CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-178

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA 21-178 GLUCOVANCE®

Glyburide component: Paragraph I & II certification

Certain toxicological data for the drug products MICRONASE® (glyburide) and DIABETA® (glyburide) were relied on in the review and approval of the glyburide component of GLUCOVANCE® (NDA 21-178). Data from the drug product GLYNASE® (glyburide) were not relied on in the review and approval of the glyburide component of GLUCOVANCE®. FDA has requested that Bristol-Myers Squibb, in accordance with section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FFDCA), provide applicable patent information for MICRONASE® and DIABETA®.

Bristol-Myers Squibb as holder of NDA 21-178 for GLUCOVANCE® hereby provides a "Paragraph I certification" that patent information on MICRONASE® and DIABETA® has not been filed with FDA. FFDCA § 505(b)(2)(A)(i). In addition, Bristol-Myers Squibb hereby provides a "Paragraph II certification" that any applicable patent on MICRONASE® and DIABETA® has expired. FFDCA § 505(B)(2)(a)(ii).

Frank P. Hoffman
Counsel, WW Medicines Group
Bristol-Myers Squibb Company

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION

The Glucophage® (metformin)/glyburide combination products described in Bristol-Myers Squibb Company's NDA No. 21-178 for which approval has been applied for September 30, , 1999, 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 new Glucophage®/glyburide combination products described in this NDA is made on the attached sheet.

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.53(c)(2)(ii)(3):

In the opinion and to the best knowledge of Bristol-Myers Squibb Company, there are no patents that claim the metformin/glyburide combination products sought in the subject NDA and on which investigations that are relied upon in this application were conducted or that claim a use of such products.

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

Dated: September 30, 1999

APPEARS THIS WAY
ON ORIGINAL

Request for Exclusivity

Upon approval of this NDA we wish to claim three years of market exclusivity under 21 CFR 314.108(b)(4). The studies presented in this application are new clinical investigations that are essential to the approval of this application. We certify that, to the best of our knowledge, published studies do not exist which would provide a sufficient basis for the approval of the products which are the subject of this NDA. In support of this, we have attached the results of a literature search which used the Medline, Derwent Drug File, Embase, Embase Alert, JICST-EPlus, and Biosis data bases.

As the sponsor of the clinical trials presented in this application, Bristol-Myers Squibb Company certifies that it provided more than 50 percent of the cost of conducting the studies.

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

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

ORIGINAL

NEW CORRESP

NDA 21-178
Glucovance™(Glyburide and Metformin HCl Tablets)

July 13, 2000

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

Dear Dr. Jenkins:

Reference is made to our pending New Drug Application for Glucovance™ (Glyburide and Metformin HCl Tablets), NDA 21-178, submitted September 30, 1999. Additional reference is made to my July 10, 2000 telephone conversation with Mr. William Koch, in which he requested that Bristol-Myers Squibb (BMS) describe procedures used to follow up with investigators who did not provide financial disclosure information.

The listing of investigators and sub-investigators provided in the financial disclosure section of NDA 21-178 is footnoted to indicate that those who did not respond to the initial request received a second request via fax. If a response was still not obtained, they were contacted by telephone. This letter is to confirm that these procedures were followed to attempt to obtain financial disclosure information from all investigators who did not provide such information; in some instances additional attempts were made.

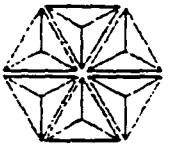
If you have any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,

Warren C. Randolph

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

WCR/ls/dk
Desk Copies: Mr. William Koch (HFD-510, Room 14B04)



BRISTOL-MYERS SQUIBB
PHARMACEUTICAL RESEARCH INSTITUTE

Metformin Hydrochloride/Glyburide Tablets
Financial Disclosure Information

Contents Page

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	TITLE
Hubert G.Pouleur, M.D.,Ph.D.	Vice-President Cardiovascular Clinical Research
FIRM/ORGANIZATION	
Bristol-Myers Squibb Company	
SIGNATURE	DATE
	Sept 14, 1999

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

ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Attached List (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Protocols CV138-011 and/or CV138-019 (*Name of clinical study*), 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	TITLE
Hubert G.Pouleur, M.D.,Ph.D.	Vice-President Cardiovascular Clinical Research
FIRM/ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE	DATE
	Sept-14, 1999

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:

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

ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Attached List (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Protocol CV138-024; (*Name of clinical study*) Protocols CV138-011 and/or CV138-019, 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	TITLE
Hubert G.Pouleur, M.D.,Ph.D.	Vice-President Cardiovascular Clinical Research
FIRM/ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE	DATE Oct 14, 99

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:

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

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 18, 1999	**DUE DATE:** February 14, 2000	**OPDRA CONSULT#:** 99-065

TO : John Jenkins, M.D.
Director, Division of Metabolic and Endocrine Drug Products
(HFD-510)

TROUGH: Jena Weber
Project Manager, Division of Metabolic and Endocrine Drug Products
(HFD-510)

PRODUCT NAMES: Glucovance (metformin hydrochloride - glyburide tablet) **NDA:** 21-178	**MANUFACTURER:** Bristol-Myers Squibb Company

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

If the presentation of the established name and the strengths are revised according to the recommendations of this consult, OPDRA does not object to the use of the proprietary name, Glucovance. See review for details.

[/S/] 2/15/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

[/S/] 2/15/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE RECEIVED: **October 18, 1999**

NDA: **21-178**

NAME OF DRUG: **Glucovance (metformin hydrochloride – glyburide tablet)**

NDA HOLDER: **Bristol-Myers Squibb Company**

I. INTRODUCTION

This OPDRA consult is in response to an October 18, 1999 request by the Division of Metabolic and Endocrine Drug Products, to review a proposed proprietary drug name, Glucovance, regarding potential name confusion with other proprietary/generic drug names. Container labels were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION
Glucovance contains two oral antihyperglycemic drugs, metformin hydrochloride and glyburide, used in the management of type 2 diabetes. These two agents have a synergistic effect and act to efficiently improve glucose tolerance by different but complementary mechanisms. Metformin acts as an insulin sensitizer to improve glucose tolerance in type 2 diabetes mellitus patients, lowering both basal and postprandial plasma glucose. Furthermore, metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Glyburide is an oral blood glucose-lowering drug of the sulfonylurea class. It appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas.

Glucovance as initial therapy is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Glucovance as second line of therapy is indicated when diet, exercise, and initial treatment with sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes mellitus. Moreover, Glucovance may be substituted for the titrated components up to the maximum recommended dose of 2000/ 20 mg per day. As initial therapy, the recommended starting dose is 250/ 1.25 mg once daily with meals. The recommended starting dose for second line therapy is 500/ 2.5 mg twice daily with meals. Dosage increases should be made every 2 weeks, up to the minimum effective dose necessary to achieve adequate glycemic control. Glucovance is supplied as 250/ 1.25 mg, 500/ 2.5 mg, and 500/ 5 mg tablets.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike Glucovance to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. Furthermore, an expert panel discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted a study of written and verbal analyses of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name.

A. Study conducted within OPDRA

1) Methodology

This study involved ninety-three health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Glucovance with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Random samples of written prescription orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions via e-mail to the medication error staff.

2) Results

Forty-seven written prescription orders and forty-six verbal orders were sent to the participants. We received responses from seventy participants. Thirty-four interpretations of written prescription orders and thirty-six interpretations of verbal prescription orders were received. Fourteen (out of seventy) participants interpreted Glucovance correctly, fifty-four participants interpreted Glucovance incorrectly, and two participant did not provide a response. The results are as follows:

---

[1] MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Repredisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

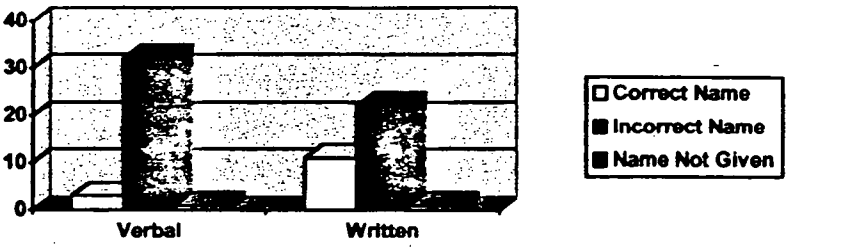
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

Glucovance



B. Expert Panel Discussion

Name Confusion With An Approved Proprietary Name

Glucovance (metformin HCL/ glyburide) and Glucophage (metformin HCL) have similar beginnings and character lengths. However, when scripted, the terminal syllables are distinctly different due to the letters, "p & g" in Glucophage. Moreover, since Glucovance contains two strengths *(for metformin and glyburide)*, there is an overlapping strength, "500 mg", between Glucovance and Glucophage. However, the second strength *(glyburide component)* of Glucovance differentiates these two drugs. Despite these debatable points, Glucovance and Glucophage are similar in that they are both available as tablets and are used in a similar clinical setting *(i.e. for use in patients with type 2 diabetes mellitus)*. Furthermore, there is an overlapping dosing interval and active ingredient. In addition, misadventures or substitution of these drugs could lead to inappropriate treatment of the existing medical condition due to the fact that Glucovance contains a second antihyperglycemic agent, glyburide, in addition to metformin.

