

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357, S010

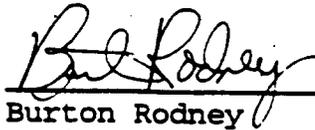
ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Certification of Patent Information

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.50(h)(ii):

In the opinion and to the best knowledge of Bristol-Myers Squibb Company, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

APPEARS THIS WAY
ON ORIGINAL



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

Dated: April 22, 1998

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA 20-357 SUPPL # 010

Trade Name: GLUCOPHAGE Generic Name: Metformin Tabs
Applicant Name: Bristol-Myers Squibb HFD-510

Approval Date OCT 1998

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 / /

b) Is it an effectiveness supplement?

YES / / NO / /

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

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 / / 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 / /

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

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8 (even if a study was required for the upgrade).

**APPEARS THIS WAY
ON ORIGINAL**

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 / /

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 8. 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 8.

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 /___/

**APPEARS THIS WAY
ON ORIGINAL**

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 8:**

- (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: _____

- (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 # _____

APPEARS THIS WAY
ON ORIGINAL

- 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.

- 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 _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / ___ /

If yes, explain: _____

/S/

Signature _____
Title: CSO

10/15/98 Date

APPEARS THIS WAY
ON ORIGINAL

/S/

Signature of Division Director _____

10-8-98 Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA

Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20357</u>	Trade Name:	<u>GLUCOPHAGE (METFORMIN HCL) 500 / 850 MG</u>
Supplement Number:	<u>10</u>	Generic Name:	<u>METFORMIN HCL</u>
Supplement Type:	<u>SE1</u>	Dosage Form:	<u>TAB</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>metformin plus insulin for type 2 diabetes</u>

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Status	-	APPEARS THIS WAY ON ORIGINAL
Formulation Status	-	
Studies Needed	-	
Study Status	-	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? ~~YES~~ NO

COMMENTS:	APPEARS THIS WAY ON ORIGINAL
none at this time	
no comments at this time	

This Page was completed based on information from a REVIEWER, ROBERT MISBIN

Signature	Date
<u>RSI</u>	<u>Oct 21, 1998</u>
APPEARS THIS WAY ON ORIGINAL	

GLUCOPHAGE® (metformin hydrochloride) Tablets

**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**

ELECTRONIC MAIL MESSAGE

Date: 13-Oct-1998 08:00am EDT
From: Solomon Sobel
Dept: HFD-510
Tel No:

TO: Robert Misbin
TO: Saul Malozowski
TO: Gloria Troendle
TO: Todd Sahlroot
TO: S. Edward Nevius
TO: Jena Weber

CC: Florence Houn
CC: James Bilstad

Subject: Approval of metformin + insulin supplement

The supplement poses some interesting problems primarily from the statistical standpoint.

There are 2 studies submitted in support of this supplement .
(Each contain few subjects.

(Study 16: 26 subjects on metformin + insulin and 28 subjects on insulin alone
Study 20: 26 subjects on metformin + insulin and 25 subjects on insulin alone)

The primary endpoint in Study 16 was HbA1c at 24 weeks. When analyzed by ANOVA the p value at 24 weeks for HbA1c (mean and mean change from baseline) was 0.14.

When analyzed by ANCOVA a significance at 0.04 was seen. (the ANCOVA adjusted values using the covariate of HbA1c at baseline).

This was somewhat problematic inasmuch as ANCOVA was not specified in the original protocol. Also, one must ask whether the linear regression for HbA1c was the same in the 2 groups. ANCOVA rests on a parallelism of the linear regression. One might suspect that the placebo group which contained one "outlier" of a subject who went from a baseline of Hb A1c of 13.2 % to a 16 week value of 5.7%

(the 24 week value was missing) would give a somewhat different linear regression for the placebo group than the metformin group, However, if one eliminates this "outlier" from analysis even the ANOVA yields significant results.

ANOVA is a correct analysis in a study comprised of 2 baseline predictor variables which were of qualitative nature, ie. metformin treatment or not. One could argue that baseline imbalances should be adjusted. (albeit that the covariate was the same, HbA1c, as the primary endpoint. (Even though the degree imbalance was small).

