

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-357/S019

ADMINISTRATIVE DOCUMENTS

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: April 14, 2000

FROM: Team Leader, Division of Biometrics 2 (HFD-715)

SUBJECT: Protocol CV 138-039 "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", Interim Analysis Tables dated October 5, 1999, and Report dated February 15, 2000, in support of pediatric exclusivity

TO: File (NDA 20-357)

The sponsor submitted data for a randomized, double-blind, placebo-controlled trial of metformin in children ages 10-17 in support of the determination of pediatric exclusivity. An interim analysis was conducted for approximately 36 patients at 8 weeks, as permitted by the Written Request. Metformin patients had significantly greater changes in fasting plasma glucose (FPG) from baseline, the primary endpoint, than did placebo patients. The mean change in FPG from baseline was -50.4 mg/dl for metformin patients (n=19) and +17.4 mg/dl for placebo patients (n=20). The difference was statistically significant at .025, the Type 1 error rate specified in the Written Request. Based on the positive statistical results and absence of any safety concerns, the placebo arm was terminated and these patients switched to open label metformin. Efficacy results for FPG at Week 16 using all randomized subjects with available data (n=73) were consistent with the interim data.

This study was conducted in accordance with the Written Request, as amended, dated September 22, 1999.

/s/

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

Cc:
Arch NDA 20-357
HFD-510
HFD-510/EColman
HFD-715/LPian, TSahlroot, DOE:
Chron

**APPEARS THIS WAY
ON ORIGINAL**

PATENT INFORMATION

The use of Glucophage® (metformin) products in pediatric patients described in Bristol-Myers Squibb Company's SNDA filed herewith for which approval has been applied for February 11, 2000, are not covered by any patents.

In accordance with 21 CFR § 314.53(c)(2)(ii)(3) and § 314.53(d)(2)(D)(iii), certification of the fact that no patents claim the use of Glucophage® products in pediatric patients described in this SNDA is made on the attached sheet.

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.53(c)(2)(iii):

In the opinion and to the best knowledge of Bristol-Myers Squibb Company, there are no patents that claim the drug (metformin) for the use in pediatric patients sought in the subject SNDA and on which investigations that are relied upon in this application were conducted.

Burton Rodney

Burton Rodney
Senior Associate Counsel - Patents
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Dated: February 11, 2000

**APPEARS THIS WAY
ON ORIGINAL**

**Glucophage® Pediatric Supplemental New Drug Application
NDA 20-357**

**DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992**

Bristol-Myers Squibb Company certifies that it did and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this supplemental application.

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 20-357 SUPPL # 019

Trade Name Glucophage Generic Name metformin HCl tablets

Applicant Name Bristol Myers Squibb HFD- 510

Approval Date 15 December 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/

If yes, what type (SE1, SE2, etc.)? SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe

the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

Firm requested 6 months PEDIATRIC EXCLUSIVITY.

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / /

The indication is NOT new, but the product is now approved explicitly for use by part of the pediatric population (ages 10 to 16 years). The new labeling contains new pediatric information in CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, and DOSAGE AND ADMINISTRATION.

If yes, NDA # 20-357 Drug Name Glucophage

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

**APPEARS THIS WAY
ON ORIGINAL**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the

investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / ___ / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / ___ /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / ___ /

If yes, explain: _____

**APPEARS THIS WAY
ON ORIGINAL**

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ / NO / ___ /

If yes, explain: _____

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / ___ / NO / ___ /

Investigation #2 YES / ___ / NO / ___ /

Investigation #3 YES / ___ / NO / ___ /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / ___ / NO / ___ /

Investigation #2 YES / ___ / NO / ___ /

Investigation #3 YES / ___ / NO / ___ /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # __, Study # _____
Investigation # __, Study # _____
Investigation # __, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant." An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

**APPEARS THIS WAY
ON ORIGINAL**

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____

FEB 25 2000

NDA 20-357/S-019

PRIOR APPROVAL SUPPLEMENT

Bristol-Myers Squibb Company
Attention: Warren C. Randolph
Director, Metabolic/Endocrine Products
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Glucophage (metformin hydrochloride) Tablets
NDA Number: 20-357
Supplement Number: S-019
Therapeutic Classification: To be determined at filing meeting
Date of Supplement: February 15, 2000
Date of Receipt: February 15, 2000

This supplement proposes to add pediatric study information to the package insert in response to a Written Request and requests six months pediatric exclusivity.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 15, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 15, 2000, and the secondary user fee goal date will be February 15, 2001.

NDA 20-357/S-019

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Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

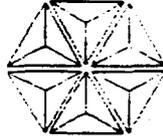
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

IS/ 2.25.00
Enid Gaffers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL



BRISTOL-MYERS SQUIBB
PHARMACEUTICAL RESEARCH INSTITUTE

Glucophage® Pediatric Supplemental New Drug Application

Financial Disclosure Information

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FDA Form 3455 and List of Investigators Reporting Payments of Other Sorts	013
Minimization of Bias Statement	015

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Hubert G.Pouleur, M.D.,Ph.D.	TITLE Vice-President Cardiovascular Clinical Research
FIRM/ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE 	DATE Jan 27, 2000

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

WITHHOLD 10

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Attached List, who participated as a clinical investigator in the submitted study Protocols CV138-038PK and/or CV138-039, is submitted in accordance with 21 CFR part

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Hubert G.Pouleur, M.D.,Ph.D.	TITLE Vice-President Cardiovascular Clinical Research
FIRM/ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE 	DATE Jan 26, 2000

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

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Rockville, MD 20857

WITHHOLD 2