Additionally, many patients who do not know the complete name of their medications, oftentimes, give a part of the name to their physician when describing their drug history. This may pose a safety risk for Glucovance and Glucophage due to the similarity of the names.

C. Summary

The results of the written and verbal analyses demonstrate that fifty-four out of seventy participants interpreted Glucovance incorrectly. Although the majority of the participants provided misspelled/phonetic variations of the drug name, two participants interpreted Glucovance as Glucophage. One of the two participants was in a verbal analysis group, and the other participant was in a written analysis group.

Moreover, a third participant, who did not interpret the name to be Glucophage, commented that the name sounds-alike Glucophage. These findings are important given the small sample size of the study and confirm the concerns expressed by the expert panel regarding the name confusion between Glucovance and Glucophage.

However, in this case, the sound-alike and look-alike properties of the two drug names are not as convincing as the overlapping metformin strength that appears first in a prescription, " **500 mg**/ 2.5 mg" and the same active ingredient "**metformin**/ glyburide" that could **trigger** and cause confusion between the two drug names. If the presentation of the established name and the strengths are revised so that the "glyburide" component appears first in the labels, the risk of confusion between the two names becomes insufficient to render the proprietary name, Glucovance, objectionable.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels of Glucovance, OPDRA has attempted to focus on safety issues relating to possible medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and/or the medical officer.

OPDRA has reviewed the current labels and has identified several areas of possible improvement, which might minimize potential user error.

CONTAINER LABEL

A. As discussed above, the established name should be revised so that the "glyburide" component appears first. In addition, the dash separating the two active ingredients of the established name does not clearly indicate that there are two active components in this combination product. Instead, the dash implies that there is only one active component with a long name. Furthermore, in the USP monographs, a dosage form descriptor is included as part of an established name. Moreover, we recommend abbreviating "hydrochloride" to HCL. We recommend the following presentation of the established name and strength on the container label:

TRADENAME
(Glyburide and Metformin HCL Tablets)

1.25 mg/250 mg

B. The container labels for the different strengths are almost identical. In order to prevent medication errors due to this similarity, we recommend differentiating the labels for the different strengths (i.e. different colors).

IV. RECOMMENDATIONS

A. If the presentation of the established name and the strengths are revised according to

the recommendations of this consult, OPDRA does not object to the use of the proprietary name, Glucovance. However, without these revisions, we do not recommend the use of the proprietary name, Glucovance.

B. OPDRA recommends the above label revisions which might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301) 827-3243.

[/S/] 2/15/2000

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

[/S/] 2/15/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 18, 1999	DUE DATE: February 14, 2000	OPDRA CONSULT#: 99-065

TO : John Jenkins, M.D.
Director, Division of Metabolic and Endocrine Drug Products
(HFD-510)

TROUGH: Jena Weber
Project Manager, Division of Metabolic and Endocrine Drug Products
(HFD-510)

PRODUCT NAMES:	MANUFACTURER: Bristol-Myers Squibb Company
Glucovance (metformin hydrochloride – glyburide tablet) NDA: 21-178	

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

If the presentation of the established name and the strengths are revised according to the recommendations of this consult, OPDRA does not object to the use of the proprietary name, Glucovance. See review for details.

[/S/] 2/15/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

[/S/] 2/15/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

JAN 13 2000

MEMORANDUM OF CONSULTATION

Date:

Between: Robert Misbin, M.D. (HFD-510)

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject: IND 52,837
Metformin/Glyburide
November 24, 1999
Proposed Pediatric Study Request

Protocol CV138-XXX is a multicenter, positive-controlled, randomized double-blind trial comparing fixed combination metformin/glyburide, metformin, and glyburide therapy titrated to control in pediatric patients with type 2 diabetes mellitus previously on insulin therapy. Protocol summary is displayed in Table 1.

Reviewer's Comments:

The primary efficacy comparison is between the combination group and the metformin monotherapy group. The comparison between the combination group and the glyburide group is secondary. To claim superiority of the combination therapy to both the metformin monotherapy and the glyburide monotherapy the sponsor should consider the statistical comparisons between combination therapy with each of the monotherapies simultaneously. Note that no adjustment for multiple comparisons would be needed since it would be required that both comparisons be significant.

The sponsor indicated that there will be a reasonable distribution of subjects across the specified age range in all treatment groups. However, it was not clear how this would be accomplished at randomization.

From the statement "The investigator will assign the randomization numbers from the lowest to the highest number within a given block" (Section 5.3) it seems the randomization is separate for each center. With 50 sites it is probable that some of the centers will have few patients. Ideally, the number of centers should be around 10 with each center randomizing at least 15 subjects (5/group). In that case, the ANCOVA model would include terms for treatment and center and baseline as a covariate.

The proposed ANCOVA analysis does not adjust for center effect. This reviewer assumes that because each center will enroll a limited number of subjects, it is impractical to include center in the model. In such case, it is also unnecessary to stratify the randomization by center.

Table 1 Protocol Summary

Treatment group 1. metformin/glyburide 250/1.25 mg 2. metformin 500 mg 3. glyburide 2.5 mg	 titrated upward to 1000/5 mg per day titrated upward to 2000 mg/day titrated upward to 10 mg/day
# of Centers	~50 US sites
Age groups ≥10 and ≤16 years	will be reasonably distributed across the age range in all treatment groups
Indication	Pediatric/Adolescent type 2 diabetes Mellitus
Sample size	≥150 with equal randomization (~50 per group)
Treatment segment 1. 2-week screening & lead-in 2. 16-week double-blind treatment 3. 52-week open label treatment	 continue current insulin therapy triple dummy, titration off insulin after 4 weeks of weekly upward titration of study medication, rescue to open-label treatment at 4, 8, & 12 weeks if glycemic criteria is met 250/1.25 mg titrated to glycemic control
Sample Size n=50 per group	To detect a difference of 0.7% in HbA_{1c} with S.D. = 1.0%, and 92% power
Primary endpoint HbA_{1c} change from baseline at week 16 **Secondary endpoint** FPG, postprandial glucose, fasting insulin, postprandial insulin, and weight	The primary comparison is between M/G combination group and the M monotherapy group A comparison of the combination group to the glyburide group will also be performed
Statistical Methods Analysis of covariance Fisher's Exact Test	ANCOVA with treatment as the main effect and with baseline value as the covariate parallelism in the ANCOVA model will be assessed The proportion of subjects discontinuing due to lack of glycemic control
Time of Reporting	on or before March 15, 2003

[/S/]
Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot [/S/] 1/6/00

Dr. Nevius [/S/] 1/11/00

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival IND 52,837
HFD-510

Metformin Hydrochloride-Glyburide Fixed Combination Tablets

DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company certifies that it did not 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 New Drug Application.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: August 2, 2000

FROM: John K. Jenkins, M.D. /S/ 8/2/00
Acting Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Director
Office of Drug Evaluation II, HFD-102

TO: NDA 21-178

SUBJECT: Overview of review issues

Administrative

NDA 21-178 for Glucovance (glyburide and metformin HCl) Tablets was submitted by Bristol-Myers Squibb on September 30, 1999. The Division assigned the application for a standard review. The 10-month user fee goal date for this application was July 31, 2000. This memorandum is written in support of the approval action for this NDA that was taken on July 31, 2000.

Clinical/Statistical

This NDA proposes a new fixed-dose combination of two already approved oral antihyperglycemic drugs; glyburide and metformin for use as initial and second-line therapy in patients with type 2 diabetes. In support of this application the sponsor submitted the results of two double-blind, randomized, controlled clinical trials that compared the safety and efficacy of Glucovance to its individual components and placebo (in the initial therapy study only). For a more detailed analysis of the results of these trials, please refer to the medical officer review prepared by Dr. Misbin and the statistical review prepared by Dr. Pian.

