

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21178/5-004

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 21-178 SUPPL # 004

Trade Name: Glucovance Generic Name: Glyburide and Metformin

Applicant Name: Bristol-Myers Squibb HFD-510

Approval Date September 30, 2002

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.)? SE-1

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?

Three (3)

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

YES / ___ / NO / ___ /
On 11/26/99

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 / ___ /

If yes, NDA # 21-178 Drug Name Glucovance

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 /___/

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

NDA #	<u>20-357</u>	Metformin HCl
NDA #	<u>17-498</u>	Glyburide
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

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: _____

(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 # 1, Study # CV-138-055
 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: _____

Jena Weber
Signature of Preparer
Title: Project Manager

Date: 9/25/02

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
10/2/02 06:05:16 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Bristol-Myers Squibb P.O. Box 4000 Princeton, New Jersey 08543-4000	3. PRODUCT NAME Glucovance (glyburide and metformin HCl) Tablets
2. TELEPHONE NUMBER (Include Area Code) (609) 252-4000	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 4233	6. LICENSE NUMBER / NDA NUMBER N021178

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE Warren C. Randolph <i>Warren C. Randolph</i>	TITLE Director, Regulatory Science	DATE November 30, 2001
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BEST POSSIBLE COPY

MEMORANDUM

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

DATE: September 30, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-178/S-004
Glucovance (glyburide & metformin)
Bristol-Myers Squibb

SUBJECT: sNDA review issues and recommended action

Background

This sNDA proposes addition of information to labeling for Glucovance to address combination therapy with thiazolidinediones (TZD), including clinical efficacy data in Clinical Pharmacology, a new indication for "triple therapy," safety information, and information on dosage and administration. Double therapies including metformin-sulfonylurea (met-SFU; e.g., Glucovance), met-TZD, and SFU-TZD are all part of approved labeling for these classes of products. This would be the first triple-therapy indication. It is based on a single study and its extension of Glucovance in combination with rosiglitazone (RZG). No studies were requested or submitted of triple therapy including the other marketed TZD, pioglitazone (see below).

**Clinical
Efficacy**

The clinical review by Dr. Misbin details the efficacy and safety data presented. The sponsor submitted the results of a single, randomized, double-blind, placebo controlled trial to assess the effects on glycemic control of rosiglitazone add-on therapy in patients inadequately controlled on Glucovance alone. Briefly, males and females, aged 20-78 with Type 2 diabetes and HbA1c between 7 and 10% on Glucovance (98% of patients on maximal dose of 2000/10) were randomized 1:1 to receive rosiglitazone or matching placebo and followed for 24 weeks of double-blind therapy. The initial dose of rosi was 4 mg daily and this was doubled to 4 mg BID after 8 weeks for patients with HbA1c still above 7%. Approximately 180 patients were randomized to each treatment.

Mean final doses of components of the triple combination were 1914 mg metformin, 9.6 mg glyburide, and 7.5 mg rosiglitazone (or placebo) at end of study.

The effect of rosiglitazone vs. placebo was an incremental 1.02 percentage unit reduction in HbA1c. The effect on FPG was ~49 mg/dL. Fructosamine was reduced 37%. The rosiglitazone group experienced a mean 3 kg weight gain on therapy, compared to 0.03 kg in the placebo

NDA # 21-178/S-004
Drug: Glucovance (metformin-glyburide)
Proposal: triple therapy with TZDs
10/02/02

group. There were mean increases in total and LDL-C in the rosi group vs. placebo, of 15% and 13% (placebo-subtracted), respectively.

313 patients were entered into an open-label extension study of 20 weeks duration. The results with regard to HbA1c lowering (among patients randomized to PBO in the double-blind phase) and rise in body weight associated with rosi therapy were essentially the same as those seen in the double-blind phase.

Safety

The notable adverse effects seen in the clinical trials of triple therapy were consistent with the known adverse event profile of rosiglitazone, namely edema and weight gain that occurred in approximately 2% of placebo patients and in 9% of rosi patients and was moderate to severe in intensity. There were no cases of CHF reported in the trials.

In addition, as would be expected with improvement in glycemic control, the incidence of hypoglycemia was increased in the rosi group vs. placebo. No events required medical assistance.

