RESPONSE TO FDA REQUEST FOR INFORMATION

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

APPEARS THIS WAY
ON ORIGINAL

July 28, 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. Additional reference is made to my July 24, 2000 telephone conversation with Ms. Enid Galliers and Mr. William Koch, in which patent certification pertaining to the glyburide component of Glucovance was requested. We are now providing the requested patent certification.

Please contact me at (609) 252-5228 if you have any questions concerning this submission.

Sincerely,

Warren C. Randolph

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

BEST POSSIBLE COPY

Desk Copies: Mr. William Koch

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

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

NDA AMENDMENT - RESPONSE TO FDA QUESTION

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

July 28, 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:

Please refer to our pending New Drug Application for Glucovance™ (glyburide and metformin HCl tablets), NDA 21-178 filed September 30, 1999. Reference is also made to two telephone communications on July 27, 2000; the first between Dr. S. Johnson (FDA) and myself (Bristol-Myers Squibb) concerning tightening the tablet dissolution specifications for metformin and glyburide and the second between Dr. X. Ysern (FDA) and myself (Bristol-Myers Squibb) concerning tightening the tablet specification for

The following information is being officially submitted to the NDA in this amendment; a paraphrased version of the question and the response is provided.

Comment 1:

Dissolution Specification for Metformin and Glyburide
The proposed dissolution specification for the metformin component is "Minimum —— (Q) in 30 minutes" and for the glyburide component is "Minimum ——(Q) in 30 minutes"; based on the data presented in the NDA, both of these specifications should be tightened to "Minimum —— (Q) in 30 minutes".

Comment 2:

[redacted] Specification

The tablet specification for related substances - glyburide should be tightened to "Maximum [redacted]" from the proposed specification of "Maximum [redacted]".

Response:

We accept the Agency's comments to change the tablet dissolution specifications to "Minimum [redacted] (Q) in 30 minutes" for both the metformin and glyburide components and to change the related substances - glyburide specification to "Maximum [redacted]". Consequently, the specifications for Glucovance™ 1.25 mg/250 mg, 2.5 mg/500 mg and 5 mg/500mg tablets have been updated and are provided in Attachment I.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the glyburide and metformin HCl drug substance and product sections which have been implemented since the September 30, 1999 filing of the NDA.

Bristol-Myers Squibb Company certifies that a field copy of this amendment will be provided to the North Brunswick office (120 N. Center Drive, North Brunswick, NJ 09802) of the Food and Drug Administration. We further certify that the field copy is a true copy of this amendment.

Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science
Phone: 609-818-5221
Fax: 609-818-5831

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Mr. W. Koch (HFD-510, Room 14B04)
Dr. S. Johnson (HFD-870, Room 14 B18)

Attachment I

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

NDA AMENDMENT

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

July 26, 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:

Please refer to our pending New Drug Application for Glucovance™ (glyburide and metformin HCl tablets) NDA 21-178 filed September 30, 1999. Reference is also made to two communications from the FDA dated, March 14 and 16, 2000 concerning recommendations for the tradename, Glucovance as proposed by the Office of Post-Marketing Drug Risk Assessment (OPDRA).

This submission provides a copy of the correspondence received from the Agency on March 14 and 16, 2000 in Attachment I.

The following information is being officially submitted to the NDA in this amendment.

The 100 and 500-count container labels for all three strengths have been revised to reflect the recommendations from OPDRA and are provided in Attachment II. The 5000-count package configuration will not be launched at this time and therefore the respective container labels are not being provided.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the Glucovance™ (glyburide and metformin HCl tablets) draft bottle labels that have been implemented since the September 30, 1999 filing of the NDA.

Bristol-Myers Squibb Company certifies that a field copy of this amendment will be provided to the North Brunswick office (120 N. Center Drive, North Brunswick, NJ 09802) of the Food and Drug Administration. We further certify that the field copy is a true copy of this amendment.

Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Mr. W. Koch (HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

RESPONSE TO FDA QUESTION

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

July 26, 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:

Please refer to our pending New Drug Application for glyburide and metformin HCl tablets, NDA 21-178 filed September 30, 1999. Reference is also made to a telephone communication on July 24, 2000 between Mr. W. Koch and Ms. Enid Galliers (FDA) and Mr. W. Randolph (Bristol-Myers Squibb) concerning whether there are differences between the clinical and commercial formulations.

This submission provides a paraphrased version of the question and the response.

Question:

Was the formulation used in clinical trials the same as that to be marketed; if the clinical trial formulation was not the same, identify the bridging studies.

Response:

As discussed in Section 4, Part II.F.7, "Dissolution Comparison", of the original NDA (Volume 1.9, pages 152 to 182), the clinical and commercial formulations are essentially the same. The tablet core composition is identical. The only difference between the clinical and commercial formulation is

the non-functional coating system which is applied for appearance and identification purposes. The clear, non-functional, hydroxypropyl methylcellulose film-coat of the clinical product was substituted with a similar, non-functional, colored film-coat for the commercial formulation to aid product strength differentiation. The clinical and commercial formulations of metformin hydrochloride-glyburide tablets, 500 mg/2.5 mg and 500 mg/5 mg are the same size and shape (biconvex capsule). The 250 mg/1.25 mg strength, clinical tablet is round, whereas the equivalent commercial tablet is a biconvex capsule shape. These changes are considered unlikely to have any detectable impact on formulation quality and performance. Under SUPAC-IR, these changes would be considered Level 1 changes. *In vitro* dissolution testing for each active ingredient (metformin hydrochloride and glyburide), according to the proposed QC dissolution test method has been performed to demonstrate equivalence between the clinical and commercial formulations. Although not post-approval changes, the approach to testing performed was based on the "Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-up and Post-approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation" and the "Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms". This approach was presented at the metformin hydrochloride-glyburide combination tablet pre-NDA meeting on December 4, 1998 and subsequently submitted to the metformin/glyburide IND; ——— in submission No.30, and was considered acceptable by FDA.

As outlined in the NDA, *in vitro* drug release comparisons have been conducted to show equivalence between similar metformin hydrochloride-glyburide tablet products. The specific studies that have been conducted to address FDA's question are as follows.

- *In vitro* dissolution tests and profile comparisons to assure equivalence between the commercial formulation and the clinical formulation (both manufactured by the same process at the same manufacturing site in ———.

The dissolution profiles of the appropriate products have been compared by calculating a difference (f1) and a similarity (f2) factor, as detailed in the Guidance documents referenced above.

All the data associated with the dissolution comparison between the clinical and commercial formulations is provided in Section 4, Part II.F.7, "Dissolution Comparison", of the original NDA (Volume 1.9, pages 152 to 182).