Glucovance was more effective than placebo and either individual component alone in lowering blood glucose and HBA_{1C} in drug treatment naïve patients. Glucovance was also more effective than the individual components alone in lowering blood glucose in patients not adequately controlled on at least half-maximum therapy with glyburide. In both studies, the dose of study treatments were titrated toward specific target fasting plasma glucose values during the trial, so the trial designs were not classic comparisons of the combination product at a fixed dose versus the individual active agents at the same fixed dose. These study designs do, however, more closely mimic how these drugs are likely to be used in clinical practice since both glyburide and metformin are titrated to effect. Of note, Glucovance was more effective than the individual components in these trials despite the fact that the mean final titrated dose of Glucovance was less than the mean final titrated dose of the individual components. These studies also adequately

demonstrated the safety of Glucovance in these patient populations with the primary adverse events being those expected for glyburide (hypoglycemia) and metformin (GI upset).

I concur with the recommendations made by Drs. Misbin and Malozowski that Glucovance is approvable from a clinical standpoint. However, I disagree with their conclusion that only the 1.25/250 and 2.5 mg/500 mg dose strengths, and not the 5 mg/500 mg dose strength, of Glucovance should be approved.

As noted above, both glyburide and metformin are currently approved antihyperglycemic drugs and are labeled for titration to maximum daily doses of 20 mg and 2550 mg, respectively, to achieve adequate glycemic control. While it is true that in the second-line therapy study there was no significant difference in the final mean FPG and HBA_{1C} for the two tablet strengths studied (i.e., 2.5 mg/500 mg and 5 mg/500 mg), this study did demonstrate that the 5 mg/500 mg tablet was safe and effective when used as second-line therapy at doses up to 20 mg/2000 mg. Despite the findings of this study with regard to mean final glycemic control, it is reasonable to conclude that there will be some patients who will require titration to a dose of 20 mg/2000 mg per day for second-line therapy in order to achieve adequate glycemic control. Such titration has been shown to be safe and effective in the Glucovance study and is consistent with the current approved labeling for glyburide and metformin.

While it is true that the 2.5 mg/500 mg tablet was associated with a much higher rate of hypoglycemia in the initial therapy study compared to the 1.25 mg/250 mg tablet, this finding was not evident in the second-line therapy study where the rate of hypoglycemic events was low. These differences are likely related to the baseline starting levels of glycemic control (i.e., baseline FPG and HBA_{1C}), the fact that the initial therapy patients were drug naïve, and in some degree are an artifact of the trial design. In both trials, patients with relatively good glycemic control at baseline (i.e., lower HBA_{1C}) were randomly assigned to either the low-strength or high-strength tablet without regard to baseline HBA_{1C}. This is not the approach that will be recommended in the labeling for clinical use of the combination drug. The labeling will recommend that patients be started at low doses and be titrated up slowly as needed in order to achieve adequate glycemic control. The labeling will also note that the incidence of hypoglycemia with the combination tablet is highest in patients with lower baseline HBA_{1C} values and the 5 mg/500 mg tablet will not be indicated or use as initial therapy. I believe that these labeling instructions can allow all tablet strengths to be used safety in clinical practice. Approval of all three dose strengths will also provide patients and physicians the necessary tablet strengths to titrate to glycemic control without the need to add an additional prescription for single ingredient glyburide to achieve a maximum glyburide dose of 20 mg/day, which would make a dosing regimen more complicated and likely lead to medication errors.

I do not believe that the sponsor should be granted a specific indication for [redacted] since no clinical trials were conducted to evaluate the safety and effectiveness of such [redacted] Since there

are currently multiple formulations of glyburide marketed in the U.S. that are not bioequivalent or interchangeable and since the glyburide component of Glucovance has not been shown to be bioequivalent to any single ingredient glyburide product, such direct mg per mg could result in altered glycemic control and potential hypoglycemia. The issues related to ———, however, are not unique to the 5 mg/500 mg tablet strength. In all likelihood physicians will ——— for convenience and expected improved compliance and this will occur with all Glucovance tablet strengths, not just the 5 mg/500 mg tablet. While I do not think a specific indication for such ——— should be granted, I do believe that cautionary statements about possible changes in glycemic control in such cases should be included in the labeling to encourage such switches to be made with caution and proper monitoring.

This application is approvable from a clinical/statistical perspective and all three proposed tablet strengths are approvable.

Pharmacology/Toxicology

No preclinical studies were included in the NDA and none were required given the long marketing history of the individual active ingredients of the combination tablet. The sponsor referenced the preclinical data from Micronase and Diabeta in support of their application and provide appropriate patent certifications for this 505(b)2 application.

This application is approvable from a pharmacology/toxicology perspective.

Chemistry, Manufacturing, and Controls

The sponsor proposes to market tablets containing 1.25 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg of glyburide and metformin, respectively. Please see the review prepared by Dr. Ysern for a detailed review of the CMC information provided by the sponsor. All CMC issues have been adequately addressed.

This application is approvable from a CMC perspective.

Clinical Pharmacology and Biopharmaceutics

Please refer to the review prepared by Dr. Johnson for details of the clinical pharmacology program submitted in support of Glucovance. The sponsor has shown that the metformin component of Glucovance is bioequivalent to marketed Glucophage. However, bioequivalence was not shown for the glyburide component of Glucovance to Micronase, and other marketed formulations of single-ingredient glyburide were not tested. These findings have implications when patients are ——— and are highlighted in the labeling as potential safety concerns (see above).

This application is approvable from a clinical pharmacology and biopharmaceutics perspective.

Data Integrity

The Division of Scientific Investigations audited the three clinical sites involved in the two phase 3 studies submitted in support of this application. All three sites were rated as NAI by DSI. No issues that raised any questions about the integrity of the data submitted in support of this application were noted by any of the primary reviewers.

Labeling and Nomenclature

The proposed tradename is acceptable to the Division and OPDRA. The final package insert and patient package insert as agreed with the sponsor during a telephone conference call on 7/31/2000 accurately describes the data submitted in support of this NDA and are acceptable.

Conclusions

This NDA was approved on July 31, 2000 with labeling as agreed with the sponsor on that same day. There are no phase 4 commitments for this NDA.

cc:

NDA 21-178
HFD-510/Division File
HFD-510/Koch
HFD-102/Jenkins

RECORD OF TELEPHONE CONVERSATION	DATE: June 13, 2000 Time: 1115 hrs Location: PKLN# 14B-45
FDA Attendees: Robert Misbin, M.D., Medical Reviewer William C. Koch, R.Ph., RPM **Objectives:** To discuss changes to the "DOSAGE AND ADMINISTRATION" section of June 12, 2000, revision of labeling. **Discussion:** The applicant deleted the paragraph labeled "[redacted] which was included in the original draft label. Dr. Misbin suggested that striking this paragraph left the physicians without necessary guidance, and that this paragraph, reinstated using different language, would address an important prescribing issue. He also stated that in his view the submitted data does not strongly support the marketing of the 5mg/500mg tablet strength, and asked the applicant to explain why this strength should be marketed. [/S/] 06/16/00 William C. Koch, R.Ph. Date Regulatory Project Manager	**Telecon initiated by:** FDA **NDA:** 21-178 **Product name:** Glucovance (glyburide and metformin HCl tablets **Firm name:** BMS **Name and title of person with whom conversation was held:** Warren C. Randolph Director, Metabolic/Endocrine Products **Telephone:** (609) 252-5228

Cc: Original NDA 21-178
HFD-510/RMisbin/WKoch
Division File

ADDENDUM

Bristol-Myers Squibb
P.O. Box 400
Princeton, NJ 08543

Attention: Warren Randolph, Director, US Regulatory Affairs

Fax: 609-252-6000

Ref: NDA 21-178; original submission dated September 30, 1999.

As a follow-up to the communication (fax) sent to you on March 14, 2000, that outlined the recommendations for the tradename, Glucovance as proposed by the Office of Post-Marketing Drug Risk Assessment, if the presentation of the established name and strengths are revised according to the recommendation by OPDRA, we do not object to the use of the proprietary name, Glucovance. However, without these revisions, we do NOT recommend the use of the proprietary name, Glucovance. Please reference this document to determine if you concur with our recommendations. If you object to either recommendations, please contact Ms. Jena Weber, Project Manager at 310-827-6422.