I believe we can accept the ANCOVA approach as a reasonable follow-through in

the evaluation and not as a post hoc "data-dredging".

In Study 20 the primary endpoints were 4 in number (HbA1C, change in insulin dosage, change in weight, and change in blood pressure. Significance was achieved for change in insulin dosage and weight loss (favoring metformin). HbA1c was not significant although changes in fasting blood sugar were.

Conclusion:

Considering the above, I would recommend approval of this NDA supplement. The medical reviewer has raised a substantial argument about not encouraging use of metformin in a population which may represent an advanced stage of diabetes (that is high insulin usage with evidence of insulin resistance). Such a group might be expected to have compromised renal function and be more vulnerable to the toxic effects of metformin. However, adherence to our labeling precautions should be sufficient to exclude patients with significant renal disease from metformin use.

Sol Sobel

/S/

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

HFD-510 - NDA 0116
HFD-510 Division Files
HFD-510 - RMISBIN / SMALOWSKI / COTRIVALE / TSAHROOT / ENUCIS
~~HFD-511~~ - SWEIBER
HFD-102 / JBILSMO / FHOON

APPEARS THIS WAY
ON ORIGINAL



Food and Drug Administration
Rockville MD 20857

NDA 20-357/S-011

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Attention: Mr. Warren C. Randolph, Director,
U.S. Regulatory Liaison

Dear Mr. Randolph:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Glucophage (metformin hydrochloride) Tablets

NDA Number: 20-357

Supplement Number: S-011

Date of Supplement: July 6, 1998

Date of Receipt: July 8, 1998

**APPEARS THIS WAY
ON ORIGINAL**

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 6, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

**APPEARS THIS WAY
ON ORIGINAL**

Sincerely,

/S/

**APPEARS THIS WAY
ON ORIGINAL**

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4000 Fax: 609 252-5360

NDA 20-357/S-010 **Glucophage® (metformin hydrochloride) Tablets**

October 21, 1998

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 specifically to our Supplemental New Drug Application filed April 23, 1998, S-010. This submission provided for revised labeling for the concomitant use of metformin and insulin in type 2 diabetes. Additional reference is made to the following:

- September 23, 1998 teleconference between representatives of Bristol-Myers Squibb (B-MS) and FDA in which FDA raised issues concerning the analyses of HbA1c data from Protocol CV138-016;
- October 2, 1998 facsimile transmission of documentation from B-MS to FDA to support the robustness of the ANCOVA analysis of HbA1c data from Protocol CV138-016;
- October 16, 1998 facsimile transmission from FDA to B-MS, proposing changes to the table of data from CV138-016 which had been submitted in the Clinical Pharmacology section of the draft labeling on April 23;
- October 20, 1998 teleconference in which B-MS and FDA representatives discussed the analyses of HbA1c data from CV138-016, presentation of data from this study in the Clinical Pharmacology section, and several other FDA proposals for changes in the April 23 draft labeling.



A Bristol-Myers Squibb Company

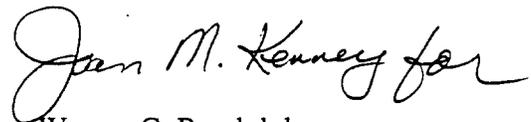
We are now providing revised draft labeling which incorporates the changes discussed at the October 23 teleconference as listed below:

- Table 4, in which results of CV138-016 are presented, has been revised to include the values proposed by FDA in the October 16 facsimile transmission. The order of the significant/non-significant statements in Footnote a have been revised to provide the significant result first, together with the p-value, and the statements for the different analyses are provided on separate lines. The p-value for the difference in change in daily insulin dose has also been added;
- Though not discussed in the teleconference, the paragraph preceding Table 4 has been revised so that it matches the revised information in the table;
- The last sentence of the paragraph following Table 4, which addressed reduction in LDL-cholesterol in CV138-016, has been deleted;
- On pages 9 and 11 of the proposed draft labeling, the response to Q7 in the Patient Information has been changed from "while reducing the need for insulin..." to "...while reducing the insulin dose...".