APPEARS THIS WAY
ON ORIGINAL

Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science
Phone: 609-818-5221
Fax: 609-818-5831

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Mr. W. Koch (HFD-510, Room 14B04)
Ms. Enid Galliers (HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

RESPONSE TO FDA QUESTION

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

July 24, 2000

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

Dear Dr. Jenkins:

Please refer to our pending New Drug Application for glyburide and metformin HCl tablets, NDA 21-178 filed September 30, 1999. Reference is also made to a telephone communication on July 24, 2000 between Mr. W. Koch and Ms. Enid Galliers (FDA) and Mr. W. Randolph (Bristol-Myers Squibb) concerning whether there are differences between the clinical and commercial formulations.

This submission provides a paraphrased version of the question and the response.

Question:

Was the formulation used in clinical trials the same as that to be marketed; if the clinical trial formulation was not the same, identify the bridging studies.

Response:

As discussed in Section 4, Part II.F.7, "Dissolution Comparison", of the original NDA (Volume 1.9, pages 152 to 182), the clinical and commercial formulations are essentially the same. The tablet core composition is identical. The only difference between the clinical and commercial formulation is

the non-functional coating system which is applied for appearance and identification purposes. The clear, non-functional, hydroxypropyl methylcellulose film-coat of the clinical product was substituted with a similar, non-functional, colored film-coat for the commercial formulation to aid product strength differentiation. The clinical and commercial formulations of metformin hydrochloride-glyburide tablets, 500 mg/2.5 mg and 500 mg/5 mg are the same size and shape (biconvex capsule). The 250 mg/1.25 mg strength, clinical tablet is round, whereas the equivalent commercial tablet is a biconvex capsule shape. These changes are considered unlikely to have any detectable impact on formulation quality and performance. Under SUPAC-IR, these changes would be considered Level 1 changes. *In vitro* dissolution testing for each active ingredient (metformin hydrochloride and glyburide), according to the proposed QC dissolution test method has been performed to demonstrate equivalence between the clinical and commercial formulations. Although not post-approval changes, the approach to testing performed was based on the "Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-up and Post-approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation" and the "Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms". This approach was presented at the metformin hydrochloride-glyburide combination tablet pre-NDA meeting on December 4, 1998 and subsequently submitted to the metformin/glyburide IND [redacted] in submission No.30, and was considered acceptable by FDA.

As outlined in the NDA, *in vitro* drug release comparisons have been conducted to show equivalence between similar metformin hydrochloride-glyburide tablet products. The specific studies that have been conducted to address FDA's question are as follows.

- *In vitro* dissolution tests and profile comparisons to assure equivalence between the commercial formulation and the clinical formulation (both manufactured by the same process at the same manufacturing site in [redacted].

The dissolution profiles of the appropriate products have been compared by calculating a difference (f1) and a similarity (f2) factor, as detailed in the Guidance documents referenced above.

All the data associated with the dissolution comparison between the clinical and commercial formulations is provided in Section 4, Part II.F.7, "Dissolution Comparison", of the original NDA (Volume 1.9, pages 152 to 182).

APPEARS THIS WAY
ON ORIGINAL

Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science
Phone: 609-818-5221
Fax: 609-818-5831

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Mr. W. Koch (HFD-510, Room 14B04)
Ms. Enid Galliers (HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

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 our July 5, 2000 submission of revised draft labeling for Glucovance and to the July 11, 2000 facsimile transmission from FDA to Bristol-Myers Squibb (BMS), which provided the Agency's proposed changes to our draft.

FDA's changes to the draft labeling included deletion of the 5mg/500mg tablet. We continue to believe that the 5mg/500mg Glucovance tablet is both useful and necessary, to provide the same dosing flexibility with a single tablet that is currently available to prescribers with the two separate agents. Without the availability of the 5mg/500mg tablet, the significant number of patients currently titrated on multiples of the doses in this tablet, e.g. 10mg/1000mg, 15mg/1500mg, etc., will not be able to substitute Glucovance for its titrated components per the instructions in DOSAGE AND ADMINISTRATION.

Instructions are provided in the Glucovance labeling for physicians who choose to use Glucovance in subjects who have already been titrated with metformin plus glyburide. In such instances, the doses of metformin and glyburide in the initial Glucovance dose should not exceed the doses of metformin and glyburide that the patient has been receiving. If the 5mg/500 mg tablet is not available and only the 2.5 mg/500 mg is available for second line therapy, any subject receiving half-maximal

glyburide (10mg daily) plus metformin will be forced to a dose of 2000mg metformin daily to get the 10mg glyburide dose and this will in many cases be more than the current metformin dose. The 5mg/500mg tablet is needed to provide dosing flexibility such that efficacious doses of glyburide can be given without having to give a maximal dose of metformin unless required for control.

Also, the flexibility provided by the 5mg/500mg tablet would accommodate optimization of glycemic control in patients who have gastrointestinal intolerance to higher doses of metformin.

To facilitate discussion of the labeling at our July 17 teleconference with the Agency, the proposed draft labeling provided herein is based upon the marked-up version which FDA provided via fax on July 11 and has been modified to indicate: 1) incorporation of the FDA-proposed modifications that BMS has accepted; 2) those FDA-proposed modifications for which BMS requests discussion at the July 17 teleconference; and 3) changes to the label that are proposed as alternatives to FDA-proposed modifications. The labeling is annotated, to correspond to a listing of applicable comments.

In order to differentiate the changes in the attached draft labeling, FDA-deleted text is shown in strikethrough font and FDA-added text is underlined. Further additions/deletions proposed by BMS are shown in alternate font.

The revised draft labeling is provided in hard copy as well as an electronic version in Microsoft Word format. The electronic portion of the submission consists of one Microsoft Word file on one 3.5 inch diskette which is enclosed in the Archival copy. The total size of the electronic submission is approximately 198 KB. The file was screened for known viruses on July 13, 2000, with [redacted] for Windows NT 4.0 [redacted] and no viruses were detected. An additional copy of the diskette is provided to Mr. William Koch as a desk copy.

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

Sincerely,

Warren C. Randolph

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

Desk Copies: Dr. Robert Misbin (HFD-510, Rm. 14B04)
Mr. William Koch (diskette included) (HFD-510, Rm. 14B04)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

ORIGINAL

NDA AMENDMENT - RESPONSE TO FDA QUESTION

NDA 21-178 ORIG AMENDMENT
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:

Please refer to our pending New Drug Application for glyburide and metformin HCl tablets, NDA 21-178 filed September 30, 1999. Reference is also made to a communication from the FDA dated July 11, 2000 concerning the Biopharmaceutic Team's comments to NDA 21-178; specifically, the comment submitted by Dr. S. Johnson regarding the particle size specification for glyburide drug substance.

