROM:

Name: Warren Randolph

Name: Su Yang

Fax No: (609) 252-6000

Fax No.: (301) 443-9282

Phone No.: (609)252-5228

Phone No.: (301) 827-6385

Location: Bristol-Myers Squibb

Location: FDA

Pages (including this cover sheet): 5

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COMMENTS:

Please call me or e-mail acknowledgement of this Glucophage Pediatric AP letter.
(yangs@cderr.fda.gov). Thanks,

Su Yang

**APPEARS THIS WAY
ON ORIGINAL**

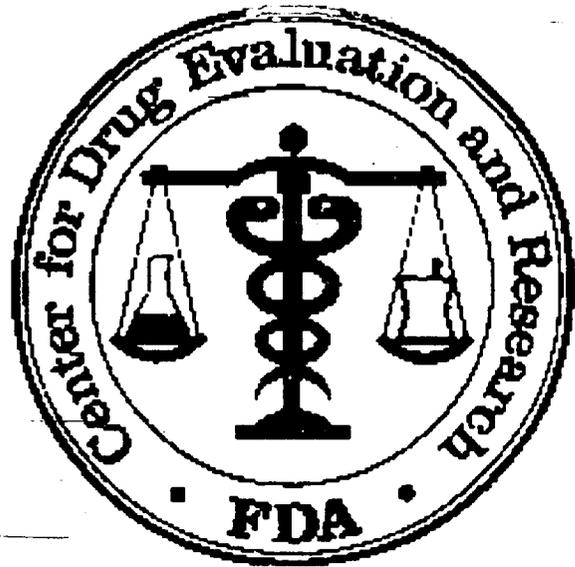
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Draft

Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE : 12/08/00



TO:
Name: Warren Randolph

FROM:
Name: Su Yang

Fax No.: (609) 252-6000

Fax No.: (301) 443 - 9282

Phone No.: (609) 525-5228

Phone No: (301) 827-6385

Location: Bristol-Myers Squibb

Location: FDA, EMEDP

Pages: (including cover) 2

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Comments:

APPEARS THIS WAY
ON ORIGINAL

NOV 6 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Fax: 609-252-6000

Reference: NDA 20-357/S-019, Glucophage (Metformin HCl Tablets); your submission dated February 15, 2000 – study report for pediatric exclusivity.

We have completed our clinical pharmacology/biopharmaceutics review this submission, and have the following comments and requests. We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

The study results observed in pediatric patients showed that the pharmacokinetic parameters were drastically different from those found in adult patients. These patients were relatively new to treatment, and since they took medications at home, compliance in this study is suspect. Specifically, 6 out of 32 enrolled patients were excluded from data analysis because of missed doses, low plasma concentrations, and only partial plasma data availability, etc. Therefore, it is suggested that an additional confirmatory single dose pharmacokinetic study of metformin be conducted in pediatric and adult patients before the information on the pediatric pharmacokinetic study is implemented in the labeling. In regards to the package labeling for this product,

_____ No revisions
should be made to the pharmacokinetics portion of the Pediatric subsection.

This information was sent to Warren Randolph on November 6, 2000.

CLEARED FOR FAXING

/S/

11/6/00

Hae-Young Ahn, Ph.D.

/S/

Jim Wei, M.D., Ph.D.

/S/

11/6/00

Jena Weber, RHPM

APPEARS THIS WAY
ON ORIGINAL



NDA 20-357

Food and Drug Administration
Rockville MD 20857

JUN 9 1999

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, US Regulatory Liaison, Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Reference is made to your Proposed Pediatric Study Request submitted on September 2, 1998, for Glucophage (metformin hydrochloride) Tablets to IND for NDA 20-357. We also refer to your amendments dated September 18 and 28, and October 29, 1998, and March 31, 1999.

To obtain needed pediatric information on metformin hydrochloride, 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. 16-week, placebo-controlled, parallel group clinical trial in children and adolescents with Type 2 diabetes mellitus to assess safety and efficacy.

Study 2. A pharmacokinetic study of metformin in children and adolescents with Type 2 diabetes mellitus.

Objectives/rationale (indications to be studied):

Study 1. Safety and effectiveness of metformin treatment in pediatric patient populations with Type 2 diabetes mellitus.

Study 2. Pharmacokinetics of metformin in pediatric patient populations with Type 2 diabetes mellitus.

Age groups in which study will be performed:

Studies 1 and 2.

Children and adolescents ≥ 8 years and ≤ 16 years of age.

BEST POSSIBLE COPY

Study design:

Study 1. Placebo-controlled, randomized, double-blind, parallel group study for 16 weeks to assess safety and efficacy. All patients must receive diet counseling. All patients will be followed for a total of 52 weeks. Rescue treatment for placebo-treated subjects will be metformin; for metformin-treated subjects, rescue will be insulin. Based on capillary glucose levels, rescue criteria are ≥ 230 mg/dL at 2 weeks, ≥ 180 mg/dL at 4 weeks, and ≥ 140 mg/dL at 6 weeks and beyond.

Study 2. Open-label, pharmacokinetic study in children and adolescents with Type 2 diabetes mellitus who are receiving insulin (NPH) and metformin (500 mg twice daily) combination therapy. Metformin blood levels are to be obtained before and sequentially after administration of 500 mg metformin with breakfast at the completion of one week of combined therapy.

Number of patients to be studied:

Study 1. A minimum of 70 subjects, approximately half randomized to receive metformin. There must be a reasonable distribution of patients across the specified age range in both treatment groups.

Study 2. At least 24 subjects with a reasonable distribution of patients across the specified age range.

Entry criteria:

Study 1. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and fasting plasma glucose (FPG) < 240 mg/dL and C-peptide > 1.5 ng/dL 90 minutes after Sustacal challenge. Patients on sulfonylureas (SFU) may be included if their HbA1c exceeds 7.5% and they have gained weight while on SFU therapy. However, SFU must be discontinued 28 days prior to randomization. (*Exclusion criteria* are the following: use of metformin within preceding 3 months or troglitazone within preceding 6 months; patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL, or abnormal creatinine clearance.)

Study 2. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and treatment with insulin for at least \longrightarrow FPG > 180 ng/mL and HbA1c $> 7\%$ at screening. (*Exclusion criteria* are the following: patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL, or abnormal creatinine clearance.)

Study endpoints:

Study 1: Primary efficacy variable: Change in fasting plasma glucose.
Secondary endpoints are changes in HbA1c, body weight, and serum lipids.

Study 2. C_{max} , T_{max} , AUC, $t_{1/2}$, and % UR.

Drug information:

Study 1.

- **Route of administration:** oral
- **Regimen:** metformin - initially 500 mg twice daily increasing to 1000 mg twice daily as tolerated
- **Dosage form:** tablets
- **Formulation:** marketed tablet

Study 2.