Use with other TZDs

Currently, the only other marketed TZD is pioglitazone. No studies were conducted to directly assess the safety and efficacy of pio as part of the triple-therapy regimen. Troglitazone was originally approved for use in combination therapy with metformin and SFU and subsequently withdrawn from the market for safety reasons unrelated to combination therapy. Pioglitazone, as is rosiglitazone, is approved in combination with either metformin or an SFU. The data presented in this sNDA support the safety and efficacy of triple therapy with rosiglitazone, metformin, and SFU. There are no specific concerns about the balance of risk and benefit of substituting pioglitazone for rosi in the triple therapy regimen. No adverse drug interactions are expected based on the absence of any two-way adverse interactions of the components (metformin-SFU, metformin-pio, SFU-pio), and incremental HbA1c lowering similar to that seen when adding rosi to metformin-SFU is expected (though obviously the label does not state this).

If and when another TZD is developed, phase 3 trials of triple therapy or drug interaction studies may be required if concerns arise as to the balance of risk and benefit of such regimens, for example because of possible interactions impacting metabolism/activity of one or more components.

Labeling

Changes to labeling include:

1. description of the efficacy results from the double-blind phase of the study in Clinical Pharmacology, Clinical Studies,
2. language added to the Indications section addressing addition of a TZD for patients not adequately controlled on Glucovance alone,
3. discussion of the edema and hypoglycemia findings in the triple therapy trial in Adverse Reactions

NDA # 21-178/S-004

Drug: Glucovance (metformin-glyburide)

Proposal: triple therapy with TZDs

10/02/02

4. and changes to the Dosage and Administration section addressing dosing of TZD and adjustments in the dosage of the glyburide component of Glucovance or other components of the anti-diabetic regimen in the event of hypoglycemia.

Biopharmaceutics

No drug interaction studies were performed or requested. This was rationalize as follows:

1. metformin is not metabolized
2. glyburide may be metabolized, at least in part, by CYP3A4 and is highly protein bound
3. rosiglitazone is metabolized by CYP2C8 and 2C9 and is highly protein bound

Therefore, no interaction affecting drug metabolism is expected to occur. In patients already on maximal doses of glyburide, even if an interaction based on displacement from protein binding were to occur, no further insulin secretory response would be expected. The hypoglycemia associated with improved glycemic control with triple therapy in the clinical study that was designed to target tight (HbA1c < 7%) control was expected. The labeling advises that if this occurs, the culprit should be assumed to be the glyburide component of Glucovance, and this should be down-titrated.

Pharmacology/Toxicology

No new studies

Chemistry/ Microbiology

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

DSI/Data Integrity

No clinical site audits were requested or performed specifically related to this application.

Financial disclosure

The financial disclosure information is in order and reviewed on page 5 of Dr. Misbin's review.

Recommendation

Labeling has been finalized. This supplement may be approved.

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David Orloff
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MEDICAL OFFICER

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MEMORANDUM

To: File, NDA 21-178

Through: Jena Weber, RPh, Project Manager
Katie Johnson, RPh, Supervisory Project Manager

From: Jeri El-Hage, Ph.D., Pharmacology Supervisor, HFD-510

Subject: NDA 21-178 SE 8, #004, November 30, 2001
Glucovance

Date: April 17, 2002

This supplement is for a labeling revision to indicate Glucovance in combination with a thiazolidinedione when adequate glycemic control is not achieved with Glucovance alone. The supplement contains a single clinical study. No new preclinical data was submitted and , therefore, a pharmacology review is not needed.

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Jeri El Hage
4/17/02 01:07:31 PM
PHARMACOLOGIST

NAI

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: September 12, 2002

To: Warren Randolph Director, Regulatory Science	From: Jena Weber Project Manager
Company: Bristol-Myers Squibb	Division of Metabolic and Endocrine Drug Products, HFD-510
Fax number: 609-252-6000	Fax number: 301-443-9282
Phone number: 609-252-5228	Phone number: 301-827-6422

151

Subject: Discipline Review Completed for NDA 21-178/S-004; FDA labeling comments for Glucovance package insert.

Total no. of pages including cover: 2 – See attached page.

Comments:

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 agreements, 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 we 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.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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The **DOSAGE AND ADMINISTRATION** section of the package insert for Glucovance should provide guidance in the event that hypoglycemia occurs in patients while on triple therapy. We are proposing that you add the following language:

[

]

Please respond in writing to your NDA file.