CLEARED FOR FAXING

[/S/] 3/16/00

Jena Weber, CSO

[/S/] 16-MAR-2000

Xavier Ysern, Ph.D.

[/S/]

Stephen Moore, Ph.D.

[/S/] 3/16/00

Robert Misbin, M.D.

[/S/] 3/16/00

Saul Malozowski, M.D.

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
P.O. Box 400
Princeton, NJ 08543

Attention: Warren Randolph, Director, US Regulatory Affairs

Fax: 609-252-6000

Ref: NDA 21-178; original submission dated September 30, 1999.

We are still in the process of reviewing your NDA. However, the following are comments and requests from the Office of Post-Marketing Drug Risk Assessment. The reviewing division (DMEDP) concurs with their evaluation.

CONTAINER LABEL

A. The established name should be revised so that the "glyburide" component appears first. In addition, the dash separating the two active ingredients of the established name does not clearly indicate that there are two active components in this combination product. Instead, the dash implies that there is only one active component with a long name. Furthermore, the USP monographs, a dosage form descriptor is included as part of an established name. Moreover, we recommend abbreviating "hydrochloride" to "HCl." We also recommend the following presentation of the established name and strength on the container label:

TRADENAME
(Glyburide and Metformin HCl Tablets)

1.25 mg/250 mg

B. The container label for the different strengths is almost identical. In order to prevent medication errors due to this similarity, we recommend differentiating the labels for the different strengths (i.e., different colors).

CLEARED FOR FAXING

[/S/] 3/14/00

Jena Weber, CSO

[/S/] 14-MAR-2000

Xavier Ysern, Ph.D.

[/S/] 3/14/2000

Stephen Moore, Ph.D.

[/S/] 3/14/2000

Robert Misbin, M.D.

[/S/] 3/14/00

Saul Malozowski, M.D.

Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Research Institute
Worldwide Regulatory Affairs - Lawrenceville

To: Distribution **Date:** November 5, 1996

From: Warren Randolph wlr **CC:**

Subject: **Minutes of BMS/FDA Meeting to Discuss Development Plans for Metformin Novel Oral Dose Form and Combination Product**

Executive Summary

Proposed development plans were presented for an extended release dose form of metformin and for a combination product containing metformin and glyburide (see FDA briefing document submitted October 1, 1996). Proposed bioavailability and pharmacokinetic studies for both programs were accepted by FDA. Safety and efficacy trials proposed for the extended release product were considered adequate for approval of the product, though a post-marketing study might be needed to assess long-term safety. The question as to whether the combination product could be approved on the basis of bioequivalence testing alone or would require safety and efficacy data was deferred pending a policy decision by FDA.

Background

Formulation work is ongoing to develop a novel oral dose form of metformin, with extended release characteristics, to provide for less frequent dosing than with current, immediate release Glucophage® tablets. In addition, a combination product consisting of metformin and glyburide is under development for use in treating NIDDM patients who do not achieve adequate glycemic control with sulfonylurea monotherapy. Development plans for both of the proposed products were provided to FDA, including outlines of the proposed clinical study protocols. in the form of a briefing document. On October 17, 1996, representatives of BMS met with FDA to discuss the proposed development plans.

BMS Attendees: J. Bedard, D. Cryer, H. DeRuyter, D. Henry, P. Marathe, H. Pouleur, D. Rader, W. Randolph, R. Soltys

Also Attending for BMS: [ ]

FDA Attendees: S. Sobel, M.D., Division Director;
G.A. Fleming, M.D., Clinical Team Leader
R. Misbin, M.D., Clinical Reviewer
X.Ysern, Ph.D., Chemistry Reviewer
R. Steigerwolt, Pharmacology Reviewer
H.-Y. Ahn, Ph.D., Biopharmaceutics
M. Fossler, Pharm.D., Biopharmaceutics
B. Taneja, Ph.D., Biometrics
M. Johnston, Project Manager

Meeting Minutes

W. Randolph first thanked the FDA members for attending and then introduced the agenda. Included in the introduction was the BMS goal of reaching agreement on plans which would support the marketing approvals for the two proposed products.

P. Marathe presented three key bioavailability and pharmacokinetic studies for the novel oral dose form (NODF). Dr. Ahn asked how many strengths would be developed and BMS responded that one strength (250 or 500mg) would be developed and multiple units would be administered. Dr. Ahn then mentioned an FDA guidance on in vivo/in vitro correlation and suggested that if such correlation was demonstrated, future formulation changes might be approved on the basis of in vitro dissolution alone.

H. Pouleur presented a summary of changes to protocol outlines which had been included in the briefing materials (copies of the revised outlines were distributed to FDA attendees) and then reviewed the designs of the proposed safety and efficacy trials for the NODF. Dr. Fleming stated that the proposed studies were a reasonable approach; while neither study alone could support approval, together they could. He then asked how the risk/benefit of the NODF might be evaluated relative to conventional tablets, especially regarding lactic acidosis and whether measurement of lactate levels would be useful.

———— commented on the difficulties of proper collection of samples for lactate determinations in a multi-center trial. He then noted that side effects of glipizide are lower with extended release and speculated that this approach may improve both safety and efficacy with metformin. Dr. Fleming said his suggestion was just for BMS to consider lactate measurements in the trials. Dr. Misbin said he would argue against the lactate measurements, due to variability and the difficulties which might arise from relatively small

differences between groups. If lactate was higher with the NODF, this would not necessarily argue against its use; if lower with the NODF, he would not recommend that this be allowed in labeling.

Dr. Pouleur asked if a study of metformin blood levels and their relationship to lactate levels should be done in a Phase I setting. Dr. Misbin replied that such a study should be done, but it addresses a different question. The question of relative safety with the NODF was left for further consideration by BMS, with revisions to the clinical plan possible (e.g., extension of the long term portions of the studies). Dr. Fleming indicated that a post-marketing study might be needed.

Dr. Marathe presented the plans for bioavailability and pharmacokinetic studies for the combination product (which were acceptable to FDA). BMS then referred to an earlier combination study (metformin plus glyburide) which was submitted in the Glucophage NDA and which showed the combination to be more effective than either monotherapy in NIDDM patients not adequately controlled on glyburide alone. FDA was asked if additional safety and efficacy data would be needed for approval of the combination product if bioavailability of its components was equivalent to the Glucophage® and Micronase® used in the combination study.

FDA reviewers did not rule out the possibility that the combination product might be approvable on the basis of bioequivalence. The BMS question appeared to relate to a policy decision which is currently under consideration. BMS commented on prior experience with cardiovascular combination products, where safety and efficacy trials have been required despite labeling which provides for concomitant use of the components and bioequivalence data. The difference in dosing between the prior study (where all patients were on maximum dose glyburide) and the current study, where both drugs would be titrated, was pointed out. FDA promised to get back to BMS with an answer regarding the need for safety and efficacy data for approval of the combination product.

Dr. Pouleur presented the proposed design for a safety and efficacy trial with the combination product, should the study be required. Dr. Misbin asked how failure would be defined and when would failures be withdrawn from the trial. [redacted] suggested that a fasting plasma glucose above 250mg/dl on three visits or gross diabetic symptoms would constitute a failure. Dr. Misbin suggested that failures in the monotherapy arms be put on combination therapy and that all patients (if not hypoglycemic) be put on maximum dose combination for the long-term extension; this would provide additional information about use of the combination in both metformin and glyburide failures, with minimal additional cost.

Dr. Ahn asked if we would attempt to obtain pharmacokinetic/pharmacodynamic data and Dr. Pouleur commented that such data is difficult to collect in multicenter trials. Dr. Ahn suggested that population kinetics be considered.

Since both metformin and glyburide are well-characterized and their use in combination is well accepted, BMS asked for concurrence that no animal toxicology studies would be needed for approval of the combination product; FDA agreed, but stated that bioavailability data with the NODF in humans and animals would have to be evaluated to determine if any toxicology testing would be needed for approval of such a product.

BMS asked if the clinical programs for the NODF and combination products could be conducted under the existing metformin IND, or if new INDs would be required. FDA promised to get back to BMS on this point.

Before the meeting adjourned, the following summarization was agreed-upon:

1) The proposed bioavailability and pharmacokinetic studies for the NODF and the combination products are adequate.

2) The proposed safety and efficacy studies for the NODF will support approval of the product, but they are not powered to provide comparative data regarding safety, tolerability or advantages. A post-marketing study may be necessary.

3) The question as to whether safety and efficacy data would be needed in addition to bioequivalence data for approval of the combination product involves a policy decision; FDA will get back to BMS when the decision is made.