- **Dosage form:** tablets
- **Route of administration:** oral
- **Regimen:** insulin titrated, with 500 mg twice daily metformin
- **Formulation:** marketed tablet

Drug specific safety concerns:

Studies 1 and 2. Diarrhea and gastrointestinal discomfort.

Statistical information, including:

Statistical analysis of the two treatment groups will be done using ANCOVA, with treatment as main effect and baseline as covariate. The primary analysis population will be the Intent to Treat (ITT) population. Subjects who are rescued due to lack of glycemic control and subsequently put on open-label treatment will have their last blinded observation carried forward for the ITT analysis.

Labeling that may result from the studies:

Study 1. There may be changes to the following sections: DOSAGE AND ADMINISTRATION, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and INDICATIONS AND USAGE

Study 2. There may be changes to the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections.

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. To satisfy the requirements for exclusivity, submit the results of Study 2 and the 16-week efficacy results and all available safety data from Study 1. The 52-week data from Study 1 should be submitted in a separate supplement when available.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before March 31, 2000. Please keep in mind that pediatric exclusivity only extends 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. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*), with FDA before developing pediatric studies. 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 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 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.

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 Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely yours, *J*

/S/

J John K. Jenkins, M.D., F.C.C.P.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**



NDA 20-357

FEB - 7 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, US Regulatory Liaison, Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Reference is made to your correspondence dated October 6, 1999, to our Written Request letter dated June 9, 1999, and to our amendment dated September 22, 1999, for pediatric studies for Glucophage (metformin hydrochloride) Tablets. We also refer to your submission dated November 16, 1999.

We are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued June 9, 1999, as amended by our September 22, 1999, letter remain the same.

Type of Study:

Study 2: A pharmacokinetic study of metformin in children and adolescents with Type 2 diabetes mellitus.

Entry criteria:

Study 2: Males and females \geq 8 years and \leq 16 years of age with a history of Type 2 diabetes mellitus and treatment with insulin for at least 14 days. FPG \geq 180 mg/dL and HbA1c \geq 7% or current treatment with insulin at screening. (*Exclusion criteria* are the following: patients with markers of Type 1 diabetes, serum creatinine $>$ 1.0 mg/dL, and abnormal creatinine clearance).

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before March 3, 2000. Please keep in mind that pediatric exclusivity only extends existing 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 study 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.

To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. 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 a 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 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.

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, please contact Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

~~Sincerely yours,~~

/S/

~~John K. Jenkins, M.D.~~

~~Director~~

Office of Drug Evaluation II

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-357

SEP 22 1999

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, US Regulatory Liaison, Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Reference is made to your correspondence dated June 28 and September 13, 1999, requesting changes to FDA's June 9, 1999, Written Request for pediatric studies for metformin hydrochloride

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on June 9, 1999, remain the same.

Study design:

Study 1. Placebo-controlled, randomized, double-blind, parallel group study for 16 weeks to assess safety and efficacy. The placebo arm can be terminated if an interim analysis at eight weeks shows significant reduction ($p < .025$, $n = 18$ in each arm) in FPG. The patients who had received placebo should be switched to metformin. Efficacy and safety data will be collected on all patients for 52 weeks. Patients should receive diet counseling. Rescue treatment for placebo-treated subjects will be metformin; for metformin-treated subjects, rescue will be insulin. Based on capillary glucose levels, rescue criteria are ≥ 230 mg/dL at 2 weeks, ≥ 180 mg/dL at 4 weeks, and ≥ 140 mg/dL at 6 weeks and beyond.

Number of patients to be studied:

Study 1. A minimum of 70 subjects, at least half of which receive metformin. There must be a reasonable distribution of patients across the specified age range in both treatment groups.

Entry criteria:

Study 1. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and fasting plasma glucose (FPG) < 240 mg/dL and C-peptide ≥ 1.5 ng/mL 90 minutes after Sustacal challenge. Patients on sulfonylureas (SFU) may be included if their HbA1c exceeds 7.5% and they have gained weight while on SFU therapy. However, SFU must be discontinued 28 days prior to randomization. (*Exclusion criteria* are the following: use of metformin within

preceding 3 months or troglitazone within preceding 6 months; patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL and abnormal creatinine clearance.)

Study 2. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and treatment with insulin for at least $\text{FPG} \geq 180$ mg/dL and $\text{HbA1c} \geq 7\%$ at screening. (*Exclusion criteria* are the following: patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL and abnormal creatinine clearance.)

Study endpoints:

Study 1. Primary efficacy variable: Change in fasting plasma glucose. Secondary endpoints are comparison of HbA1c between metformin and placebo at 16 weeks and changes in body weight and serum lipids.

Statistical information, including:

Statistical analysis of the two treatment groups will be done using ANCOVA, with treatment as main effect and baseline as covariate. The primary analysis population will be the Intent-to-Treat (ITT) population. Subjects who are rescued due to lack of glycemic control and subsequently put on open-label treatment will have their last blinded observation carried forward for the ITT analysis.

The alpha level of the final analysis will be .03355 to preserve an overall alpha level of .05.

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. To avoid uncertainty, we recommend you seek a written agreement, with FDA before developing pediatric studies. 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.

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NDA 20-357

Page 3

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If you have any questions, call Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely yours,

/S/

~~John K. Jenkins, M.D., F.C.C.P.~~

~~Director~~

Office of Drug Evaluation II

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 , Fax: 609 252-6000

Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science



NDA 20-357/S-019
GLUCOPHAGE® (metformin hydrochloride) Tablets

December 13, 2000

David Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for Glucophage (metformin hydrochloride) Tablets, NDA 20-357, and specifically to our pending supplemental application of February 15, 2000 (S-019). This supplement provided for the use of Glucophage for the treatment of pediatric patients with type 2 diabetes. Additional reference is made to your telephone conversation of December 12 with Messrs. Bedard and Kessler of Bristol-Myers Squibb. As requested in that discussion, the first sentence under CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Pediatrics (page 5 of 31), has been revised to read "No pharmacokinetic data from studies of pediatric patients are currently available."

We have evaluated the suggestion concerning the maximum recommended dose of Glucophage® in pediatric patients and at this time have chosen to retain the maximum dose employed in our clinical program in pediatrics, i.e., 2000 mg daily. We will be evaluating the single-dose pharmacokinetics of metformin in adult and pediatric subjects

Attached is a revised, draft insert which incorporates the changes mentioned above. In addition, the change requested in the December 8, 2000 facsimile from Ms. Su Yang regarding the insertion of a minus sign on "Table 4" (Table 5 of current draft insert) has been incorporated. The other change proposed in the December 8 facsimile, concerning relocation of the n values in "Table 5" (Table 10 of current draft insert), had already been made in the draft submitted November 16, 2000.

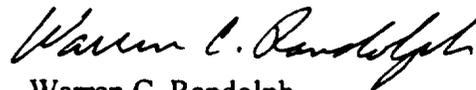


A Bristol-Myers Squibb Company

December 13, 2000

If you have any questions or require additional information, please contact me at (609) 252-5228.