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NDA 21-178/S-004

PRIOR APPROVAL SUPPLEMENT

Bristol-Myers Squibb
Attention: Warren C. Randolph
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:	Glucovance® (glyburide and metformin HCl) Tablets
NDA Number:	21-178
Supplement Number:	S-004
Review Priority Classification:	Standard (S)
Date of Supplement:	November 30, 2001
Date of Receipt:	November 30, 2001

This supplement proposes concomitant use of Glucovance® with a thiazolidinedione when glycemic control is not obtained with Glucovance® alone. 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 January 29, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 30, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632).

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We note that you have requested a full waiver of pediatric assessment requirements.

We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application.

In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. We note that you submitted a Proposed Pediatric Study Request to IND ~~_____~~ That proposal is currently pending.

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/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
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
12/31/01 08:42:55 AM

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Division of Metabolic and Endocrine Drug Products, HFD-510

PROJECT MANAGER LABELING REVIEW

Application Number: 21-178/S-004

Name of Drug: Glucovance (glyburide and metformin HCl) Tablets, 1.25 mg/250mg; 2.5 mg/500 mg; 5 mg/500 mg.

Sponsor: Bristol-Myers Squibb (BMS)

Material Reviewed: Draft Labeling (PI)

Submission Date: November 30, 2001

Receipt Date: November 30, 2001

Background and Summary: Glucovance was approved by DMEDP on July 31, 2000, on draft labeling. This combination product is indicated as an adjunct to diet and exercise in the treatment of patients with Type 2 Diabetes Mellitus. Supplement 004 provides for revised labeling for the use of Glucovance with a thiazolidinedione when glycemic control is not obtained with Glucovance alone. This supplement provides for changes to the **CLINICAL PHARMACOLOGY** section, **Clinical Studies** subsection, **INDICATIONS AND USAGE** section, **CONTRAINDICATIONS** section, **PRECAUTIONS** section, **ADVERSE REACTIONS** section, **Hypoglycemia** subsection, **Gastrointestinal Reactions** subsection, and the **DOSAGE AND ADMINISTRATION** section.

The PPI and PI are considered as one document. That is, the PPI appears at the end of the PI, and is not separated from the PI via perforation.

Supplement 002 (submitted as a CBE) on November 21, 2000, provided for the addition of the section, **Special Warning on Increased Risk of Cardiovascular Mortality** (the "UDGP" Warning) that was inadvertently omitted from the original label.

Review: The approved PI and PPI labeling (from supplement 002, Identifier code 1116046A2, approved February 28, 2001) was compared to the proposed labeling that accompanied S-004, and to the final draft labeling agreed upon between BMS and the Division on September 30, 2002. They are identical except for the changes specified. The company has stated that a new identifier code will be assigned at the time of printing.

Conclusion: Request FPL.

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-178/S-004

Name of Drug: Glucovance (glyburide and metformin HCl) Tablets
1.25 mg/250 mg; 2.5 mg/500 mg; 5 mg/500mg

Sponsor: Bristol-Myers Squibb

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: November 30, 2001

Receipt Date: November 30, 2001

Filing Date: January 29, 2002 **User-fee Goal Date:** September 30, 2002

Proposed Indication: Glucovance is indicated as initial therapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

Other Background Information: Glucovance plus the use of a thiazolidinedione (Avandia) for both first and second line therapy when glycemic control is not obtained by using Glucovance alone.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	✓		Volume 1
2. Form FDA 356h (original signature)	✓		Volume 1

a. Establishment information		✓	Not needed
b. (facilities ready for inspection?)			
b. Reference to DMF(s) & Other Applications		✓	N/A
3. User Fee FDA Form 3397	✓		Volume 1
4. Patent information & certification			Volume 1
5. Debarment certification (Note: Must have a definitive statement)	✓		Volume 1
6. Field Copy Certification		✓	Not needed.
7. Financial Disclosure	✓		Volume 1
8. Comprehensive Index	✓		Volume 1
9. Pagination	✓		
10. Summary Volume	✓		Volume 1
11. Review Volumes	✓		Electronic
12. Labeling (PI, container, & carton labels)	✓		Volume 1, PI only
a. unannotated PI	✓		Volume 1
b. annotated PI	✓		Volume 1
c. immediate container		✓	N/A
d. carton		✓	N/A
e. patient package insert (PPI)	✓		Volume 1
f. foreign labeling (English translation)		✓	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	✓		Electronic – datatoc.pdf