We believe the changes to the draft labeling provided herein are consistent with our discussion at the October 20 teleconference. If this supplement is approved on the basis of the draft labeling provided herein, B-MS commits to submission of final printed labeling identical to the draft.

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

Sincerely,



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

WCR/dk
Attachments

Desk Copies: Dr. R. Misbin (HFD-510, PKLN 14B-04)
Dr. Solomon Sobel (HFD-510, PKLN 14B-04)
Ms. Jena Weber (HFD-510, PKLN 14B-04)

BS

**Bristol-Myers Squibb
Pharmaceutical Research Institute**

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

NDA SUPPLEMENT

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

ORIGINAL



NDA-20-357/S-10
Glucophage® (metformin hydrochloride) Tablets

July 16, 1998

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 and 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 Supplemental New Drug Application which we submitted April 23, 1998 (S-10). This SNDA provided for the concomitant use of metformin and insulin in type 2 diabetes. Additional reference is made to my telephone conversation with Dr. Lee-Pian on June 24, 1998, in which she requested electronic data sets for the two Bristol-Myers Squibb trials reported in S-10 (Protocols CV138-016 and CV138-020).

At this time we are providing electronic data for CV138-020 on two diskettes, one of which provides the raw database and another which provides four analysis data sets, as follow:

- LAB1 which contains the primary lab endpoints at baseline and at study visits as well as some demographic information. It also contains last observation carried forward (LOCF) value in the variable name RESULT2. The PROC CONTENTS printout is provided for additional clarification.
- INS_DOSE contains information regarding total daily insulin dose in a similar fashion as LAB1. It also contains LOCF value.

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> MAIL <input type="checkbox"/> MEMO

July 16, 1998

- LAB2 is for the secondary endpoints, basically C-Peptide and lipids. This file does not have LOCF values.
- WEIGHT is for body weight which is one of the secondary variables; it is separated since it is not a lab value. This file does not include LOCF values.

For the current data sets for CV138-020, the OPTIONS statement (OPTIONS NOFMterr;) should be used in the SAS program.

We are also providing PROC CONTENTS and PROC PRINT outputs. The diskettes are provided only in the desk copy for Dr. Pian, as a reviewing aid. Annotated case report forms for both the CV138-016 and CV138-020 studies are included in this submission. The electronic data sets for CV138-016 were submitted July 1, 1998. The contents of this submission are described in the Table of Contents following this letter.

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

Sincerely,



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

WR/HMK/jsb/lp
Attachments

Desk Copy: Dr. Lee Pian (includes diskettes) - HFD-715, PKLN 14B-18

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

NDA 20-357

Glucophage® (metformin hydrochloride) Tablets

July 15, 1998

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 and 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 Supplemental New Drug Application submitted on April 23, 1998, S-10. This supplement provided for revised labeling for the concomitant use of metformin and insulin in type 2 diabetes. Additional reference is made to my July 7, 1998 telephone conversation with Ms. Jena Weber, in which I informed her that we had discovered that the report for study CV138-020 (Bergental), submitted in S-10, contained errors in calculation of mean changes in daily insulin dose. I requested that the reviewers be informed that revised documents would be provided.

At this time we are providing replacements for Volumes 48.1, 48.8 and 48.9 of the supplement. The volumes are numbers 51.1, 51.2, and 51.3 respectively, indicating their current submission, but the labels also indicate the volumes which they replace in S-10. Changes incorporated into the replacement volumes are as follow:

Volume 48.1:

Draft Labeling. Clinical Pharmacology section revised to incorporate corrected insulin data for the CV138-020 (Bergental) study. Changes to the proposed, draft labeling are bolded in the current submission.



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Volume 48.1 (continued)

Application Summary. Tables and text revised to provide corrected data for mean changes in daily insulin dose for the CV138-020 (Bergental) study. Affected pages are 28, 43, 97, 104, 105, 131 and 133.