Sincerely,



Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

WCR/HMK/dk
Attachments

Desk copies: Dr. Robert Misbin (HFD-510, Room 14B04)
Ms. Su Yang (HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 • Fax: 609 252-6000

Warren C. Randolph
Director

Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 20-357/S-019
GLUCOPHAGE® (metformin hydrochloride) Tablets

December 8, 2000

David Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357, and specifically to our pending supplemental application of February 15, 2000 (S-019). This supplement provided for the use of Glucophage for the treatment of pediatric patients with type 2 diabetes.

Additional reference is made to our November 16, 2000 submission of revised, draft labeling to NDA 20-357/S-019 and to my December 8, 2000 telephone discussion with Ms. Su Yang, in which she requested that we provide this labeling in MS WORD on disk.

At this time we are providing disks with the labeling as submitted in hard copy on November 16. This submission consists of 1 file on one diskette which is enclosed in the Archival copy submitted to the Division. An additional copy of the diskette is provided to Ms. Su Yang as a desk copy. The total size of the electronic submission is approximately ———. The files were screened for known viruses on December 8, 2000 with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected.



A Bristol-Myers Squibb Company

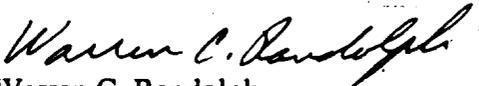
December 8, 2000

At this time we wish to correct an error in the November 16, 2000 submission. The header at the top of the cover letter incorrectly specified the supplement as ~~—~~ and it should have been designated S-019. Please change the designation to S-019 for this submission.

Additionally, concerning our commitment to perform a single-dose pharmacokinetic study with metformin in pediatric and adult populations, we will initiate this trial in March, 2001.

If you have any questions, or require additional information, please contact me at (609) 252-5228.

Sincerely,


Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

WCR/lb/dk

Desk copies: Ms. Su Yang (HFD-510, Room 14B04, w/ diskette)

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Bristol-Myers Squibb Company	DATE OF SUBMISSION December 8, 2000
TELEPHONE NO. (Include Area Code) 609-252-4000	FACSIMILE (FAX) Number (Include Area Code) 609-252-6000
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 4000 Princeton, NJ 08543-4000	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-357/S-019		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Metformin hydrochloride	PROPRIETARY NAME (trade name) IF ANY Glucophage®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N,N-Dimethylbiquanide	CODE NAME (If any)	
DOSAGE FORM: Tablets	STRENGTHS: 500 mg, 850 mg, 1000 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: 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.		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Holder of Approved Application
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Draft Labeling
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____	THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.	

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1. Index
2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))
4. Chemistry section
A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
15. Establishment description (21 CFR Part 600, if applicable)
16. Debarment certification (FD&C Act 306 (k)(1))
17. Field copy certification (21 CFR 314.50 (k)(3))
18. User Fee Cover Sheet (Form FDA 3397)
19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/> 20. OTHER (Specify) Response to FDA Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Warren C. Randolph</i>	TYPED NAME AND TITLE Warren C. Randolph, Director, U.S. Regulatory Liaison	DATE December 8, 2000
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 4000, Princeton, New Jersey 08543-4000		Telephone Number (609) 252-5228

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA-20-357/S-020
GLUCOPHAGE® (metformin hydrochloride) Tablets

November 16, 2000

David Orloff, M.D.
Director, Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for Glucophage (metformin hydrochloride) Tablets, NDA 20-357, and specifically to our pending supplemental application of February 15, 2000 (S-019). This supplement provided for the use of Glucophage for the treatment of pediatric patients with type 2 diabetes.

Additional reference is made to the following:

- November 6, 2000 telephone conversation between Dr. Misbin and myself;
- November 6, 2000 facsimile transmission from Ms. Jena Weber (copy attached), providing comments from Drs. Wei and Ahn on the previously-submitted Glucophage pediatric pharmacokinetic (PK) data;
- November 8, 2000 telephone conversation between Dr. Wei and myself; and
- My November 9, 2000 telephone conversation with Dr. Misbin.

The above communications requested that BMS: 1) submit the proposed, draft pediatric labeling on the new package insert for Glucophage and Glucophage XR; 2) delete _____ and 3) perform a single-dose PK study with Glucophage in adults and pediatric subjects.



A Bristol-Myers Squibb Company

November 16, 2000

At this time we are submitting the proposed, draft pediatric labeling on the new Glucophage/Glucophage XR package insert. Proposed additions to the label are underlined, and proposed deletions are shown as strikeouts. The proposed labeling is the same as that in our February 15, 2000 submission, except that the _____ have been removed and modifications to clearly indicate that the pediatric use applies only to Glucophage and not to Glucophage XR have been made.

BMS will conduct a single-dose PK study with Glucophage in pediatric and adult populations. The pediatric group will consist of 12 patients 12 to 16 years of age, with either type 1 or type 2 diabetes (a minimum of six will be type 2). Twelve normal, healthy adults will also be studied. Each participant will receive a single 500mg Glucophage tablet with breakfast following an overnight fast and blood samples will be collected at predetermined intervals over the following 24 hours.

BMS will provide a detailed outline for the single-dose PK study for Agency review and comment by December 15, 2000 and the final protocol will be submitted by March 1, 2001. The final study report will be submitted by the end of May, 2002.

If you have any questions or require additional information, please contact me at (609) 252-5228.

Sincerely,



Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

WCR/lis/dk
Attachments

Desk copies: Dr. Robert Misbin (HFD-510, Room 14B04)
Ms. Jena Weber (HFD-510, Room 14B04)
Dr. Xiaoxong Wei (HFD-870, Room 14B45)

**APPEARS THIS WAY
ON ORIGINAL**

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 20-357/S-019
GLUCOPHAGE® (metformin hydrochloride) Tablets

September 1, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Additional reference is made to the following:

1. Our supplemental application S-019, dated February 15, 2000, which provided information to support a new indication for the use of metformin hydrochloride in pediatric patients.
2. My telephone conversations with Ms. Jena Weber and Dr. Robert Misbin of the Division on June 28 and 29, 2000 in which they requested an update of the safety and efficacy data for this supplement.

We are now providing the requested update of the safety and efficacy information. This document contains an update of safety and efficacy data for the open-label portion of study CV138-039, titled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Study of the Efficacy and Safety of Metformin Hydrochloride for the Treatment of Pediatric Subjects with Type 2 Diabetes Mellitus." It also contains additional safety data from the following studies:



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1. CV138-038, titled "A Multicenter, Randomized, Open-Label, Parallel Study of the Pharmacokinetics, Safety, and Efficacy of Metformin Hydrochloride Plus Insulin Compared to Insulin Monotherapy for the Treatment of Pediatric Subjects with Type 2 Diabetes Mellitus"
2. CV138-045, titled "A Multicenter, Randomized, Double-Blind, Controlled, Parallel Group Study of the Efficacy and Safety of Metformin Hydrochloride Titration for the Control of Type 2 Diabetes Mellitus in Pediatric Subjects on Prior Metformin Therapy."