14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	✓		Electronic – crftoc.pdf
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Y = Yes (Present), N = No (Absent)

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	✓		Volume 1
2. Foreign Marketing History	✓		Volume 1
3. Summary of Each Technical Section	✓		Volume 1 (prn)
a. Chemistry, Manufacturing, & Controls (CMC)		✓	N/A
b. Nonclinical Pharmacology/Toxicology		✓	N/A
c. Human Pharmacokinetic & Bioavailability		✓	N/A
d. Microbiology		✓	N/A
e. Clinical Data & Results of Statistical Analysis	✓		Volume 1
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	✓		Volume 1
5. Summary of Safety	✓		Volume 1
6. Summary of Efficacy	✓		Volume 1

Y = Yes (Present), N = No (Absent)

APPEARS THIS WAY
ON ORIGINAL

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	✓		Electronic – Financial Disclosure
2. Controlled Clinical Studies	✓		Volume 1
a. Table of all studies	✓		Volume 1
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	✓		Volume 1
c. Optional overall summary & evaluation of data from controlled clinical studies	✓		Volume 1
3. Integrated Summary of Efficacy (ISE)		✓	N/A
4. Integrated Summary of Safety (ISS)		✓	N/A
5. Drug Abuse & Overdosage Information		✓	N/A
6. Integrated Summary of Benefits & Risks of the Drug	✓		Volume 1
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		✓	N/A – See “Special Populations” subsection of labeling.

Y=Yes (Present), N=No (Absent)

**APPEARS THIS WAY
ON ORIGINAL**

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	✓		Request for waiver of pediatric studies
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		✓	N/A
a. Proposed unannotated labeling in MS WORD	✓		Volume 1
b. Stability data in SAS data set format (only if paper submission)		✓	N/A
c. Efficacy data in SAS data set format (only if paper submission)	✓		Electronic
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		✓	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		✓	N/A
3. Exclusivity Statement (optional)	✓		Volume 1

Y=Yes (Present), N=No (Absent)

^a“GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS” (FEBRUARY 1987).

^b“GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS” (FEBRUARY 1987).

^c“GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS” (JULY 1988).

NDA REGULATORY FILING REVIEW

NDA 21-178/S-004

Glucovance (glyburide and metformin HCl) Tablets

1.25 mg/250 mg; 2.5 mg/500 mg; 5 mg/500 mg

Applicant: Bristol-Myers Squibb

Date of Application: November 30, 2001

Date of Receipt: November 30, 2001

Date of Filing Meeting: January 28, 2002

Filing Date: January 30, 2002

Indication requested: This sNDA proposes concomitant use of Glucovance with a thiazolidinedione when glycemic control is not obtained with Glucovance alone.

Type of Application: Full NDA _____ Supplement SE-1

(b)(1) _____ (b)(2) _____

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classifications: S _____ P _____

Resubmission after a withdrawal or refuse to file NO

Chemical Classification: (1,2,3 etc.) 1

Other (orphan, OTC, etc.) N/A

User Fee Status: Paid _____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES _____ NO _____

User Fee ID# 4233

Clinical data? YES _____ NO _____ Referred to _____

Date clock started after UN N/A

User Fee Goal date: September 30, 2002

Action Goal Date (optional) N/A

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Submission complete as required under 21 CFR 314.50? YES
If no, explain:

- If electronic NDA, does it follow the Guidance? YES

- Patent information included with authorized signature? YES

- Exclusivity requested? YES; If yes, 3 years

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"

- Financial Disclosure included with authorized signature? YES- as per 21 CFR 54.5(c)(a) (Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? NO

- Pediatric assessment of all ages? NO

(If multiple indications, answer for each indication.)

If NO, for what ages was a waiver requested?

Full waiver requested.

For what ages was a deferral requested?

N/A

- Field Copy Certification (that it is a true copy of the CMC technical section)? NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in DSS? YES

If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in DSS? YES

If not, have the Document Room make the corrections.