This submission provides a copy of the correspondence received from the Agency on July 11, 2000 in Attachment I.

The following information is being officially submitted to the NDA in this amendment.

Comment:

Particle Size
The three tiered particle size distribution specifications is generally sound. However, the particle size distribution of NMT ——is not acceptable. The value should be designated a value which is supported by the PK data presented in this application.

Response:

Although we believe our original specification is reasonable and would ensure suitable batch to batch reproducibility, we accept your comment to change the
Consequently, the specifications for glyburide drug substance have been updated and are provided in Attachment II.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the glyburide and metformin HCl drug substance and product sections which have been implemented since the September 30, 1999 filing of the NDA.

Bristol-Myers Squibb Company certifies that a field copy of this amendment will be provided to the North Brunswick office (120 N. Center Drive, North Brunswick, NJ 09802) of the Food and Drug Administration. We further certify that the field copy is a true copy of this amendment.

Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science
Phone: 609-818-5221
Fax: 609-818-5831

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Mr. W. Koch (HFD-510, Room 14B04)
Dr. S. Johnson (HFD-870, Room 14 B18)

APPEARS THIS WAY
ON ORIGINAL

NC

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

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

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

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

July 5, 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 the following:

- Draft labeling provided in the September 30, 1999 submission of NDA 21-178;

- Revised draft labeling submitted to NDA 21-178 on June 12, 2000. The revisions included use of both the tradename and established name as recommended by FDA and also removed references to replacement therapy for subjects already receiving metformin and glyburide, since neither clinical nor bioequivalence data exist to support replacement therapy.

- June 13, 2000 telephone conversation between Dr. Robert Misbin and myself, in which Dr. Misbin indicated that the Glucovance labeling should provide some guidance for its use in those instances where physicians make a decision to use Glucovance to replace current treatment with the individual components.

We are now providing revised draft labeling which incorporates the changes submitted June 12, 2000 and also addresses the guidance for physicians who decide to use Glucovance to replace individually titrated components in some patients. This guidance is addressed in a second paragraph which has been added under the "GLUCOVANCE As Second Line Therapy" subsection in DOSAGE AND ADMINISTRATION.

The revised draft labeling is provided in hard copy as well as an electronic version in Microsoft Word format. The electronic portion of the submission consists of one Microsoft Word file on one 3.5 inch diskette which is enclosed in the Archival copy. The total size of the electronic submission is approximately 149 KB. The file was screened for known viruses on July 5, 2000, with ——— for Windows NT 4.0 ——— and no viruses were detected. An additional copy of the diskette is provided to Mr. Bill Koch as a desk copy.

Please contact me at (609) 252-5228 if there are any questions concerning this submission.

Sincerely,

Warren C. Randolph

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

WCR/JBS/ls/kb
Desk Copies: Dr. Robert Misbin (hard copy) (HFD-510, Rm. 14B04)
Mr. William Koch (diskette included) (HFD-510, Rm. 14B04)

APPEARS THIS WAY
ON ORIGINAL

N/A BL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

DUPLICATE

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

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

June 23, 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 our June 12, 2000 submission of changes to the draft labeling contained in the original NDA submission and my telephone conversation with Mr. William Koch on June 22, 2000. Mr. Koch requested that Bristol-Myers Squibb provide electronic copies of the labeling submitted on June 12.

Per Mr. Koch's request, we are providing two disks with the draft labeling as submitted on June 12; one disk is for archival purposes and the other is provided with Mr. Koch's desk copy. Hard copy of this labeling text is also enclosed.

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

Sincerely,

Warren C. Randolph

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

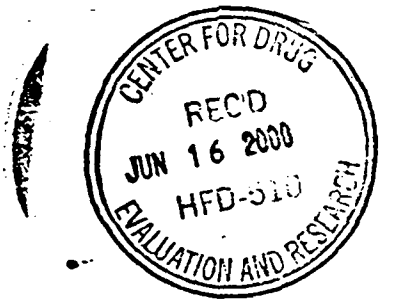
BEST POSSIBLE COPY

WCR/dk
Attachments

Desk Copy: Mr. William Koch (with disk) (HFD-510, Room 14B04)

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000



NDA AMENDMENT

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

June 16, 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:

Please refer to our pending New Drug Application for glyburide and metformin HCl tablets, NDA 21-178 filed September 30, 1999. Reference is also made to a telephone conversation on June 8, 2000 between Dr. X. Ysern and myself (Bristol-Myers Squibb) concerning the drug product stability data presented in the original NDA and the proposed ——— expiry period. As a result of the phone conversation, in support of a ——— expiry period for the tablets, additional stability data are being provided at this time. In addition, the "Packaging and Labeling Procedures" used by Bristol-Myers Squibb's facility in Evansville, Indiana are being updated as well.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the glyburide and metformin HCl drug product sections which have been implemented since the September 30, 1999 filing of the NDA.

Bristol-Myers Squibb Company certifies that a field copy of this amendment will be provided to the North Brunswick office (120 N. Center Drive, North Brunswick, NJ 09802) of the Food and Drug Administration. We further certify that the field copy is a true copy of this amendment.

The contents of this submission are described in the Table of Contents. Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Ms. J. Weber (HFD-510, Room 14B04)

REVIEWS COMPLETED

ACTION:
LETTER N.A.I. MEMO

CSO INITIALS DATE

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

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

June 12, 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, and specifically to the draft labeling provided in that submission. At this time we are providing revised draft labeling for Glucovance. Changes from the draft labeling provided in the September 30, 1999 submission are as follow:

- The tradename (Glucovance), established name (Glyburide and Metformin HCl Tablets) and the order of presentation of the potencies of tablet contents (glyburide/metformin) as recommended in the FDA facsimile transmissions of March 14 and 16, 2000 (copies attached) have been incorporated into the labeling.

- In the INDICATIONS AND USAGE section (page 9) the statement "———————— ———————— "has been removed.

- The following changes have been made in DOSAGE AND ADMINISTRATION (page 19):

  - The subsection "———————————————' has been removed.

- The subsection "Glucovance as Second Line Therapy" has been modified to add the 5mg/500mg potency to indicate that the initial dose is 2.5mg/500mg or 5mg/500mg and that dose increments every two weeks should be in increments of 2.5mg/500mg or 5mg/500mg.