Please consult the Reviewer's Guide and the Table of Contents for additional information pertaining to the contents of this submission.

If you have any questions concerning this submission or require additional information, please contact me at (609) 252-5228.

Sincerely,



Warren C. Randolph,
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

WCR/HMK/dk
Attachments

Desk Copy: Dr. Robert Misbin (HFD-510, Room 14B04)
Ms. Jena Weber (HFD-510, Room 14B04)

**APPEARS THIS WAY
ON ORIGINAL**

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

Warren C. Randolph
Director

Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 20-357/S-019

Glucophage® (metformin hydrochloride) Tablets

August 9, 2000

John Jenkins, M.D.

Acting Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets (NDA 20-357) and to our pending Supplemental Application for the use of metformin in pediatric type 2 diabetes, S-019. Additional reference is made to my telephone conversations with Dr. Misbin (July 28, 2000) and Dr. Wei (July 26, 2000). Drs. Misbin and Wei requested additional information from both the pediatric and adult trials which provided the comparative pharmacokinetic (PK) data proposed for the draft labeling submitted in S-019.

Reports of both the pediatric and adult PK studies (CV138-038 and CV138-035, respectively) were included in S-019. At this time we are providing the following data from these trials:

- Subject demography, adults, Study CV138-035.
- Individual PK data from the study in adults (CV138-035). These data are provided in two separate tables; that designated Table S.11.2.2B provides data from the 26 subjects included for summary statistics of the PK parameters, Period A, a.m. dose. The "Table 2" provides individual PK data for all 32 subjects who completed CV138-035, for periods A and B and for both a.m. and p.m. doses. Since the two tables employ different subject numbering systems, a subject number key is provided. This key is also needed to relate the PK data in Table S.11.2.2B to the corresponding subject in the table of subject demography.



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- Individual PK data for pediatric subjects (CV138-038).
- Raw data from the pediatric PK study in Excel format, on disk. This electronic review aid consists of one diskette containing three files. The total size is less than — The files were screened for known viruses on August 9, 2000 with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected. One copy of the disk is provided, with Dr. Wei's desk copy of this submission.

The mean renal clearance of metformin in the pediatric PK trial was 648 ml/min, 18% higher than the reported renal clearance of 550 ml/min in adults. This difference could explain part of the difference in metformin exposure in the pediatric and adult PK studies.

I will contact Ms. Jena Weber in about one week to make arrangements for a teleconference to discuss the pediatric PK data. In the meantime, if there are any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,



Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

Desk Copies: Dr. Robert Misbin (HFD-510, Room 14B04)
Ms. Jena Weber (HFD-510, Room 14B04)
Dr. Xiaoxong Wei (HFD-870, Room 14B45) (w/ diskette)

**APPEARS THIS WAY
ON ORIGINAL**

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 20-357/S-019 Glucophage® (metformin hydrochloride) Tablets

June 22, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357, and to the following:

- Our Supplemental Application, submitted February 15, 2000, in support of labeling for the use of metformin in pediatric subjects with type 2 diabetes (S-019).
- My June 9, 2000 telephone conversation with Dr. Lee Pian and Ms. Jena Weber, in which Dr. Pian requested the interim analysis dataset for the placebo-controlled trial in pediatric subjects with type 2 diabetes.
- My June 13, 2000 telephone conversation with Ms. Weber, in which she indicated that our submission of the interim analysis dataset should be as a review aid, rather than as part of the formal electronic submission.

At this time we are providing three interim analysis datasets on two floppy disks. The disks are provided only with Dr. Pian's desk copy. A file entitled "readme.doc", on disk 1 of 2, describes the datasets and provides other pertinent information. This file is also provided herein as hard copy following this letter.



A Bristol-Myers Squibb Company

The data consist of four files, with a total size of less than — The files were checked for viruses on June 20, 2000 with Norton Antivirus Software (Version 5.01.01 for Windows NT 4.0) and no viruses were detected.

If there are any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,



Warren C. Randolph

Director

Metabolic/Endocrine Products

FDA Liaison and Global Strategy Unit

Regulatory Science

WCR/lb/dk

Desk Copies: Dr. Lee Pian (Includes disks) (HFD-715, Room 14B18)
Ms. Jena Weber (HFD-510, Room 14B04)

**APPEARS THIS WAY
ON ORIGINAL**

**Bristol-Myers Squibb
Pharmaceutical Research Institute**

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

ORIGINAL
NDA SUPP AMEND

S-019-B0

Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs



NDA 20-357

Glucophage® (metformin hydrochloride) Tablets

February 24, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Reference is also made to our supplemental new drug application of February 15, 2000 which included revised labeling to provide for the use of Glucophage® in the treatment of pediatric patients with type 2 diabetes.

In accordance with 21CFR§314.108(b)(5) we are now submitting a claim for three years of exclusivity for this new indication upon the approval of the supplemental NDA. The February 15 submission included reports of two, new Bristol-Myers Squibb (BMS) sponsored clinical trials. The BMS sponsored clinical trials are titled:

1. "A Study of the Pharmacokinetic Profile of Metformin Hydrochloride in Pediatric Subjects; a Substudy of a Multicenter, Randomized, Open Label, Parallel Study of the Pharmacokinetics, Safety, and Efficacy of Metformin Hydrochloride Plus Insulin Compared to Insulin Monotherapy for the Treatment of Pediatric Subjects with Type 2 Diabetes Mellitus," Protocol CV138-038.
2. "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Study of the Efficacy and Safety of Metformin Hydrochloride for the Treatment of Pediatric Subjects with Type 2 Diabetes Mellitus," Protocol CV138-039.



A Bristol-Myers Squibb Company

The protocols for these trials were originally submitted to our IND _____ on October 29, 1998 and July 17, 1998, respectively.

We certify that to the best of our knowledge, published studies do not exist which would provide a sufficient basis for the approval of our proposed labeling changes and that the two, new BMS sponsored clinical trials are essential to the approval of this supplement. In support of this certification we are providing a printout of the results of a literature search conducted in connection with this supplement. The following literature databases were used in the search: Medline, Derwent Drug File, Biosis Previews, EMBASE, EMBASE Alert, and JICST-EPlus. This search was performed in February, 2000.