4) FDA will inform BMS if new INDs are needed for clinical trials for either of the proposed products.

Meeting Date: July 26, 2000 Time: 4:30 pm Location: PKLN Room #14B-04

NDA 21-178 Glucovance (glyburide and metformin)

Type of Meeting: Labeling Teleconference

External Participant: Bristol-Myers Squibb

Meeting Chair: David G. Orloff, M.D., Deputy Director

External Participant Lead: Warren Randolph, Director, Regulatory Science

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

David G. Orloff, M.D., Deputy Director
Robert Misbin, M.D., Medical Officer
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees (by phone) and titles:

Steve Bass, Ph.D., Associate Director, Regulatory Science
John Bedard, Vice President, Regulatory Science
Scott Canterberry, Director, Metabolics Marketing
David Henry, Principal Statistician, Biostatistics
Porter Layne, Ph.D., Senior Director, Regulatory Science
Kathleen Meriwether, Senior Director, Regulatory Services
Cathleen O'Connell, Ph.D., Director, Regulatory Science
Frank Pasqualone, Vice President, Metabolics Marketing
Beth Anne Piper, M.D., Director, Cardiovascular/Metabolics Clinical
Warren Randolph, Director, Regulatory Science
Ann Seymour, Ph.D., Director, Medical Affairs

Meeting Objectives:

To finalize the package insert on NDA 21-178 based upon Division recommendations of July 24, 2000.

Discussion Points:

1. The applicant requested that the term "glycemic control" be reinstated in the text in place Of "blood glucose control".

2. The applicant requested that the term "synergistic" be reinstated to the **DESCRIPTION** Section.

3. The applicant requested that in the **CLINICAL PHARMACOLOGY** section, **Mechanism of Action** paragraph the term ——— be reinstated and the term ——— be removed .

4. The applicant requested that the paragraph following Table 1., which summarizes the results of that table, be reinstated.

5. The applicant requested that the term Fasting Plasma Glucose (FPG) be used consistently throughout the text in place of Fasting Blood Glucose (FBG).

6. In the **DOSAGE AND ADMINISTRATION** section the applicant requested that the terms "Initial Therapy" and "Second-Line Therapy" be used in the paragraph headings.

7. The Division requested that a sentence be added by the applicant to the paragraph headed "Glucovance ——— as Initial Therapy" in the **DOSAGE AND ADMINISTRATION** section stating that the 5mg/500mg strength dosage form not be used as initial therapy.

Decisions (agreements) reached:

- The Division agreed with the requests numbered 1, 3, 5, and 6.
- The Division will seek further guidance on the request numbered 2.
- The Division agreed to consider the request numbered 4 pending applicant submission of revised wording.
- The applicant will submit a sentence compliant with the Division's request in number 7.

Unresolved or issues requiring further discussion:

- Refer to bullet point #2 under Decisions.

Action Items:

- Revised labeling will be submitted by the applicant based upon the decisions made at this meeting.

Prepared by: [/S/] 07/31/03, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

Concurrence: [/S/] 7/31/03, Meeting Chair
David G. Orloff, M.D., date
Deputy Director

Meeting Date: July 10, 2000 Time: 02:30 pm Location: PKLN Room #14B-45

NDA 21-178 Glucovance (glyburide and metformin HCl tablets)

Type of Meeting: Internal labeling

Meeting Chair: Saul Malozowski, M.D., Medical Team Leader

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Saul Malozowski, M.D., Medical Team Leader
Robert Misbin, M.D., Medical Officer
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
Steven Johnson, Pharm.D., Biopharmaceutics Reviewer
Ronald W. Steigerwalt, Ph.D., Pharmacology Team Leader
Lee-Ping Pian, Ph.D., Biometrics 2 Reviewer
William C. Koch, R.Ph., Regulatory Project Manager

Meeting Objectives:

To discuss, among members of the review team the Division's recommendations for the labeling of Glucovance.

Decisions (agreements) reached among the team members:

- The team proposed deletion of the 5 mg/500mg strength from the heading (refer to Medical Officer review).
- In the **DESCRIPTION** section the team proposed changing "a synergistic" in the second sentence to "an additive".
- In the **CLINICAL PHARMACOLOGY** section, **Mechanism of Action** paragraphs, second paragraph the team proposed deleting "acts as an insulin sensitizer to" and modifying "type 2 Diabetes mellitus patients" to read "patients with type 2 diabetes.
- In the **Clinical Studies** paragraphs, the team proposed deletion of the phrase [ ]
- In the second original sentence the team proposed changing the mean values to uper limit values.
- The team proposed deletion of "2 hr postprandial" and "final HbA1c Distribution" from Table 1.
- In the third paragraph of **Clinical Studies** paragraphs, the team proposed that the applicant Reword the sentence beginning with ———————————, and relocate the sentence beginning with ——————————— to immediately following the second paragraph.

- In the newly created third paragraph of **Clinical Studies**, the team proposed that the applicant kraft a sentence regarding patient weight gain to be added following the first sentence.
- The team proposed, in the fifth paragraph of **Clinical Studies**, that the wording of the second sentence be changed to [redacted]
- The Team proposed changing the heading of Table 2. To read [redacted]
- In the "Second Line Therapy" paragraphs, the team proposed that the applicant kraft a third, closing paragraph regarding patient weight gain.
- In the **INDICATIONS AND USAGE** section, the team deleted the [redacted] sentence.
- The review team proposed combining tables # 6 and #7, and deleting p values from both tables.
- In the **GLUCOVANCE As Second Line Therapy** paragraphs, the team proposed a qualifying sentence regarding [redacted] and requested that the applicant kraft a sentence regarding [redacted]
- The team proposed deleting the entire statement in the [redacted] paragraph.
- In the **HOW SUPPLIED** section the team proposed deletion of reference to the 5/500 strength.

Unresolved or issues requiring further discussion:

- Changes to **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy,** and **Nursing Mothers** sections faxed by pharm/tox team on July 09, 2000.

- In the second paragraph in the **DESCRIPTION** section the biopharmaceutics team proposed changing the 75% undersized particle distribution value from — to 21 micrometers. This was faxed to the applicant on July 11, 2000.

- Changes to **Pharmacokinetics** paragraphs, "Absorption and Bioavailability" paragraph faxed By biopharmaceutics team on July 14, 2000.

Action Items:

- None

APPEARS THIS WAY
ON ORIGINAL

Prepared by: _____, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

Concurrence: _____, Meeting Chair
Saul Malozowski, M.D., date
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENTS:

1. Biopharmaceutics Team recommendations faxed 07/14/00
2. 06/29/00 applicant draft label with Division notations of 07/10/00

MEMORANDUM OF MEETING

Meeting Date: Tuesday November 16, 1999; @ 1:00 pm, Room 1456

Application: BMS application for GLUCOVANCE (metformin HCl/Glyburide) fixed combination, NDA 21-178.

Type of Meeting: Filing meeting

Meeting Recorder and Chair: Jena Weber, CSO

/S/ 11/17/99

FDA Attendees

Robert Misbin, M.D.	Medical Officer
Saul Malozowski, M.D.	Team Leader, Medical Officer
Xavier Ysern, Ph.D.	Chemist
Lee Pian, Ph.D.	Statistician
Stephen Johnson, Pharm.D.	Biopharmaceutics
Jena Weber	RHPM

Meeting Objectives: To determine if this application is fileable, priority or standard review, therapeutic classification, and whether an advisory committee should be assembled.

Comments: First application that contains a "fixed-dose" therapy for the treatment of Type 2 diabetes.

Pharmacology/Toxicology:	No issues, no relevant material submitted for review.
Biopharmacology:	No issues, filable.
Chemistry (CMC):	No issues, filable, should be designated 4S.
Statistics:	No issues, filable.
MO:	No issues, filable. AC is a consideration, but not a necessity. It has been noted that the combination of the two drugs has been associated with an increase in CV death.
DSI:	Dr. Blay will be notified.

Conclusions:

1. Application is **fileable.**
2. Submission will be assigned **Standard review** status.
3. No Advisory Committee will be required.

cc: NDA 21-178
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-511/JWeber
HFD-510/SSobel/RMisbin/SMalozowski/HYAhn/SJohnson/XYsern/SMoore
Lpian/TSahlroot/RSteigerwalt
HFD-46/RBlay

Drafted by:Jweber 11/18/99
Final: Jweber 11/18/99

MEETING MINUTES

Memorandum of Meeting Minutes

Meeting Date: Monday, May 24, 1999 **Time:** 3:30 **Location:** 1456

Application: IND 47,342

Type of Meeting: Pre-NDA (CMC and Biopharm)

Meeting Chair: Hae-Young Ahn, Ph.D., and Stephen Moore, Ph.D.