We are removing labeling text that described Glucovance as [redacted] for two reasons: (1) we did not perform clinical trials to evaluate the effects of [redacted] and (2) the glyburide component of Glucovance has not been shown to be bioequivalent to any marketed version of glyburide. The addition of the 5mg/500mg Glucovance tablet to the "Glucovance as Second Line Therapy" subsection is consistent with the use of this strength in the CV138-011 trial and provides dosing instructions to accompany the statement "... there was no experience with doses above 20mg/2000mg per day."

The new draft is based upon that previously submitted, with additions underlined and deletions shown with strikeout.

Please contact me at (609) 252-5228 with any questions or if additional information is required.

Sincerely,

Warren C. Randolph

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

WCR/ls/dk
Attachments

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

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-178
Metformin Hydrochloride/Glyburide Fixed Combination Tablets

May 18, 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 fixed combination metformin/glyburide tablets, NDA 21-178. Additional reference is made to my telephone conversation of May 10, 2000 with Dr. Robert Misbin, in which he requested that BMS respond to questions pertaining to this NDA. The following presents Dr. Misbin's questions and our responses:

- Tables 10.1.1D and 10.2.1D in Volume 38 (report on long-term, open-label extension of first line study CV138-019) both present means and mean changes over time, with the former providing data for HbA1c and the latter having FPG data. However, the tables have different numbers of subjects (n=104 in Table 10.1.1D and n=291 in Table 10.2.1D). Why are the numbers for all subjects different in these tables?

  Response: Tables 10.1.1D and 10.2.1D include data from subjects who had at least one post-baseline measurement. This is stated in the referenced Supplemental Tables, but is not clearly expressed in the text tables. The first post-baseline measurement for FPG was at two weeks, while that for HbA1c was not until 13 weeks. At the time of datalock for the interim report on the open-label extension, more subjects therefore qualified for inclusion in the table of FPG data (10.2.1D).

- In Table 12.5.4 of Volume 33 (report on first line study CV138-019), mean lactate levels in the placebo group decreased, while the mean change from baseline is positive. Is this the result of dropouts?

  Response: The effect is primarily due to dropouts, i.e. those subjects for whom data were available at baseline, but not at week 32. Additionally, there were a few subjects for whom data were available at week 32, but who did not have baseline measurements. These were included for the means, but not for mean changes.

Please contact me at (609) 252-5228 if you have any questions concerning this submission.

Sincerely,

Warren C. Randolph

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

WCR/ls/dk

Desk Copy: Dr. Robert Misbin (HFD-510, Room 14B04)
Mr. William Koch (HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 5400 Princeton, NJ 08543-5400 609 818 5000

NDA AMENDMENT

NDA 21-178
Metformin Hydrochloride - Glyburide Tablets

April 28, 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:

Please refer to our pending New Drug Application for metformin hydrochloride - glyburide tablets, NDA 21-278. Reference is also made to a telephone conversation on March 16, 2000 between Dr. X. Ysem and myself (Bristol-Myers Squibb) discussing the changes to the Chemistry, Manufacturing and Controls (CMC) section of the NDA that Bristol-Myers Squibb would like to submit. These changes involve the addition of a drug product packaging site, a 30-count bottle presentation (sample packs only) and modification of the process for all three strength tablets at the manufacturing facility in Humacao, Puerto Rico. Since that phone conversation, other minor changes have been made that Bristol-Myers Squibb would like to submit as well. These changes involve the addition of a new closure and bottle and DMF page references for all the packaging components.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the metformin hydrochloride - glyburide drug product sections which have been implemented since the September 30, 1999 filing of the NDA.

Bristol-Myers Squibb Company certifies that a field copy of this amendment will be provided to the North Brunswick office (120 N. Center Drive, North Brunswick, NJ 09802) of the Food and Drug Administration. We further certify that the field copy is a true copy of this amendment.

The contents of this submission are described in the Table of Contents. Please contact me at (609) 818-5221 with any questions.

Sincerely,

Mary T. Peters

Mary T. Peters
Manager, Regulatory Science

Desk Copy: Dr. X. Ysern (HFD-510, Room 14B04)
Ms. J. Weber (HFD-510, Room 14B04)

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

NDA 21-178
Metformin Hydrochloride/Glyburide Tablets

February 14, 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
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our pending New Drug Application for metformin hydrochloride/glyburide tablets, NDA 21-178. Additional reference is made to the following:

- January 28, 2000 telephone discussion between Dr. Robert Misbin and myself, in which he requested baseline data for specified subjects in the CV138-019 clinical trial;
- Dr. Misbin's fax of the data request (copy attached); and
- Follow-up discussion between Dr. Misbin and myself (February 2, 2000) in which the request was changed to specify subject 102/19 instead of subject 109/19.

At this time we are submitting the requested data in tabular form. If there are any questions concerning this submission, please contact me at (609) 252-5228.

Sincerely,

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

Desk Copy: Robert Misbin, M.D. (HFD-510, Room14B04)

To: Warren Randolph

BMS Fax (609) 21-2-6000

re: NDA 21-178

protocol CV 138-019

please provide baseline data (Age, sex, BMI, insulin, C peptide, glucose)

on 43/6	20/12
86/17	25/11
86/41	20/5
87/10	86/21
109/19	86/42
144/5	92/5
	101/8
	102/10

From Mishin MD - FDA

HFD 510

/S/

1/28/00

Listing of Baseline Characteristics
FDA-requested Subjects

Site/ Subject	Age (yrs)	Sex	BMI (kg/m2)	FPG (mg/dL)	2-hr. PPG (mg/dL)	Fasting Insulin (uiu/mL)	Postprandial Insulin (uiu/mL)	C-peptide (ng/mL)
Treatment: Glyburide								
43/ 6	63	Male	29.0	252	299	14	45	5.8
86/17	58	Female	30.9	243	341	17	67	9.1
86/41	54	Male	26.1	318	427	8	13	2.6
87/10	40	Male	24.7	308	406	ə	8	1.7
102/19	38	Female	31.0	166	235	16	61	8.2
144/ 5	44	Male	24.8	230	314	ə	17	3.2
Treatment: Metformin								
20/12	52	Female	32.2	187	253	27	54	6.0
25/11	44	Female	37.7	200	244	36	74	7.5
28/ 5	50	Male	26.9	218	314	8	12	3.6
86/21	25	Female	35.7	289	381	8	21	4.9
86/42	39	Female	32.5	292	387	14	18	3.3
98/ 5	50	Male	30.0	266	293	ə	ə	ə
101/ 8	60	Male	27.8	224	266	11	30	4.4
102/18	29	Male	35.0	224	362	17	36	6.1

ə No baseline measurement available

DUPLICATE

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-178
(metformin hydrochloride/glyburide) Tablets

January 28, 2000

Roy Blay, Ph.D.
Good Clinical Practices, Branch 1
Division of Scientific Investigations
Office of Medical Policy, Room 107
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20835

Dear Dr. Blay:

Reference is made to our pending New Drug Application for metformin hydrochloride/glyburide tablets, NDA 21-178. Additional reference is made to your facsimile transmission on January 11, 2000 (copy is enclosed following this letter) in which you requested information pertaining to 3 investigators (listed below) that participated in the Phase III double-blind trials included in NDA 21-178:

- [redacted] (participated in studies CV138-011 and CV138-019);
- [redacted] (participated in studies CV138-011 and CV138-019); and
- [redacted] participated in study CV138-019).