If there are any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director, Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

WR/HMK/dk
Attachment

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> FINAL <input type="checkbox"/> MEMO
CSO INITIALS	DATE

**APPEARS THIS WAY
ON ORIGINAL**

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26
**Bristol-Myers Squibb
Pharmaceutical Research Institute**

P.O. Box 4000 Princeton, NJ 08543-4000
609 252 5228 Fax: 609 252-6000

Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

**SUBMISSION OF PEDIATRIC STUDY REPORTS
PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**

**NDA 20-357
GLUCOPHAGE® (metformin hydrochloride) Tablets**

February 15, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Additional reference is made to the following:

- Pediatric provisions (Section 111) of the FDA Modernization Act of 1997;
- FDA's Written Request for Pediatric Studies with metformin hydrochloride, dated June 9, 1999, and amendments to the Written Request, dated September 22, 1999 and February 7, 2000 (copies enclosed);
- Guidance for Industry, "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act", Revised, September 1999;
- Protocol CV138-038, "A Multicenter, Randomized, Open Label, Parallel Study of the Pharmacokinetics, Safety, and Efficacy of Metformin Hydrochloride Plus Insulin Compared to Insulin Monotherapy for the Treatment of Pediatric Subjects With Type 2 Diabetes Mellitus"; and



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- Protocol CV138-039, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Study of the Efficacy and Safety of Metformin Hydrochloride for the Treatment of Pediatric Subjects With Type 2 Diabetes Mellitus".

At this time we are submitting reports of studies that were conducted in accordance with and responsive to the Written Request, as amended. Two separate reports are provided for Protocol CV138-039; the first includes all data from the double-blind portion of the trial and the other provides all open-label safety data prior to January 26, 2000. The CV138-038 PK substudy report only addresses those subjects included in the pharmacokinetic substudy; significant safety data from other subjects in the ongoing CV138-038 trial are summarized in the Application Summary. Bristol-Myers Squibb (BMS) did not enter into a written agreement for conduct of the pediatric studies, but the studies were conducted in accordance with commonly accepted scientific principles and protocols.

Copies of the Written Request and amendments to the Written Request immediately follow the Reviewer's Guide to this submission. We have also provided word-processed reproductions of the portions of the Written Request and its amendments which describe the design, conduct and reporting of the pediatric studies. These are annotated and each numerical citation is then referenced to the pertinent report and section.

Protocols CV138-038 and CV138-039 (as amended) provided for the study of pediatric subjects with Type 2 diabetes who were 8 through 16 years of age in the pharmacokinetic (PK) substudy and the double-blind study. Though 34 subjects aged 8 or 9 years were screened for the CV138-039 trial, none were eligible for randomization. Recruitment efforts for the PK substudy of Protocol CV138-038 led to screening of only one subject under the age of 10 years, and this subject did not qualify for the study. Twelve of 82 subjects randomized in Protocol CV138-039 were ages 10 or 11 years and one subject under the age of 12 qualified for the PK substudy of CV138-038 (this 10 year old subject subsequently did not swallow the dose on the day of sampling and therefore no PK data are available for subjects under the age of 12 years).

Based on our experience in recruiting and screening for pediatric subjects with type 2 diabetes, it appears that this condition predominantly occurs at age 12 or older, though there are some children with type 2 diabetes between the ages of 10 and 12 years. The incidence below the age of 10 years appears to be very low and therefore the proposed pediatric labeling for Glucophage is for treatment of type 2 diabetes in ages 10-16 years, inclusive.

The aforementioned reports are submitted in this Supplemental New Drug Application. All summarizations are provided in the Application Summary; separate integrated summaries of safety and efficacy are not provided. The proposed, draft labeling herein includes results from our pediatric studies and provides dosing recommendations for use of Glucophage® in this population. This supplement provides for a new indication for the use of metformin in a pediatric population and therefore no user fee is submitted, per Section 103 of the FDA Modernization Act.

February 15, 2000

The case report tabulation for this Supplemental New Drug Application are being provided electronically. The media for this electronic submission is approximately — There are 100 files and 23 folders. The files have been checked for viruses on February 11, 2000 with Norton Antivirus Software (Version 5.01.01 for Windows NT 4.0) and no viruses were detected. The electronic submission is being provided on one CD-ROM disk to the Central Document Room in accordance with FDA Guidance procedures.

Copies of the cover letter and form 356h for this submission are being provided to the Director, Office of Generic Drugs.

If you have any questions concerning this submission or require additional information, please contact me at (609) 252-5228.

Sincerely,



Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

WCR/lb/dk
Attachments

Desk Copy: Dr. Robert Misbin (HFD-510, Room 14B04) (Vols. 55.1 & 55.2)
Ms. Jena Weber (HFD-510, Room 14B04) (Vols. 55.1 & 55.2)

APPEARS THIS WAY
ON ORIGINAL

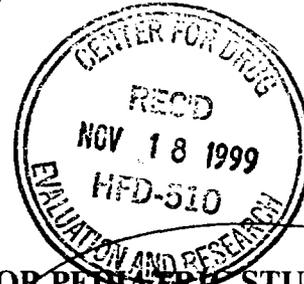
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Bristol-Myers Squibb Pharmaceutical Research Institute

SUPPL NEW CORR 68P

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4656 Fax: 609 252-6000

John F. Bedard
Vice President
Worldwide Regulatory Affairs



PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES

NDA 20-357
GLUCOPHAGE® (metformin hydrochloride) Tablets

November 16, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrinology
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
<i>[Signature]</i>	
ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>[Signature]</i>	<i>2/7/00</i>
CSO INITIALS	DATE

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357 and to the formal Written Request for pediatric studies with metformin, dated June, 1999. Additional reference is made to the following chronology pertaining to the Written Request:

June 28, 1999

Bristol-Myers Squibb (BMS) submission of Proposed Changes in Written Request. One of the requested changes pertained to "Entry Criteria: Study 2" (pharmacokinetic study) so that the Written Request would stipulate that subjects were to be treated with insulin for at least 14 days prior to study entry, rather than the _____ stated in the Written Request. The protocol for the pharmacokinetic study requires 14 days on insulin at study entry and the change in the Written Request is to achieve agreement. Since there would be no reason to require _____ on insulin prior to the study of metformin pharmacokinetics, we believe that the wording in the Written Request was inadvertent.



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September 22, 1999

FDA amendment of Written Request, in which most of the changes in the BMS request of June 28 were addressed. However, the entry criterion pertaining to the time on insulin for entry into the pharmacokinetic study was not changed. ←

October 6, 1999

BMS submission of Proposed Changes in Written Request, which again requested that the entry criteria for Study 2 be changed in the Written Request, to require at least 14 days on insulin rather than and also requested two additional changes pertaining to this study:

- Correction of a discrepancy within the Written Request itself, which describes the pharmacokinetic study (Study 2) as under Type of Studies, but then indicates that sampling should occur “at the completion of one week of combined therapy” under Study Design. The latter is in agreement with the agreed-upon study design and we requested that the section entitled Type of Studies be changed to indicate that pharmacokinetics will be studied after subjects have completed at least one week of dosing with metformin.
- Change in “Entry Criteria, Study 2”, to indicate that subjects could be entered if FPG ≥ 180 mg/dL and HbA1c ≥ 7% at screening or current treatment with insulin at screening. The second part of the criterion, i.e. “or current treatment with insulin” appears to have inadvertently been omitted in the Written Request.