Meeting Recorder: Jena Weber, RHPM

FDA Attendees:

Stephen Moore, Ph.D.	Team Leader, Chemistry
Xavier Ysern, Ph.D.	Chemistry Reviewer
Hae-Young Ahn, Ph.D.	Team Leader, Biopharmaceutics
Ronald Kavanagh, Ph.D.	Biopharmaceutics Reviewer
Jena Weber, BS	Project Manager

BMS Attendees:

Melody Brown, BS	Director, CMC, Worldwide Regulatory Affairs
Gill Cave, BS	Pharmaceutical Scientist
Punit H. Marathe, Ph.D.	Senior Research Investigator
Sarah Nicholson, Ph.D.	Pharmaceutical Scientist
Mary Peters, BA	Manager, CMC, Worldwide Regulatory Affairs
Robert Simon, BS	VP, CMC Worldwide Regulatory Affairs

Discussion Points: see attached brochure/outline from BMS. Mostly CMC and biopharm issues for the development program and information that will be included in the metformin hydrochloride modified release (biphasic) New Drug Application. In addition, some outstanding issues from the previous pre-NDA CMC meeting (December 4, 1998) on the metformin hydrochloride/glyburide tablets were addressed.

- At the pre-NDA CMC meeting (December 4, 1998), BMS proposed to use the same dissolution method for the metformin component of the combination tablets that is already approved for the single entity Glucophage® Tablets. The conditions given were 100 rpms with paddles. Dr. Ahn (FDA) questioned whether the 100 rpm paddle speed was in the approved Glucophage application method since the biopharm review of the NDA stated that the FDA would not agree to a paddle speed of 100 rmp.

- She also stated that the review indicated that a specification of "minimum ——(Q) dissolved in 30 minutes would be preferable to "——(Q) dissolved in 45 minutes". During the presentation Ms. Brown confirmed that the dissolution method approved in the Glucophage® NDA No. 20-357 uses the USP apparatus 2 (paddles at 100 rpm) and the medium is pH 6.8 phosphate buffer at a volume of 1000 mL. In addition, she confirmed that the approved specification is "minimum —(Q) dissolved in 45 minutes".

- Ms. Brown proposed that the dissolution method for the metformin hydrochloride/glyburide product be the same as Glucophage® but the specification would be tightened to "minimum —— (Q) dissolved in 30 minutes". Dr. Ahn (FDA) again questioned whether the 100 rpm paddle speed was in the approved method for glucophage. BMS said that they had copies of the relevant pages from the NDA that indicated a paddle speed of 100 rpm. In addition, the company said that they had copies of correspondence between —— and the FDA indicating the 100 rpm speed, but using a rotating basket.

- Dr. Ahn indicated that 100 rpm speed would be acceptable for a dissolution method using a rotating basket but not paddles; therefore, if the intended dissolution method for the metformin hydrochloride/glyburide tablets is USP apparatus 2 (paddle method), a 100 rpm paddle speed is unacceptable.

- BMS indicated that they would revise the dissolution method accordingly and submit the details in an amendment to the Agency for input/comments. Everyone agreed that there was still some confusion regarding the approved Glucophage® dissolution method, but FDA and BMS would work together to resolve this matter. Copies were made of the relevant Glucophage® NDA pages and the correspondence between —— and FDA.

- Regarding the particle size of glyburide, an update of the information that has become available since the pre-NDA CMC meeting held on December 4, 1998, was presented. The glyburide lots used in the clinical studies were identified and presented in a table format. Two tables, one that listed the lots used in clinical studies as of December 1998, and another listing all the lots used in clinical studies to date. Two bio-studies have been completed since the previous meeting, the definitive bioavailability study (CV138-024) and a bioequivalency study (CV138-042).

- Study CV138-024 was conducted to demonstrate comparable bioavailability of two strengths of combination tablets (lots 9114 and 9117) relative to Glucophage® and Micronase®. Dr. Marathe presented the results of the study which indicate that the objective was achieved; typical combination tablet batches show bioequivalence to Glucophage® for the metformin component and comparable bioavailability to Micronase® for the glyburide component.

- Study CV138-042 was performed to characterize the bioavailability of different glyburide drug substance lots used in the manufacture of combination tablet batches. The glyburide lots differed in their particle size. Three lots of combination tablet batches were used in the

study. Lot 9117 is the same lot used in study CV138-024 which compared this combination lot to the individual components; therefore, lot 9117 is considered the reference batch with regard to its particle size.

- Lot 9118 which has a particle size of glyburide that is representative of future lots produced by the commercial process at the commercial scale was also used in the study. Lot 9101 manufactured from glyburide lot —/97/G1 and was used earlier in the clinical program before the had been determined. Dr. Marathe explained that glyburide lot 9118 was bioequivalent to the reference batch 9117 and lot 9101 fails the bioequivalence criteria compared to the reference batch (9117). Therefore, a particle size distribution similar to —/97/G1 which was used in lot 9101, will be excluded in the final particle size specification.

- Dr. Marathe indicated that the particle size methodology is finalized and a particle size specification is proposed taking into consideration all of these factors.

- Regarding the glyburide particle size methodology and proposed specification, Mr. Cave explained the issues/problems with the provisional method that was used to generate the data presented at the pre-NDA CMC meeting (December 4, 1998), and the benefits of the revised validated method. All of the glyburide drug substance lots used in the Phase III clinical studies and the long-term stability studies were re-measured using the revised validated method and the results were presented.

- Mr. Cave emphasized that the particle size specification has been based on glyburide lots received from the vendor that have beer
  A graph was presented illustrating typical for
  —— glyburide lots from the vendor. The distributions for all the lots were similar which demonstrates the robustness of

- Mr. Cave also presented back-up slides which were not part of the original presentation but were added based on comments received from Dr. Kavanagh prior to the meeting. The 95% confidence intervals for the particle size distributions of the seven lots were introduced. Method reproducibility was extremely important in determining the final specification.

- Taking into account sample, operator and instrument variability for the method, a three point specification to control the shape of the whole particle size distribution was proposed as follows:
  In conclusion, the results of studies CV138-024 and CV138-042 were emphasized. The reproducible nature of the glyburide particle size distributions produced by the vendor's
  with the proposed particle size specification, ensures a consistent product can be manufactured.

- It was also pointed out that even though drug product lot 9101 manufactured using glyburide lot —97/G1 did not demonstrate bioequivalence to the reference combination lot, 9117, clinical study results (CV138-011) demonstrate a positive outcome and the study objectives have been met.

- The Biopharm and chemistry reviewers were satisfied with the work BMS had done to resolve this issue. Dr. Ahn commented that only the two lots, 9117 and 9118, in the bioequvalence study could be used to set the specification and then the manufacturing capability and method variability should be taken into account.

- Dr. Ahn also wanted to know if there were any differences in the clinical data between the lots. BMS said that they did not know and that their clinical colleagues would have to comment on this. Dr. Ahn asked if BMS would be having a pre-NDA Clinical meeting and they indicated that there was probably not going to be enough time. She also questioned the need for a bioequivalency study at the Dr. Kavanagh understood that the specifications were already tight and that the method reproducibility was a very important factor in setting the specifications. Mr. Simon indicated that batches would be rejected if ould not have a product. Dr. Moore said the firm will need to take into consideration the manufacturing

- Drs. Ahn and Kavanagh agreed that another bioequivalency study to justify the particle size specification was not necessary; however, they will ask the statisticians to comment on the differences between the lots in the clinical program (patient to patient variability). In addition, Dr. Ahn commented that the commercial lots manufactured so far seemed acceptable based on the particle size data by the provisional method presented at the December meeting but understood the need to base the particle size specification on data generated by the revised method. Dr. Ysern would have preferred to see a linear representation of the particle size nstead of the log data because the range in particle size is mainly between

- Ms. Brown asked how FDA would like to see the data presented in the NDA. Dr. Kavanagh indicated confidence intervals around the whole curve. Mr. Cave showed plots of the size distribution that demonstrated how lot —/97/J10 was similar to and how lot —97/G1 clearly differed from the commercially produced glyburide and confirmed that our proposed final particle size specification would exclude material of a distribution similar to —97/G1.