Lastly, reference is made to our telephone conversations of January 12-14, 2000 in which the following clarifications were made to this request:

- For those sites that conducted both protocols CV138-011 and CV138-019, the request applies to both studies, but should be limited to the double-blind portions of the studies.

- Criteria used for identification of the significant violations are to be provided, together with a list of the individual violators and the violation(s) for each.

- Listings are to include, in addition to those specified in the request, efficacy data and any other information considered pertinent.

At this time we are submitting the requested information. Please refer to the first volume for each investigator, which contains a Table of Contents documenting all of the information supplied.

Two copies of the cover letter for this submission are being provided (as desk copies to Ms. Weber) for NDA 21-178. If you have any questions regarding this submission, I can be reached at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
U.S. Regulatory Liaison

WCR/JBS/dk
Attachments
Desk Copy: Ms. Jena Weber (2 copies - letter only) for NDA 21-178
(HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

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

SV

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

FOUR MONTH SAFETY UPDATE

NDA 21-178
Metformin hydrochloride/Glyburide Tablets

January 27, 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 metformin hydrochloride/glyburide tablets, NDA 21-278. In accordance with 21 CFR 314.50 (d) (5) (vi) (b) (1) we are submitting an update of the safety information which is required four months after the initial submission of the NDA. The data and analyses contained in this update confirm and support the safety conclusions in the original application. Please refer to the Table of Contents and the Reviewer's Guide for additional details regarding this submission.

This submission has both paper and electronic portions. With respect to the electronic submission the media has been prepared as follows:

The total size of the electronic submission is approximately 543 MB. There are approximately 180 files and 59 folders.

The files have been checked for viruses on January 27, 2000 with ———— Software (———— for Windows NT 4.0) and no viruses were detected.

The electronic submission has been provided on 1 CD-ROM disk to the Central Document Room.

If there are any questions, please call me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
U.S. Regulatory Liaison
Regulatory Science

WCR/HMK/dk

Desk Copy: Dr. R. Misbin (HFD-510, Room 14B04) (Vol. 1 only)
Ms. J. Weber (HFD-510, Room 14B04) (Vol. 1 only)

Faxed
/S/
2/9/00

Noted
/S/
3/29/00

REVIEWS COMPLETED
/S/ 06/06/00
CSO INITIALS DATE

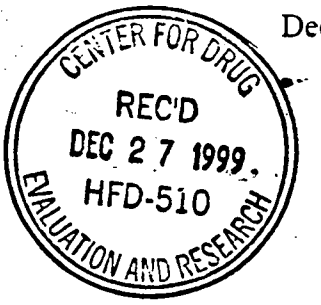
CD rom sent to Conrad Dr Rom
Sent, Project manager
2-08-00

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

John F. Bedard
Vice President
Worldwide Regulatory Affairs

December 24, 1999



John Jenkins. M.D.
Director, Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-570)
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 21-178; Metformin Hydrochloride/Glyburide Fixed Combination Tablet

Dear Dr. Jenkins:

This is in regard to the subject application and our on-going discussions of the review classification assigned to the application. In follow-up to our December 21, 1999 teleconference that Dr. Smaldone and I had with you, we are providing the additional information that we discussed.

Briefly, our request for Priority (P) classification is based upon the unmet medial needs of patients with type 2 diabetes and the therapeutic advance that will be provided by a low dose combination of metformin/Glyburide as initial therapy for type 2 diabetes. As we have presented previously, the claim for a therapeutic advance is supported by; 1) superior efficacy, 2) improved safety and tolerability, and 3) the absence of dosage forms and prescribing information to duplicate the low dose combination which demonstrated these advantages in Study CV138-019, the first line therapy protocol. As requested, we are providing additional information from the safety database as an attachment.

We would like to call your attention to the section "Incidence of Hypoglycemia and Related Events" in the attachment. The tabled incidence of hypoglycemia and hypoglycemic events in the low dose (250/1.25mg) combination arm was about one-half of that in the glyburide monotherapy arm, while in the higher dose (500/2.5mg) combination arm the incidence was almost twice that of glyburide monotherapy. It must be noted that doses were titrated in all treatment arms and that the first titration step was from one (active) tablet in the morning to one in the morning and one in the evening. Sixty percent of subjects in the low dose combination arm achieved glycemic control with two tablets daily, but though the total doses of metformin and glyburide were the same as the starting dose for the 500/2.5 product, the advantage of the split

dose is apparent in the reduced incidence of hypoglycemia and hypoglycemic symptoms in this treatment arm.

Until Study –019 was conducted, doses less than 500mg were considered subtherapeutic and therefore. the smallest currently available initial dose of metformin is 500 mg, as an unscored tablet. Forty percent of naïve patients reached glycemic control with a single 250/1.25 mg tablet in Protocol CV 138-019; this dose cannot be achieved with currently available products. An additional 20% of patients in the low dose arm were controlled with two 250/1.25mg tablets. Though the total daily dose of 500/2.5 mg can be matched with available component drug products. the incidence of hypoglycemia from CV138-019 in patients receiving 500mg metformin with 2.5mg glyburide in a single dose shows that this regimen puts patients at significantly increased risk the for this event. Only with the low dose combination product can patients have the advantage of improved glycemic control, compared to monotherapies, without increasing the risk for hypoglycemia.

In closing. we continue to believe the data with the low dose combination meet the criteria for Priority classification. After you have had an opportunity to review this correspondence, we would like an opportunity to speak with you. We will try to arrange a teleconference during the week of December 27, 1999.

Thank you for your consideration of this request.