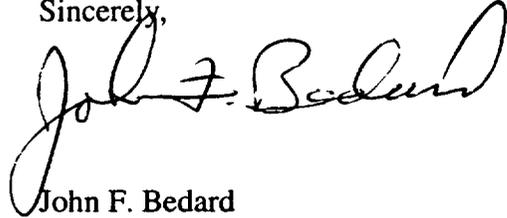
Our October 6 submission of Proposed Changes in Written Request pertained only to the pharmacokinetic trial in our pediatric program (Study 2), and we therefore have attempted to discuss these changes with Biopharmaceutics Reviewers, to obtain concurrence or comments. Thus far these attempts have been unsuccessful.

The recent guidance pertaining to qualification for pediatric exclusivity stresses the importance of complete agreement between the Written Request and the study reports. Therefore, we believe that it is important that the Written Request be amended prior to our submission of the pediatric study reports.

For your convenience, we are attaching copies of the relevant correspondence and strikeout/redline text which shows changes in pertinent sections of the current Written Request that would address the remaining issues (Attachment 5). We would appreciate an expeditious resolution, i.e. amending the Written Request, to ensure that no ambiguities or inconsistencies could jeopardize the agreement between the Written Request and the reports of our pediatric studies.

Please contact me at (609) 252-4656 if you have any questions.

Sincerely,



John F. Bedard
Vice President
Regulatory Science

Attachments
JFB/LS/jh

Desk Copies: Dr. Hae-Young Ahn (HFD-870, Room 14B18)
Ms. Enid Galliers (HFD-510, Room 14B04)
Dr. Robert Misbin (HFD-510, Room 14B04)
Dr. Solomon Sobel (HFD-510, Room 14B04)
Ms. Jena Weber (HFD-510, Room 14B04)
Dr. Mei Ling Chen (HFD-870, Room 13B17)

Handwritten notes:
Kotab
ISI
11/24/99

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5. Proposed Modification to Specific Sections of Written Request, per Oct. 6 Proposal	015

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NDA 20-357

BEST POSSIBLE COPYFood and Drug Administration
Rockville MD 20857

JUN 9 1999

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, US Regulatory Liaison, Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Reference is made to your Proposed Pediatric Study Request submitted on September 2, 1998, for Glucophage (metformin hydrochloride) Tablets to IND — for NDA 20-357. We also refer to your amendments dated September 18 and 28, and October 29, 1998, and March 31, 1999.

To obtain needed pediatric information on metformin hydrochloride, 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. 16-week, placebo-controlled, parallel group clinical trial in children and adolescents with Type 2 diabetes mellitus to assess safety and efficacy.

Study 2. A pharmacokinetic study of metformin in children and adolescents with Type 2 diabetes mellitus.

Objectives/rationale (indications to be studied):

Study 1. Safety and effectiveness of metformin treatment in pediatric patient populations with Type 2 diabetes mellitus.

Study 2. Pharmacokinetics of metformin in pediatric patient populations with Type 2 diabetes mellitus.

Age groups in which study will be performed:

Studies 1 and 2.

Children and adolescents ≥ 8 years and ≤ 17 years of age.

Study design:

Study 1. Placebo-controlled, randomized, double-blind, parallel group study for 16 weeks to assess safety and efficacy. All patients must receive diet counseling. All patients will be followed for a total of 52 weeks. Rescue treatment for placebo-treated subjects will be metformin; for metformin-treated subjects, rescue will be insulin. Based on capillary glucose levels, rescue criteria are ≥ 230 mg/dL at 2 weeks, ≥ 180 mg/dL at 4 weeks, and ≥ 140 mg/dL at 6 weeks and beyond.

Study 2. Open-label, pharmacokinetic study in children and adolescents with Type 2 diabetes mellitus who are receiving insulin (NPH) and metformin (500 mg twice daily) combination therapy. Metformin blood levels are to be obtained before and sequentially after administration of 500 mg metformin with breakfast at the completion of one week of combined therapy.

Number of patients to be studied:

Study 1. A minimum of 70 subjects, approximately half randomized to receive metformin. There must be a reasonable distribution of patients across the specified age range in both treatment groups.

Study 2. At least 24 subjects with a reasonable distribution of patients across the specified age range.

Entry criteria:

Study 1. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and fasting plasma glucose (FPG) < 240 mg/dL and C-peptide > 1.5 ng/dL 90 minutes after Sustacal challenge. Patients on sulfonylureas (SFU) may be included if their HbA1c exceeds 7.5% and they have gained weight while on SFU therapy. However, SFU must be discontinued 28 days prior to randomization. (*Exclusion criteria* are the following: use of metformin within preceding 3 months or troglitazone within preceding 6 months; patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL, or abnormal creatinine clearance.)

Study 2. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and treatment with insulin for at least FPG > 180 ng/mL and HbA1c $> 7\%$ at screening. (*Exclusion criteria* are the following: patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL, or abnormal creatinine clearance.)

Study endpoints:

Study 1. Primary efficacy variable: Change in fasting plasma glucose.
Secondary endpoints are changes in HbA1c, body weight, and serum lipids.

Study 2. C_{max} , T_{max} , AUC, $t_{1/2}$, and % UR.

Drug information:

Study 1.

- **Route of administration:** oral
- **Regimen:** metformin - initially 500 mg twice daily increasing to 1000 mg twice daily as tolerated
- **Dosage form:** tablets
- **Formulation:** marketed tablet

Study 2.

- **Dosage form:** tablets
- **Route of administration:** oral
- **Regimen:** insulin titrated, with 500 mg twice daily metformin
- **Formulation:** marketed tablet

Drug specific safety concerns:

Studies 1 and 2. Diarrhea and gastrointestinal discomfort.

Statistical information, including:

Statistical analysis of the two treatment groups will be done using ANCOVA, with treatment as main effect and baseline as covariate. The primary analysis population will be the Intent to Treat (ITT) population. Subjects who are rescued due to lack of glycemic control and subsequently put on open-label treatment will have their last blinded observation carried forward for the ITT analysis.

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Labeling that may result from the studies:

Study 1. There may be changes to the following sections: DOSAGE AND ADMINISTRATION, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and INDICATIONS AND USAGE

Study 2. There may be changes to the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections.

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. To satisfy the requirements for exclusivity, submit the results of Study 2 and the 16-week efficacy results and all available safety data from Study 1. The 52-week data from Study 1 should be submitted in a separate supplement when available.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before March 31, 2000. Please keep in mind that pediatric exclusivity only extends 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. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*), with FDA before developing pediatric studies. 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 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 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.

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 Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely yours, 

/s/

 John K. Jenkins, M.D., F.C.C.P.
Director

Office of Drug Evaluation II
Center for Drug Evaluation and Research

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Bristol-Myers Squibb Pharmaceutical Research Institute

2355 East 17th Avenue, North Wales, PA 19381
(610) 272-1212, FAX (610) 272-1000

Warren C. Randolph

Director

Pharmaceutical Research Institute

2355 East 17th Avenue, North Wales, PA 19381

PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES

NDA 20-357

GLUCOPHAGE® (metformin hydrochloride) Tablets

June 28, 1999

Solomon Sobel, M.D.

Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Center for Drug Evaluation and Research

Food and Drug Administration

Department of Health & Human Services

5600 Fishers Lane

Rockville, MD 20857

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Additional reference is made to the Written Request for pediatric studies with metformin hydrochloride, dated June 9, 1999 (copy attached). At this time we are requesting consideration of amendments to the Written Request of June 9. The proposed amendments are to correct some minor errors and also to address differences between the Written Request and our Proposed Pediatric Study Request, submitted to IND on September 2, 1998, and amended September 18 and 28, October 29, 1998 and March 31, 1999. The proposed changes to the Written Request, together with the reason for each change, follow:

Entry Criteria: Study 1

The units for the C-peptide should be ng/mL, rather than ng/dL, and the criterion should be greater than or equal to 1.5 ng/mL, rather than only greater than. The fasting plasma glucose should be less than or equal to 240 mg/dL, rather than only less than.

Reason: The protocol for Study 1(CV138-039) incorrectly stated the units for C-peptide and we now wish to make this correction. The changes to include "equal to" the values for C-peptide and FPG are to make the Written Request consistent with the protocol.



A Bristol-Myers Squibb Company

Entry Criteria: Study 2

The entry criteria for FPG and HbA1c should be greater than or equal to 180 mg/dL and 7%, respectively, rather than only greater than these values. The units for FPG should be mg/dL, rather than ng/mL. Additionally, the time on insulin for entry into the study should be at least 14 days, rather than _____

Reason: Subjects for Study 2 (pediatric pharmacokinetics) are a subset from Protocol CV138-038, as described in our submission of October 29, 1998 to IND _____ (Serial No. 153). The proposed changes are to make the Written Request consistent with this protocol. Please refer specifically to Sections 7.1 and 11.2 of the October 29 pharmacokinetic proposal.

Entry Criteria: Studies 1 and 2

The exclusion criteria for both studies should be serum creatinine >1.0 mg/dL and abnormal creatinine clearance, rather than or abnormal creatinine clearance.

Reason: These changes are to make the Written Request consistent with the study protocols. The protocols describe circumstances in which creatinine clearance will be determined.

Study Endpoints: Study 1

The secondary endpoint for HbA1c should be comparison between metformin and placebo at 16 weeks, _____

Reason: This change is proposed for consistency with the study protocol (CV138-039).

Timeframe for submitting reports of studies:

Based upon the March 3, 1995 approval of NDA 20-357, we believe that the date for submission of reports of the pediatric studies should be March 3, 2000, rather than March 31.

Provision for Interim Analysis:

Proposed revisions to Study 1 (Protocol CV138-039), were initially submitted via facsimile transmission for FDA review and comment on March 1, 1999 and those that were agreed-upon were subsequently submitted as a Protocol Amendment on March 31, 1999. One of the changes provided for establishment of a Data Safety Monitoring Board (DSMB) to review safety and to evaluate the change from baseline in fasting plasma glucose at eight weeks after data from half of the patients (n=36) are available. The criterion for consideration of termination of the trial on the basis of convincing efficacy results was established as a difference in FPG between the groups with $p < 0.025$.

June 28, 1999

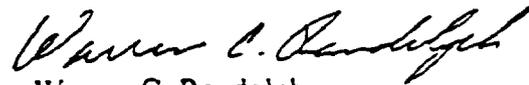
-3-

We believe that if this level of significance is seen with 36 subjects, there should be no need to enter additional subjects into a placebo-controlled trial and therefore are requesting that this provision be included in the Written Request. If there are any concerns about a need to provide data supporting the safety of metformin in a larger population, we would be glad to commit to providing safety data from approximately 65 subjects who have received metformin (together with insulin) in the open-label trial from which our PK subjects were drawn (CV138-038).

Since we will shortly reach randomization of 36 subjects in Study 1, (and the interim analysis is planned when eight weeks data are available from this number) we would appreciate action upon our proposed amendments as soon as possible, so (if criteria are met) the placebo-controlled trial can be terminated at that point.

We would be glad to participate in a teleconference or meeting to discuss the proposed amendments to the written request. Please contact me at (609)252-5228 if you have any questions concerning this submission.

Sincerely,



Warren C. Randolph

Director

US Regulatory Liaison

Worldwide Regulatory Affairs

WCR/JSB/dk

Desk Copy: Ms. Enid Galliers (HFD-510, Room 14B04)
Dr. Robert Misbin (HFD-510, Room 14B04)
Ms. Jena Weber (HFD-510, Room 14B04)

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NDA 20-357

SEP 22 1999

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, US Regulatory Liaison, Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Reference is made to your correspondence dated June 28 and September 13, 1999, requesting changes to FDA's June 9, 1999, Written Request for pediatric studies for metformin hydrochloride

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on June 9, 1999, remain the same.

Study design:

Study 1. Placebo-controlled, randomized, double-blind, parallel group study for 16 weeks to assess safety and efficacy. The placebo arm can be terminated if an interim analysis at eight weeks shows significant reduction ($p < .025$, $n = 18$ in each arm) in FPG. The patients who had received placebo should be switched to metformin. Efficacy and safety data will be collected on all patients for 52 weeks. Patients should receive diet counseling. Rescue treatment for placebo-treated subjects will be metformin; for metformin-treated subjects, rescue will be insulin. Based on capillary glucose levels, rescue criteria are ≥ 230 mg/dL at 2 weeks, ≥ 180 mg/dL at 4 weeks, and ≥ 140 mg/dL at 6 weeks and beyond.

Number of patients to be studied:

Study 1. A minimum of 70 subjects, at least half of which receive metformin. There must be a reasonable distribution of patients across the specified age range in both treatment groups.

Entry criteria:

Study 1. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and fasting plasma glucose (FPG) < 240 mg/dL and C-peptide ≥ 1.5 ng/mL 90 minutes after Sustacal challenge. Patients on sulfonylureas (SFU) may be included if their HbA1c exceeds 7.5% and they have gained weight while on SFU therapy. However, SFU must be discontinued 28 days prior to randomization. (*Exclusion criteria* are the following: use of metformin within

preceding 3 months or troglitazone within preceding 6 months; patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL and abnormal creatinine clearance.)

Study 2. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and treatment with insulin for at least FPG ≥ 180 mg/dL and HbA1c $\geq 7\%$ at screening. (*Exclusion criteria* are the following: patients with markers of Type 1 diabetes, serum creatinine > 1.0 mg/dL and abnormal creatinine clearance.)

Study endpoints:

Study 1. Primary efficacy variable: Change in fasting plasma glucose.
Secondary endpoints are comparison of HbA1c between metformin and placebo at 16 weeks and changes in body weight and serum lipids.