List referenced IND numbers: _____

End-of-Phase 2 Meeting? NO

If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES, (PPI on 1/28/02)
Trade name and labeling (PI) sent to ODS? NO
Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
If no, did sponsor submit a complete environmental assessment? NO
- EA consulted to Nancy Sager (HFD-357)? NO
- Establishment Evaluation Request (EER) package submitted? NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? N/A

505(b)(2) NA

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?

Yes _____ No _____

(Normally, FDA will refuse-to-file such applications.)

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

Yes _____ No _____

If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

Yes _____ No _____

If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

_____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

_____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

_____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity?
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES _____ NO _____

ATTACHMENT

FILING MEETING MINUTES

DATE: Monday, January 28, 2002

BACKGROUND: This efficacy supplement proposes to add a thiazolidinedione (Avandia – rosiglitazone maleate, reference NDA 21-071) to Glucovance (glyburide/metformin, reference NDA 21-178), as triple therapy in the treatment of patients with Type 2 Diabetes Mellitus.

ATTENDEES: David Orloff, M.D.	Division Director
Robert Misbin, M.D.	Medical Reviewer
Todd Sahlroot, Ph.D.	Team Leader – Statistics
Jena Weber, BS	Project Management

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Robert Misbin, M.D.
Secondary Medical:	N/A
Statistical:	Todd Sahlroot, Ph.D.
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemist:	N/A
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	N/A
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Project Manager:	Jena Weber
Other Consults:	ODS (Karen Lechtner – PPI)

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? YES

CLINICAL – File Refuse to file _____

• Clinical site inspection needed: YES _____ NO

MICROBIOLOGY CLINICAL – N/A

STATISTICAL – File Refuse to file _____

BIOPHARMACEUTICS – File Refuse to file _____

• Biopharm. inspection Needed: YES _____ NO

PHARMACOLOGY –

N/A

CHEMISTRY –

- Establishment ready for inspection? N/A

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

The application is unsuitable for filing. Explain why:

Jena Weber
Project Manager, HFD-510

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

/s/

Jena Weber
10/1/02 08:44:58 AM
CSO

Jena Weber
10/1/02 08:48:08 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Screening of New NDAs
Division of Biometrics II, HFD-715

NDA #: 21-178 /SE8-004

Priority Classification: standard

Trade Name: Glucovance

Sponsor: BMS

Generic Name: metformin/glyburide

Indication: type 2 diabetes

No. of Controlled Studies: 1

Date of Submission: 11/30/01

User Fee Goal Date: 9/30/02

Volume numbers in statistical section: 2-6

Date of Filing Meeting: 1/28/02

Screened by: J. Todd Sahlroot

Anticipated Review Completion Date:

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications/labelling requested	No
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel	

Item	Check (NA if not applicable)
statistical methodology (if present)	NA
Sufficient data listings and intermediate analysis tables to permit a statistical review	Yes
Data from primary studies in EDR	Yes
Intent-to-treat analyses	Yes
Effects of dropouts on primary analyses investigated	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes

BRIEF SUMMARY OF CONTROLLED TRIALS
(or attach relevant table from summary volume of NDA)

Study ID	# of Centers	Total Sample Size	Type of Control	Design primary variable	Duration Of Treatment
CV 138-055	65	Met/gly + rosi (n=181) Met/gly + plac (n=184) total n=365	placebo	. R, DB, PC HbA1c change from baseline	24 weeks

APPEARS THIS WAY
ON ORIGINAL

Weber, Jena M

From: Weber, Jena M
Sent: Monday, September 30, 2002 6:00 PM
To: CDER-APPROVALS
Subject: Reference NDA 21-178/S-004

From the Division of Metabolic and Endocrine Drug Products, HFD-510

Approval date: Monday September 30, 2002

DA: 21-178/S-004

Drug: Glucovance (glyburide + metformin HCl)

Sponsor: Bristol-Myers Squibb

Indication: Provides for the use of Glucovance with a thiazolidinedione when glycemic control is not obtained with glucovance alone.

Dosage form: oral tablets; 1.25 mg/250 mg; 2.5 mg/500mg; 5 mg/500mg; not a new dosage form or combination.

Key only

Standard review, oral hypoglycemic agent.

Thanks,

Jena

APPEARS THIS WAY
ON ORIGINAL