Sincerely,

John F. Bedard
Vice President
Regulatory Science

Copies to:

Dr. S. Sobel
Dr. S. Malozowski
Dr. R. Misbin
Ms. J. Weber
NDA 21-178; Metformin Hydrochloride/Glyburide

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

BM

NDA 21-178
Metformin Hydrochloride/Glyburide Fixed Combination Tablets

December 16, 1999

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

Dear Dr. Sobel:

Please refer to our pending New Drug Application for fixed combination metformin/glyburide tablets, NDA 21-178. Additional reference is made to the following:

- Facsimile transmission from Dr. Robert Misbin, dated November 26, 1999, in which he requested that BMS provide "individual glucose and HbA1c data for the patients on glyburide monotherapy and metformin monotherapy who were rolled over because of lack of glycemic control into the open label study of the metformin/glyburide combo."

- My December 1, 1999 telephone conversation with Dr. Misbin, in which he indicated that we were only to provide the requested data for the trial in first line use of the combination (Protocol CV138-019) and that all levels for each patient, from randomization through open label treatment, were to be provided.

At this time we are providing a tabular listing of the requested information, organized by double-blind monotherapy assignment. Patients are included in the listing if they discontinued a monotherapy arm of Protocol CV138-019 due to lack of glycemic control and were entered into the open label study with the combination. Values for HbA1c and FPG in the attached tables are those from the central laboratory. Some patients whose central laboratory values did not meet the protocol criteria for discontinuation were, however, discontinued from double-blind therapy and put into the

open label study based on other criteria for lack of glycemic control, e.g. office fingersticks. These patients are included herein.

Three subjects are included in the listing who were subsequently found not to have met the criteria of Dr. Misbin's request:

- Site number/subject number (033/007) was confirmed by the site to have discontinued from the double-blind treatment phase due to symptoms of hypoglycemia.
- Site number/subject number (123/017) was confirmed by the site to have completed the double-blind treatment phase.
- Site number/subject number (147/001) was confirmed by the site to have completed the double-blind treatment phase.

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

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Science

Desk Copies: Dr. Robert Misbin (HFD-510, Room 14B04)

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-178
(metformin hydrochloride/glyburide) Tablets

December 07, 1999

Roy Blay, Ph.D.
Good Clinical Practices, Branch 1
Division of Scientific Investigations
Office of Medical Policy, Room 107
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20835

Dear Dr. Blay:

Reference is made to our pending New Drug Application for metformin hydrochloride/glyburide Tablets, NDA 21-178. Additional reference is made to our phone conversations on November 23 and December 1, 1999 in which you requested the following information pertaining to the Phase III double-blind trials in our NDA 21-178:

- The names and addresses of the investigators for the Phase III trials and a listing, by site, of the number of subjects randomized, completed and the number of SAEs in the double-blind portion of each of the studies.

- A copy of the NDA volume containing the Application Summary for NDA 21-178.

At this time we are submitting the requested information. A Table of Contents, detailing the attachments contained in this submission, follows this letter.

Two copies of the cover letter for this submission are being provided (as desk copies to Ms. Weber) for NDA 21-178. The attachments are being provided only to DSI, as the information is already contained in the initial NDA.

If you have any questions regarding this submission, I can be reached at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
U.S. Regulatory Liaison

WCR/JBS/pc
Attachments
Desk Copy: Ms. Jena Weber (2 copies - letter only) for NDA 21-178
(HFD-510, Room 14B04)

Table of Contents

Volume 1: Investigator/Enrollment/SAE Information

Volume 2: Application Summary for Fixed Combination Metformin/Glyburide (Original NDA Volume 1.2)

Table of Contents (continued)

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5992 Fax: 609 252-3619

December 2, 1999

Laurie Smaldone, M.D.
Senior Vice President
Worldwide Regulatory Affairs

John K. Jenkins, MD., Director, Office of
Drug Evaluation II
Solomon Sobel, MD., Director, Division of Metabolisim
and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, Maryland 20857

Subject: NDA 21-178; Metformin Hydrochloride/Glyburide Fixed Combination Tablet

Dear Drs. Jenkins and Sobel:

This letter concerns the above NDA filed on September 30, 1999, and recent communications to Bristol-Myers Squibb Company from the Agency that it has assigned the application a Standard (S) review classification. Based upon strong scientific evidence that this new product of low dose metformin HCl and low dose glyburide represents a significant improvement in the treatment of type 2 diabetes compared to marketed products, we request reconsideration of this decision and assignment of a Priority (P) classification to the NDA .

The expert consensus is that current marketed therapies do not adequately meet the medical needs of the vast majority of the estimated 12 million patients treated for type 2 diabetes, a leading cause of death and disability in the United States. The Agency has recognized the seriousness and extent of this unmet medical need by granting a P classification to the last four NDAs filed for treatment of type 2 diabetes, including three in the same class (thiazolidinediones). We believe NDA 21-178 further advances the treatment of type 2 diabetes, and due to its superior efficacy and improved safety and tolerability, merits a P classification. Our request for reconsideration is based upon data from Study CV138-019, "Safety and Efficacy Of Fixed Combination Metformin/Glyburide Products As First Line Therapy In Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control With Diet" and the following considerations relative to the unmet medical needs of patients with type 2 diabetes:

- NDA 21-178 fulfills the criteria for Priority classification per the FDA MAPP for Priority Review Policy, i.e., significant improvement compared to marketed products in treatment of a disease.

- Data from Study CV138-019 demonstrate that low doses of a metformin/glyburide combination as initial therapy provide significantly improved safety and efficacy compared to currently available treatments.

- In Study CV138-019, 40% of the patients reached glycemic control with one low dose (250/1.25) tablet, and an additional 20% reached glycemic control with two low dose tablets dosed b.i.d. Also, as discussed below, patients in the low dose combination treatment arm had a lower incidence of symptoms of hypoglycemia and GI adverse events.

- The starting dosage form studied in CV138-019 is not marketed. Also, health care providers cannot know that the regimen proposed in the NDA represents a significant advance in clinical practice; further, this treatment is markedly different from what is recommended in currently approved product labeling.

- Even if both components of the fixed combination were marketed products, FDA has acknowledged that supplemental efficacy applications relating to a marketed product may qualify for priority review if they otherwise meet the standards set forth in FDA's MAPP on Priority Review.*

Support for the above are presented for your consideration.

I. FDA Criteria for Priority Classification

FDA MAPP 6020.3 describes the review priority classification for NDAs and efficacy supplements. The definition of a Priority application is that "the drug product, if approved would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease." Examples provided are: 1) increased effectiveness, 2) elimination or substantial reduction of a treatment-limiting drug reaction, 3) enhancement of patient compliance, or 4) safety and effectiveness in a new subpopulation. The data presented in NDA 21-178 meet the Priority definition because of superior efficacy as well as improved safety and tolerability and are fully consistent with the examples set forth in FDA MAPP 6020.3.