Statistical information, including:

Statistical analysis of the two treatment groups will be done using ANCOVA, with treatment as main effect and baseline as covariate. The primary analysis population will be the Intent-to-Treat (ITT) population. Subjects who are rescued due to lack of glycemic control and subsequently put on open-label treatment will have their last blinded observation carried forward for the ITT analysis.

The alpha level of the final analysis will be .03355 to preserve an overall alpha level of .05

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. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. 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 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 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.

NDA 20-357

Page 3

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 Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely yours,

/S/

~~John K. Jenkins, M.D., F.C.C.P.~~

~~Director~~

Office of Drug Evaluation II
Center for Drug Evaluation and Research

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011

Bristol-Myers Squibb Pharmaceutical Research Institute

Box 4000, Princeton, NJ 08542-4000
Tel: 609-746-7000

Warren C. Randolph

Director

Division of Metabolism and Endocrine Drug Products

Center for Drug Evaluation and Research

PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES

NDA 20-357

GLUCOPHAGE® (metformin hydrochloride) Tablets

October 6, 1999

Solomon Sobel, M.D.

Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Center for Drug Evaluation and Research

Food and Drug Administration

Department of Health & Human Services

5600 Fishers Lane

Rockville, MD 20857

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357, and to the following (copies attached):

- FDA's Written Request for pediatric studies with metformin, dated June 9, 1999.
- Bristol-Myers Squibb (BMS) submission of Proposed Changes in Written Request for Pediatric Studies, dated June 28, 1999.
- FDA letter of September 22, 1999, in which amendments to the Written Request of June 9 were provided to BMS.



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Additional reference is made our October 29, 1998 submission of the Proposed Pediatric Study Request for a pharmacokinetic (PK) study of metformin in pediatric type 2 diabetics. Though the agency has not indicated any disagreement with the PK study design as submitted, the Written Request of June 9 contains language that might be construed as describing a study which differs in some details from that which is being conducted. We believe the changes which are requested herein to resolve these differences are only in the nature of clarifications or resolution of ambiguities.

One of these points, pertaining to insulin treatment in PK subjects, was identified in our Proposed Changes in Written Request of June 28, but was not reflected in the September 22 amendments to the Written Request. Two others (an inconsistency concerning the multiple dose nature of the PK study in the June 9 Written Request and an omission of a portion of an entry criterion) were not previously addressed by BMS. In order to ensure that there is no disagreement between the BMS PK study design and the Written Request, we are requesting amendments to the June 9 Written Request and to the amendments dated September 22, to address the following:

- 1) The June 9 Written Request, under "Type of studies, Study 2", states "a _____ pharmacokinetic study...". The same Written Request, under "Study design, Study 2", states "metformin blood levels are to be obtained before and sequentially after administration of 500 mg metformin with breakfast at the completion of one week of combined therapy". The latter statement is in agreement with the design of the BMS PK study and we are requesting that "Type of studies, Study 2" be revised to indicate that the pharmacokinetics will studied after subjects have completed at least one week of dosing with metformin.
- 2) The June 9 Written Request, under "Entry criteria, Study 2" describes the population as "Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes and treatment with insulin for at least _____. Our June 28 Proposed Changes in Written Request had requested that the time on insulin be changed to "at least 14 days", rather than _____ to agree with our PK study design. Since there would be no reason to require a history of _____ of insulin prior to the PK study, we believe that the current wording of the Written Request was inadvertent, but wish to have the ambiguity removed so the Request is consistent with the PK study design.
- 3) Also under "Entry Criteria, Study 2", the wording of the Written Request is currently "FPG ≥ 180 mg/dL and HbA1c $\geq 7\%$ at screening". The entry criterion in the protocol is "FPG ≥ 180 mg/dL and HbA1c $\geq 7.0\%$...at screening...or current treatment with insulin at screening". We are requesting that the "or current treatment with insulin at screening" be added to the text of the Written Request for consistency with the study protocol.

As stated earlier, we believe that these changes to the Written Request constitute only clarifications or resolution of ambiguities, rather than any disagreement on the PK study itself. However, we also believe that the changes are needed to ensure that our study report, when submitted, is in accord with the Written Request.

Please contact me at (609) 252-5228 with any questions.

Sincerely,



Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Affairs

Desk Copies: Dr. Hae-Young Ahn (HFD-870, 14B18)
Ms. Enid Galliers (HFD-510, 14B04)
Dr. Robert Misbin (HFD-510, 14B04)
Ms. Jena Weber (HFD-510, 14B04)

**APPEARS THIS WAY
ON ORIGINAL**

**PROPOSED CHANGES TO JUNE 9, 1999 WRITTEN REQUEST
FOR METFORMIN PEDIATRIC STUDIES**

Type of studies:

Study 2. A ~~Phase I~~ Pharmacokinetic study of metformin in children and adolescents

~~with the following objectives: to determine the pharmacokinetics of metformin in children and adolescents with Type 2 diabetes mellitus; to determine the effect of metformin on glucose tolerance in children and adolescents with Type 2 diabetes mellitus; to determine the effect of metformin on insulin resistance in children and adolescents with Type 2 diabetes mellitus.~~

Entry Criteria:

Study 2. Males and females ≥ 8 years and ≤ 16 years of age with a history of Type 2 diabetes mellitus and treatment with insulin for at least ~~3 months~~. FPG > 180 ng/mL and HbA1c $> 7\%$ ~~on oral treatment with insulin~~ at screening. (Exclusion criteria are the following: patients with markers of Type 1 diabetes. Serum creatinine > 1.0 mg/dL — abnormal creatinine clearance.)

*via SMS - does not require
THIS PART ~~as per consensus~~
W. Randolph 2/1/00*

/S/

and

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Bristol-Myers Squibb Company		DATE OF SUBMISSION November 16, 1999	
TELEPHONE NO. (Include Area Code) 609-252-4000		FACSIMILE (FAX) Number (Include Area Code) 609-252-6000	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 4000 Princeton, NJ 08543-4000		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-357		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Metformin hydrochloride	PROPRIETARY NAME (trade name) IF ANY Glucophage®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N,N-Dimethylbiguanide	CODE NAME (If any)	
DOSAGE FORM: Tablets	STRENGTHS: 500 mg, 850 mg, 1000 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: 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.		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER		
REASON FOR SUBMISSION		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED _____	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
	2. Labeling (check one) Draft Labeling Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. OTHER (Specify) Proposed Changes in Written Request for Pediatric Studies

CERTIFICATION

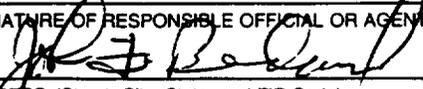
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE John F. Bedard, Vice President, Regulatory Science	DATE November 16, 1999
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 4000, Princeton, New Jersey 08543-4000	Telephone Number (609) 252-4656	

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