Volume 48.8

Study Report. A revised report is provided for CV138-020, "A Study of the Effects of Insulin and Metformin Combination Therapy Compared to Placebo on Insulin Dosage and Metabolic Parameters in Adults with Insulin-Resistant Type II Diabetes." A summary of changes to this report follows this letter, indicating the page changed, previous content and current content. The revised portions in the summary are bolded on the "changed to" copy.

Appendix IIIA. The p value for week 0 in Table IIIA3 has been corrected. This correction is included in the summary of changes following this letter.

Volume 48.9

Appendix IV. Statistical Analysis. Pages 87 through 99 have been replaced to provide corrected data for mean changes in daily insulin doses. Though Appendix IV is continued in Volume 48.10, changes only affected Volume 48.9 and Volume 48.10 has not been replaced.

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

Sincerely,



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

WR/HMK/jsb/lp
Attachments

Desk Copy: Ms. Jena Weber (Volume 51.1 only), HFD-510, PKLN 14B-04

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

SEI-010 C

NEW CORRESP

ORIGINAL

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

NDA 20-357
Glucophage® (metformin hydrochloride) Tablets

Noted

ISI

7/22/98

July 10, 1998



*Noted
S/S
7/25/98*

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 and Human Services
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
 LETTER N.A.I. MEMO
CSO INITIALS _____ DATE _____

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Reference is also made to our submission of April 23, 1998 which included revised labeling to provide for the concomitant use of insulin with metformin in type 2 diabetes.

In accordance with 21CFR§314.108(b)(5) we are now submitting a claim for three years of exclusivity for this indication upon the approval of the supplemental NDA. This supplement includes a review of relevant literature articles as well as reports of two, new Bristol-Myers Squibb (BMS) sponsored clinical trials. 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 literature search conducted in connection with this supplement. The following literature data bases were used in the search: Medline, Derwent Drug File, Biosis Previews, Int. Pharm. Abs., Embase, and SciSearch. The original search was performed in September 1996. Update searches were performed in February 1997, June 1997, and February 1998.

*By [Signature]
7/25/98*

July 10, 1998

The BMS sponsored clinical trials are titled: 1. "The Effect of Metformin vs. Placebo in Poorly Controlled Insulin-Treated Non-Insulin Dependent Diabetes Mellitus," Protocol CV138-016. 2. "A Study of the Effects of Insulin and Metformin Combination Therapy Compared to Insulin and Placebo on Insulin Dosage and Metabolic Parameters in Adults with Insulin-Resistant Type II Diabetes," Protocol CV138-020. The protocols for these trials were originally submitted to our on April 3, 1997 and August 28, 1997, respectively.

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

Sincerely,

**APPEARS THIS WAY
ON ORIGINAL**



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

WR/HMK/lp
Attachment

**APPEARS THIS WAY
ON ORIGINAL**

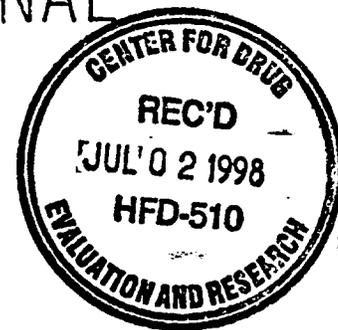
**Bristol-Myers Squibb
Pharmaceutical Research Institute**

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

SEI-010
BS

**NDA SUPPLEMENT
AMENDMENT**

ORIGINAL



Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs
NDA 20-357/S-10

Glucophage® (metformin hydrochloride) Tablets

July 1, 1998

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 and Human Services
5600 Fishers Lane
Rockville, MD 20857

Noted

JSI

7/10/98

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357, and to the Supplemental New Drug Application which we submitted April 23, 1998 (S-10). This SNDA provided for the concomitant use of metformin and insulin in type 2 diabetes. Additional reference is made to my telephone conversation with Dr. Lee Pian on June 24, 1998, in which she requested electronic data sets for the two Bristol-Myers Squibb trials reported in S-10 (Protocols CV138-016 and CV138-020).