* *Guidance for Industry, Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements.* Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (Procedural Guidance 4 May 1998).

A. Improved Efficacy

Protocol CV138-019 studied a low dose combination arm (250 mg metformin HCl/1.25 mg glyburide) as initial therapy compared to placebo, or to monotherapy with metformin or glyburide, in type 2 diabetes patients who had failed to achieve glycemic control with diet and exercise (see Attachment I, Study Synopsis, for additional details).

This low dose combination had not been previously studied. The medically important data from the study are summarized in the attached tables: Table I – Mean Change in HbA_{1c} from Baseline, Table II – Mean Change in FPG from Baseline, Table III – Mean Change in Two-Hour PPG from Baseline, Table IV-A – Number of Subjects with Treatment-Emergent Gastrointestinal Adverse Events, Table IV-B – Number of Subjects with Hypoglycemic Symptoms.

The clinical data that represent a significant therapeutic advance in the treatment of diabetes are summarized below:

- The low dose combination provided greater reductions in all long term and short term parameters of glucose control studied, including HbA_{1C}, postprandial glucose excursion, fasting glucose and fructosamine, when compared to placebo and to either glyburide or metformin monotherapy.

- Significantly larger mean decreases in absolute postprandial glucose were observed for the low dose combination compared to placebo and to either glyburide or metformin monotherapy. Evaluation of the excursions from fasting glucose to postprandial glucose demonstrates that the low dose combination is the most powerful agent in decreasing postprandial glucose excursion.

- The efficacy of the low dose therapy is superior to any currently available first line therapy and cannot be duplicated by marketed therapies. See II below.

B. Improved Safety and Tolerability

Improved safety and tolerability was seen with the low dose combination (250/1.25) compared to either monotherapy. The 250/1.25 dose had a significantly lower frequency of symptoms of hypoglycemia compared to glyburide monotherapy, and this dose also had significantly fewer reports of gastrointestinal side effects compared to metformin monotherapy. Both of these adverse events present significant challenges to achieving and sustaining glucose control. Further, poor tolerability can often result in poor adherence to drug regimens. Without substantial compliance with

treatment, long term control of blood glucose and commensurate reductions in the complications of type 2 diabetes is made more difficult.

II Lack of Available Dosage Forms and Prescribing Information

Already noted, 60% of the patients treated in the low dose treatment arm of pivotal study CV138-019 achieved control on one or two (dosed b.i.d.) low dose tablets, a dosage form that is not available currently.

Glyburide is currently available as 1.25 mg tablets, but metformin is currently available only as 500, 850 and 1000 mg unscored tablets. Therefore, physicians do not currently have the means to readily duplicate the doses that were sufficient to provide glycemic control in 60% of the type 2 diabetes patients in the low dose combination treatment arm of Study CV138-019.

Additionally, until Study CV138-019 was conducted, there were no data available to provide insight into the significant benefits to patients when treated with a low-dose combination earlier in their disease process. In fact, no combination of products is currently approved as first line therapy for the treatment of type 2 diabetes. If approval of this NDA is delayed, physicians will lack not only the prescribing and scientific information necessary to initiate this new treatment approach, but also the ability to prescribe the drug for this sub-optimally treated population. Again, this concern is specifically addressed by the Agency in the MAPP.

In conclusion, the low dose fixed combination provides superior efficacy as first line therapy in patients with type 2 diabetes, along with significantly improved safety and tolerability over monotherapy. This product is not available; the dosage forms studied cannot be duplicated by currently marketed drugs, and information about the new treatment and how it can and should be used is not known to clinicians. This product profile meets the criteria for Priority classification, per the FDA MAPP for Priority Review, which applies to marketed drugs as well as NCEs.

Bristol-Myers Squibb respectfully requests reconsideration of the standard review designation assigned to NDA 21-178. As additional support for our position, we are providing letters from Dr. James R. Gavin III, Senior Scientific Officer of the Howard Hughes Medical Institute, and from Dr. Richard Beaser, Executive

Director of Continuing Medical Education at the Joslin Diabetes Center. These letters further articulate the compelling benefits to patients and doctors afforded by this novel treatment.

Thank you for your consideration.

Sincerely,

Laurie Smaldone

Laurie F. Smaldone, MD

Att.

Cc: Dr. M. Lumpkin, Deputy Center Director
Dr. S. Malozowski, Medical Team Leader
Dr. R. Misbin, Medical Director

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL
NEW CORRESP
NC

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

CENTER FOR DRUG
REC'D
NOV 0 8 1999
HFD-510
EVALUATION AND RESEARCH

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

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-178
Metformin hydrochloride/Glyburide Tablets

November 5, 1999

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

Dear Dr. Sobel:

Reference is made to our pending New Drug Application for metformin hydrochloride/glyburide Tablets, NDA 21-278. Additional reference is made to the teleconference of October 22, 1999 with Dr. Lee Ping Pian of the FDA. During the teleconference Dr. Pian requested the following items for studies CV138-011 and CV138-019 (double-blind portions only):

noted
LP

1. Inclusion of a single variable that identifies patients in the analysis and supplemental data sets

2. Addition of a treatment variable to the data sets DISPST011.xpt and DISPST019.xpt

3. New data sets containing one record for each patient at each protocol-specified visit for each efficacy variable. The data sets should contain two additional variables:

   a) The measurement value for each time point. If multiple measurements were taken at a particular time point, the one included in the analysis should be used.

b) If no measurement was taken, the last prior measurement (last observation carried forward) should be used.

4. A better copy (larger print) of Appendix 5.0A (protocol) of the report of study CV138-011. (A post-teleconference check of the corresponding appendix for CV138-019 revealed that the type size was satisfactory.)

Our submission of October 29, 1999 provided the above materials for study CV138-011 and a commitment to provide the corresponding data sets for CV138-019 on November 5. We are now providing a CD-ROM disk containing the requested data sets for CV138-019.