- Ranges for the were questioned, but the company indicated that the specification was very stringent in that a three-point specification was being proposed to control the distribution. FDA generally agreed with the data that was presented and understood the rationale for the However, the information regarding this issue still needs to be reviewed in the NDA, but FDA thought that no additional raw data need to be generated.

- BMS indicated that Dr. Misbin had some issues with the previous presentation in December and that BMS was asked if they could follow-up with him regarding the additional information presented at this meeting to get his comment/input.

Action Items for follow-up:

- BMS will revise the dissolution method/specification for the metformin component of the combination tablets accordingly and submit the details in an amendment to get input/comments from FDA, if necessary.

- BMS and FDA will work together to resolve the discrepancy regarding the approved Glucophage® dissolution method.

- BMS will follow-up with Dr. Misbin regarding the additional information presented at this meeting to get his comment/input.

Metformin Hydrochloride Modified Release ——— Tablet

- Ms. Peters presented an overview of the project including the timelines for filing the NDA and summarized the key issues that BMS would like to cover at this meeting. The key issues are in regard to the dissolution method/specification and the stability program.

- Dr. Nicholson summarized the biopharmaceutical properties of metformin hydrochloride. The principle of action of a .blet was presented followed by the specific metformin hydrochloride modified release product composition and manufacturing process. She explained the proposed mechanism of drug release from the matrix tablet and properties of the product during dissolution testing. The proposed QC dissolution methodology was then presented; USP type 2 apparatus, paddle rotation speed at 100 rpm in 1000 mL of pH 6.8 phosphate buffer. The proposed dissolution methodology is influenced by several factors: ———— Therefore, the lowest speed to give reproducible results (100 rpm) was chosen. The proposed dissolution specification will be based on the in vitro performance of clinical lots manufactured by the commercial process at the commercial manufacturing site. A dissolution value at ——— (mean dissolution value from all clinical lots +/- 10%), ——— (mean dissolution value from all clinical lots +/- 10%) and ——— (greater or equal to —— of drug released) will be proposed.

- Dr. Nicholson presented the stability program; minimum [redacted] data will be provided in the NDA for three batches manufactured at the commercial site at [redacted] of the intended commercial scale by the commercial process. In addition, all packaging configurations will be placed on test.

- Dr. Moore questioned whether the medium at 6.8 pH buffer and the 100 rpm speed was a grading the tablet due to forceful agitation instead of dissolving the tablet. Furthermore, Dr. Ahn asked whether at the lower speeds, the tablet remains stuck to the vessel wall throughout the testing, or does it stick temporarily. BMS indicated that [redacted].

- The firm only provided data for one batch, Dr. Ahn asked for additional data to justify using the 100 rpm speed in the dissolution method and indicated that data for three batches ([redacted] tablets) at 75 rpm in three pH media should be included in the NDA. BMS said that they would prefer to submit the additional data in an IND amendment to get their input/comments prior to filing the NDA. Dr. Ahn also indicated that if the method is revised to a speed of 75 rpm, then amendment to the proposed specification for quantitative release ([redacted](Q) in 10 hours) may need to be considered.

- Dr. Ahn asked what Biopharmaceutic studies were conducted for this product and Dr. Marathe summarized them as follows.

  A Single Dose Pharmacokinetic Comparison of the Biphasic Tablet with Immediate Release Glucophage (CV138-021)

  An Ascending-dose, Steady State Pharmacokinetic Study and Comparison to Glucophage (CV138-028)

  A Food Effect Study with High Fat and Low Fat Dinner and Comparison to Fasted Condition (CV138-031)

- Dr. Ahn questioned the 6.5 hour fast time for the food effect study and said that she prefers a 10 hour fast time. BMS commented that the design of the food effect study was discussed with the FDA and their agreement was sought before the study was conducted.

- Dr. Moore indicated that the stability program was very straight forward and acceptable.

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ON ORIGINAL

Action Items for follow-up:

- Submit the additional data to justify using the 100 rpm speed in the dissolution method as an IND amendment to get FDA input/comments prior to filing the NDA.
- Submission of the official minutes to the IND.

[/S/] 10/21/99

Jena Weber, RHPM

[/S/] 10/21/99

Hae-Young Ahn, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: Friday December 4, 1998

Time: 1p - 3:00p

Location: Room 1456

Application: IND 52,837; Bristol-Myers Squibb

Type of Meeting: End of Phase II/ pre-NDA for Metformin/Glyburide Tablets

Meeting Chair: Stephen Moore, Ph.D.

Meeting Recorder: Jena Weber, CSC

FDA Attendees, titles, and Office/Division:

Hae-Young Ahn, Ph.D.	Team Leader, Biopharmaceutics
Ronald Kavanagh, Ph.D.	Biopharmaceutics
Xavier Ysern, Ph.D.	Chemist
Stephen Moore, Ph.D.	Chemistry Team Leader
Jena Weber	RHPM

BMS Attendees and titles:

Melody Brown	Director, CMC Regulatory Affairs
Andrew Dennis, Ph.D.	Manager, Pharmaceutical Science
Gill Cave	Pharmaceutical Scientist
Punit Marathe, Ph.D.	Sr. Research Investigator
Peter Timmins, Ph.D.	Director, Pharmaceutical Research Institute
Robert L. Simon	V.P., CMC, Worldwide Regulatory Affairs

Discussion Points: see attached brochure containing outline/discussion points

BMS will check SUPAC Guidance for future submission advice.

Efficacy parameters the drug itself is variable.

Review of pilot bioavailability studiesof pilot bioavailability studies

Objective: to assess PK and bioavailability of different formulations of metformin/glyburide combination tablets relative to coadministered Glucophage and Micronase; to assess impact of altering glyburide particle size distribution on bioavailability; to select one formulation for Phase III safety and efficacy studies.

Bioavailability studies were conducted on pre-clinical prototypes using 500 mg metformin and 2.5 mg glyburide (referred to as Combo 1,2,3 and 4). These combos differed in particle size distribution on glyburide. Combo 4 was considered most comparable to the individual components of metformin and glyburide. The Glyburide particle size distribution was related to the *in vivo* characteristics of the combination product. Food effect study will be done as proposed in 1996; effects show delay in Tmax, Cmax are not issues.

Randomized, open-label, crossover in healthy male and female subjects;

All test treatments utilized clinical formulations;

All treatments administered after an overnight fast with 240 mL of 20% glucose solution.

Subjects drank 60 mL of 20% glucose solution every 15 minutes for 4 hours post dose.

Serial plasma samples collected for analysis of metformin and glyburide.

Conclusions from pilot studiesfrom pilot studies

All combination tablets were bioequivalent to the reference treatment in the metformin component.

The sponsor claimed that combination tablet 4 had comparable bioavailability for glyburide relative to the reference treatment.

Combination tablet-4 was selected for further development.

Glyburide Particle Size analysis and rationale for Establishing a Particle Size Specification.

———————media gives true particle size.

Counts are the same between different facilities;
Container/closure systems are also the same;

RK particle size problematic— lots ——space is based on particle size; our concern is ability to maintain the particle size. The effect could be seen on bioavailability; they will come up w specs to meet our requirements. Size-range particle size will be met according to the vendor.

Target particle size of glyburide for use in a Phase III safety and efficacy clinical program was identified. The clinical formulation has been developed for 3 strengths of a combination product:
500mg/5mg; 500mg/2,5 mg; 250 mg/1.25mg. The clinical formation has a clear, non-functional film coat applied for aesthetic purposes.

Dissolution properties of glyburide are governed by its particle size; a poorly soluble but permeable drug substance (———————).

Control of gluburide drug substance particle size is therefore critical to the *in vivo* performance of the combination product.

Particle size measured by a ——————— method;

Glyburide drug substance is dispersed in a ——media;

Cumulative % undersize is recorded, i.e. % of material in a distribution below x microns.

Final particle size specification will be defined based on the glyburide lots used in pre-clinical formulations (————) prototypes; clinical studies; batches involved in long-term stability studies.

BMS stated that they would go back and examine the actual partical used in various studies and no only the nominal value. This was based on the variability mentioned above. Dr. Ahn suggested that bioequivalence data may be needed at particle size extremes.

The dissolution testing method currently used by the company for glyburide (ie USP apparatus) is
different than previously recommended by the FDA to the innovator (USP apparatus). BMS will investigate.

There are no concerns with the proposed use of the 500/5 and 500/2.5 mg combination tablets in comparative bioavailability study while using a dissolution test for the 250/1.25 tablet as it is a direct dose multiple.