At this time we are providing electronic data for CV138-016 on two diskettes, one of which provides the raw database and another which provides four analysis data sets, as follow:

- LAB1 which contains the primary lab endpoints at baseline and at study visits as well as some demographic information. It also contains last observation carried forward (LOCF) value in the variable name RESULT2. The PROC CONTENTS printout is provided for additional clarification.
- INS_DOSE contains information regarding total daily insulin dose in a similar fashion as LAB1. It also contains LOCF value.
- LAB2 is for the secondary endpoints, basically C-Peptide and lipids. This file does not have LOCF values.



A Bristol-Myers Squibb Company

July 1, 1998

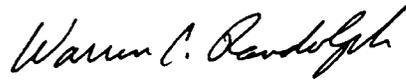
- WEIGHT is for body weight which is one of the secondary variables; it is separated since it is not a lab value. This file does not include LOCF values.

We are also providing PROC CONTENTS and PROC PRINT outputs. The diskettes are provided only in the desk copy for Dr. Pian, as a reviewing aid.

Electronic data for the other Bristol-Myers Squibb trial included in S-10 (CV138-020) will be forwarded in about one week.

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

Sincerely,



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

**APPEARS THIS WAY
 ON ORIGINAL**

WR/jsb
 Attachments

Desk Copy with diskettes: Dr. Lee Pian (HFD-715, Room 14B-18)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

**APPEARS THIS WAY
 ON ORIGINAL**

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08545-4000
609 252 5228 Fax: 609 252 6000

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

NDA 20-357 Glucophage® (metformin hydrochloride) Tablets

April 30, 1998

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 and Human Services
5600 Fishers Lane
Rockville, MD 20857

**APPEARS THIS WAY
ON ORIGINAL**

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Reference is also made to our April 23, 1998 submission which provided for the use of Glucophage® with insulin.

At this time we are providing the Environmental Assessment report associated with the April 23 SNDA. A Table of Contents for the report appears on page ii.

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

Sincerely,

**APPEARS THIS WAY
ON ORIGINAL**



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

WR/HMK/lp
Attachments

Desk copy: Ms. Jena Weber, HFD-510, PKLN 14B-04



A Bristol-Myers Squibb Company

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08545-4000
609 252-5228 Fax: 609 252-6000

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

NDA 20-357
Glucophage® (metformin hydrochloride) Tablets

April 23, 1998

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 and 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. At this time Bristol-Myers Squibb (BMS) is submitting a Supplemental New Drug Application which provides for revised labeling for the concomitant use of metformin and insulin in type 2 diabetes. Data to support the labeling change derive from two BMS-sponsored trials in which the concomitant use of metformin with insulin improved glycemic control over that achieved with insulin alone or maintained glycemic control with a lower insulin dose. A number of published reports have also described the use of metformin and insulin in type 2 diabetes and data from these sources is summarized herein as additional support.

Since this application contains only clinical data, a single summary document is provided as the Application Summary. The Application Summary incorporates the integrated summaries of safety and efficacy. Please refer to the Reviewer's Guide and Overall Table of Contents for a complete description of the structure of this application.

Though troglitazone is already approved for use with insulin in the United States, we believe that approval of the concomitant use of insulin and metformin will constitute a significant medical advance, based upon the following:



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April 23, 1998

- The major cause of death for patients with type 2 diabetes is cardiovascular disease and two recognized risk factors for such disease are body weight and elevated LDL-cholesterol. The combination of troglitazone and insulin has been shown to increase both body weight and LDL-cholesterol, while these parameters remain stable or decrease when metformin is given with insulin.
- The concomitant use of troglitazone with insulin requires frequent assessment of liver function over a prolonged period of time. This testing will be inconvenient at best and will likely prove impossible for some patients and providers. Since use of metformin does not require any similar surveillance, the opportunity for long-term use is enhanced.

Since the above provide significant advantages for the use of metformin with insulin, compared to the combination of troglitazone with insulin, we believe that the current supplement qualifies for Priority Application status.

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

Sincerely,



APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

WR/jsb/lp
Attachments

Desk Copy: Mr. Michael Johnston (Volume I only), HFD-510, PKLN 14B-04