If there are any questions, please call me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
U.S. Regulatory Liaison
Regulatory Science

WCR/HMK/dk

Desk Copy: Dr. Lee Ping Pian (HFD-715, Room 14B18) with CD-ROM Disk

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

CSO INITIALS

DATE

ORIGINAL

NEW CORRESP

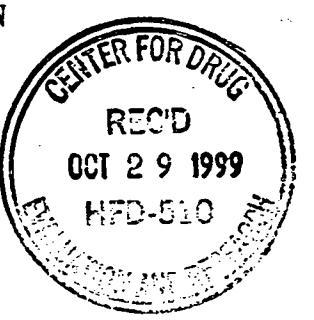
NC

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

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

RESPONSE TO FDA REQUEST FOR INFORMATION



NDA 21-178
Metformin hydrochloride/Glyburide Tablets

October 28, 1999

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

noted [S] 11/3/99

Dear Dr. Sobel:

Reference is made to our pending New Drug Application for metformin hydrochloride/glyburide Tablets, NDA 21-278. Additional reference is made to the teleconference of October 22, 1999 with Dr. Lee Ping Pian of the FDA. During the teleconference Dr. Pian requested the following items for studies CV138-011 and CV138-019 (double-blind portions only):

1. Inclusion of a single variable that identifies patients in the analysis and supplemental data sets

2. Addition of a treatment variable to the data sets DISPST011.xpt and DISPST019.xpt

3. New data sets containing one record for each patient at each protocol-specified visit for each efficacy variable. The data sets should contain two additional variables:

    a) The measurement value for each time point. If multiple measurements were taken at a particular time point, the one included in the analysis should be used.

b) If no measurement was taken, the last prior measurement (last observation carried forward) should be used.

4. A better copy (larger print) of Appendix 5.0A (protocol) of the report of study CV138-011. (A post-teleconference check of the corresponding appendix for CV138-019 revealed that the type size was satisfactory.)

For CV138-011 we are now providing a CD-ROM disk containing the requested data sets and an improved copy of Appendix 5.0A. The CD-ROM disk containing the corresponding data sets for CV138-019 will be delivered to the FDA on November 5, 1999.

If there are any questions, please call me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
U.S. Regulatory Liaison
Regulatory Science

WCR/HMK/dk

Desk Copy: Dr. Lee Ping Pian with CD-ROM Disk and Replacement Appendix (HFD-715, Room 14B18)

REVIEWS COMPLETED
CSO ACTION: [/S/] N.A.I. MEMO
CSO INITIALS DATE 10/8/99

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

Warren C. Randolph
Director
Regulatory Science
Worldwide Regulatory Affairs

NDA 21-178
Metformin Hydrochloride/Glyburide Fixed Combination Tablets

October 8, 1999

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

Dear Dr. Sobel:

Please refer to our pending New Drug Application for fixed combination metformin/glyburide tablets, NDA 21-178. We are now submitting our proposed tradename for the product, GLUCOVANCE®.

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

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
Regulatory Science

APPEARS THIS WAY
ON ORIGINAL

WCR/ls/dk

Desk Copies: Ms. Jena Weber (HFD-510, Room 14B04)
Dr. Xavier Ysern (HFD-510, Room 14B04)

Bristol-Myers Squibb
Pharmaceutical Research Institute

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Warren C. Randolph
[illegible]

NDA 21-178
Metformin Hydrochloride/Glyburide Fixed Combination Tablets

September 30, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Sobel:

At this time, in accord with 21CFR314.50, Bristol-Myers Squibb (BMS) is submitting a New Drug Application for fixed combination metformin/glyburide tablets, NDA 21-178. As background to this submission, we refer to the following:

- October 17, 1996 meeting between BMS and the Division of Metabolism and Endocrine Drug Products, at which proposed development plans for a fixed combination metformin/glyburide product were discussed.

- My telephone conversations of February 26 and 27, 1997 with Dr. Misbin, in which he informed me of the Division's opinion that labeling for the fixed combination product should be for both first line and second line (sulfonylurea failure) use, with studies to support both uses.

- Teleconferences of October 15 and November 14, 1997 between representatives of BMS and the Division, in which design of the first line study was discussed.

- My August 12, 1999 telephone conversation with Ms. Peggy Hail, in which she assigned the number 21-178 to this NDA.

The safety and efficacy of fixed combination metformin/glyburide tablets is supported in this application by the results of two double-blind, placebo controlled trials. Protocol CV 138-011 is a

study of a fixed combination therapy in type 2 diabetics who have failed to achieve glycemic control with sulfonylurea therapy (second line use). Protocol CV138-019 investigated the safety and efficacy of the fixed combination in type 2 diabetics who had failed to achieve glycemic control with diet and exercise (first line use). As discussed with the Division on October 15, 1997 the double-blind portion of the first line use trial was extended to 32 weeks to demonstrate the durability of effect. Long-term, open-label extensions of both studies are ongoing and interim results of these are submitted herein.

Consistent with an earlier study [NDA 20-357, Glucophage® (metformin hydrochloride)Tablets] the fixed combination was clearly superior to either metformin or glyburide monotherapy in the control of hyperglycemia in type 2 diabetics who had failed such control on sulfonylureas.

The significant, new information that resulted from our clinical program was in the case of combination therapy for first line treatment of type 2 diabetics who had failed glycemic control with diet and exercise. Though such patients generally respond well to monotherapy with metformin or sulfonylureas, we found that the combination of metformin and glyburide produced clearly superior efficacy, compared to either agent alone, after titration of each regimen. The superior glycemic control with the combination was evidenced in greater reductions in HbA1c and fasting plasma glucose after 20 weeks of double-blind treatment.

The first line therapy trial incorporated a low-dose combination arm (250 mg metformin and 1.25 mg glyburide) and in these subjects the low dose was as effective in controlling hyperglycemia as a higher dose combination (500 mg metformin plus 2.5 mg glyburide). This low dose, while providing efficacy superior to monotherapy treatment, produced less hypoglycemia than glyburide monotherapy and fewer gastrointestinal adverse events than metformin monotherapy.

The data herein established both the superior efficacy and improved side effect profile of the low dose combination, compared to metformin and glyburide monotherapies in first line treatment of type 2 diabetes. These factors contribute a significant improvement in the treatment of type 2 diabetes and therefore we are requesting that this application receive Priority Classification.

We are not including a proposal for the tradename in this initial application, but will subsequently submit our proposal as an amendment.

The media for the electronic submission has been prepared as follows:

The total size of the electronic submission is approximately 919 MB. There are approximately 400 files and 142 folders.

The files have been checked for viruses on September 28, 1999 with ——————————
(——————————→ and are virus free.

The electronic submission has been provided on two CD-ROM disks to the Central Document Room.

The contents of this submission are described in both the Table of Contents and the Reviewer's Guide. Please contact me at (609) 252-5228 with any questions.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Affairs

WCR/ls/dk

Desk Copies: Dr. Robert Misbin (Volume 1.1 – 1.3)
Ms. Jena Weber (Volume 1.1 – 1.3)

APPEARS THIS WAY
ON ORIGINAL