Using dissolution studies to compare commercial formulations manufactured at the ——— and Humacao, PR facilities is acceptable.

Dissolution Methodologies Proposed for use as QC Release Test MethodsMethodologies Proposed for use as QC Release Test Methods

Current filed Glucophage method, BMS- NDA 20-357 using:

Apparatus	USP Apparatus 2 (paddles)
RPM	100
Medium	pH of 6.8 phosphate buffer
Volume	1000 mL

FDA noted that earlier method used basket not paddles; 100 rpm paddle method was never approved. BMS will verify this and get back with us.

Currently, there is no official monograph for the glyburide drug product.

During formulation prototype selection for *in vivo* assessment, glyburide release assessed based on a method proposed by Blume et al (1993).

Drug Development and Industrial Pharmacy, 19 (20), 2713-2741.

Apparatus	USP Apparatus 2 (paddle)
RPM	75
Medium	pH of 7.4 Phosphate buffer
Volume	900 mL

Not suitable as a QC method as sink conditions not satisfied for 500 mg/ 5 mg combination product; solubility < (3 times drug dose) and does not assure complete release.

BMS proposes to use draft FDA method for Micronase

FDA Guidance: Glyburide In vivo Bioequivalence and In vitro Dissolution Testing:

Apparatus	USP Apparatus 2 (paddle)
RPM	75 —
Medium	0.05M Borate buffer pH 9.5
Volume	500 mL

Plans for Pivotal Bioavailabity Study Plans for Pivotal Bioavailabity Study

Objective: To assess PK and bioavailabilty of commercial formulations of 500/2.5 and 500/5 combination strengths relative to coadministered Glucophage and Micronase.

Randomized, open-label, two-treatment crossover study in 2 groups.

Comparative Dissolution Testing ProposalsDissolution Testing Proposals

Three strength products (500 mg/5 mg, 500 mg/2.5 mg, 250 mg/1.25 mg);
Two from a common granulation (500 mg/2.5 mg and 250 mg/1.25 mg).

Three tablet presentations all having the same tablet core composition

Clinical formulation;
Commercial formulation with example ——— and no —— edge to tablet (for long-term stability studies);
Commercial formulation with final ———; also for long-term stability studies.

Dissolution equivalence for each active component to be demonstrated between clinical and commercial formulation two strengths of the same formulation (500 mg/ 2.5 mg and 250 mg/ 1.25 mg) commercial formulation manufactured at ——— and Humacao

Clinical vs. Commercial ——— Product)

Equivalence of dissolution profiles to be demonstrated between tablets of each potency using proposed QC release test dissolution media.

Biowaiver for lower strength tablet to support requestfor lower strength tablet to support request

Equivalence of dissolution profiles to be demonstrated between tablets of 500 mg/2.5 mg and 250/ 1.25 mg potency compressed from a common granulation using proposed QC release test media plus two additional media of different pH.

Proposed additional media for metformin component:

0.1M HCl
0.1M acetate buffer pH of 4.5
Proposed additional media for glyburide component:
High pH (range 6-9), with or without surfactant

Commercial (——) vs. Commercial (Humacao)

Equivalence of dissolution profiles to be demonstrated between tablets of each potency and using the proposed QC release test dissolution media.

Stability Programs in Operation Programs in Operation

Two stability studies ongoing co-ordinated by BMS involving product manufactured at—— site at ————

product manufactured at BMS site at Humacao, PR.

—— **Product StabilityProduct Stability**

Minimum ———— data at time of filing;
— batches of each strength manufactured at intended commercial scale
Packaged in 100, 500 and 5000 count —— bottles; ————
blister.

Humacao Product StudyProduct Study

Minimum ——— data at time of filing;
— batches of each strength manufactured at at least — intended commercial scale;
Packaged in 100, 500 and 5000 count ——bottles.

Storage conditions described in stability protocols for each product based on ICH guidelines:

Up to 6 months cumulative data under accelerated conditions at 40C/60%·RH;
light exposure;
All pack configurations on test.

All stability test conditions/timepoints (for each active ingredient) include assay, appearance, impurity/related substance analysis, and dissolution.

Additional testing at selected conditions/timepoints to include: tablet hardness, friability, gauge and disintegration.

Developed commercial formulation from clinical formulation by substituting the clear coat with a pigmented film coat to aid product strength differentiation (used in long-term stability studies). The formulations used in clinical studies and stability studies have identical tablet core compositions.

Diabeta7 and Glynase7 are other available glyburide formulations that are not bioequivalent to Micronase7 and have not been evaluated. Switchability with these products also needs to be considered.]

Bioavailability correlated with particle size, with increased glyburide bioavailability with decreasing glyburide particle size. (Table II)

Table II. Particle Size and In Vivo Data

Formulation	Glyburide Particle Size[A]		In Vivo Data	
	50% undersize (microns)	90% undersize (microns)	Cmax (ng/ml)	AUC (0-T) (ng/ml ! hr^{-1})
Combo 2	[redacted]		54	353[B]
Combo 1			76	507[B]
Combo 3			67	531[C]
Combo 4			93	716[C]

A Provisional Method B AUC 0-24 C AUC 0-48

Particle size distribution data from different lots used in the clinical trial material (Table III), show that in at least one case (i.e. lot 1) the particle size is closer to the particle size in combo tablet 3 —— vs. —— difference 4/14) than to combo tablet 4 (—— vs. —— difference 8/16).

Table III. Glyburide Particle Size Data

Glyburide Lot	Glyburide Particle Size[A]	
	50% undersize (microns)	90% undersize (microns)
Combo 4		
1		
2		
3		
4		
5		
6		

A Provisional Method

In a post meeting discussion with Dr. Misbin (medical officer) the lack of bioequivalence was clearly of concern. Glyburide must be considered a narrow therapeutic range compound. Due to the variability in each patient's disease state, population pharmacokinetic pharmacodynamic relationships are difficult to find. However individual PK/PD relationships may be easier to examine.

The clinical study report was examined several days post-meeting. The absorption profile for all combination tablets show a double peak, whereas the glyburide (Micronase®) tablets show a single peak with a lag phase. Rate of absorption cannot be considered comparable. There was also a difference in peak concentration related side effects in at least one subject due to higher peak concentrations achieved with Micronase®.

The clinical trials will need to be closely evaluated for lack of switchability; paying particular attention to drop-outs and the reason for drop-out, and for loss of efficacy in patients already poorly controlled at each dose level of glyburide.

Conclusions:

NDA targeted for submission in September 1999.

Minutes Preparer [/S/] 3/16/99

Chair Concurrence: [/S/] 3/16/99

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MEMORANDUM OF TELEPHONE CONVERSATION

N 216 RO, GC 9.2.99 - 9.16.99

Date: OCT 2 5 1999

Between: Amy Grant, Bristol-Myers Squibb

And: Lee-Ping Pian, Ph.D. (HFD-715)

Subject:	IND —— Electronic Submission Proposal Dated September 9, 1999

This telephone conversation is to address the sponsor's efficacy data for NDA 21-178 in the Electronic Document Room. In addition, the sponsor requested input for the electronic submission for an upcoming NDA for modified release dosage form of metformin HCl. Since the two data format are similar, the request applies to both NDA 21-178 and the incoming NDA (IND ——).

1. The efficacy dataset only contains data from the last time point. This reviewer requests the efficacy data to include data from all protocol specified visits.
2. To request unique patient number for all the dataset. The sponsor's data started patient number from 1 under each investigational site.
3. To include treatment group for patients in the disposition dataset.

[/S/]

Lee-Ping Pian, Ph.D.
Mathematical Statistician

cc:
Archival IND ——
HFD-510
HFD-510/SSobel/ SMalozowski/RMisbin/JWeber
HFD-715/JChoudhury/TSahroot/division file/LPian/Chron

APPEARS THIS WAY
ON ORIGINAL

310/Wilson

NDA 21-178

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

Dear Mr. Randolph:

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

Name of Drug Product:	Metformin Hydrochloride/Glyburide 500mg/5mg, 500mg/2.5mg, 250mg/1.25mg Tablets
Therapeutic Classification:	To be determined at filing meeting
Date of Application:	September 30, 1999
Date of Receipt:	September 30, 1999
Our Reference Number:	NDA 21-178

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 November 29, 1999, in accordance with 21 CFR 314.101(a).

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. 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. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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, contact Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

[/S/] 10.01.99

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