CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-202

CORRESPONDENCE

E L E C T R O N I C M A I L M E S S A G E

itivity: COMPANY CONFIDENTIAL

Date: 10-Sep-2000 11:03am EDT
From: Jena Weber
WEBERJ
Dept: HFD-510 PKLN 14B04
Tel No: 301-827-6422 FAX 301-443-9282

TO: Karen Lechter (LECHTERK)

Subject: Re: Glucophage PPI

Karen,

Many thanks!!!
Jena

>Attached is the Glucophage PPI from DDMAC. I discussed it with Barbara
>Chong before sending it. Due to time constraints, I was unable to write
>a cover memo explaining the changes I suggest. Ask Barbara if you have
>any questions.
>
>Thanks
>Karen

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 36 PAGE (S)

DRAFT

LABELING

MESSAGE CONFIRMATION

10/13/00 17:15
ID=DMEDP-CDER-FDA

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529	TX		

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ON ORIGINAL

TELEFAX

TO: BMS- Att. Warren Randolph

Ref NDA 21-202 AP LETTER !!!

FAX: 609-252-6000

PHONE:

FM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-

Electronic Mail Message

Date: 9/11/00 12:19:42 PM
From: Lauren Lee (LEEL)
To: Jena Weber (WEBERJ)
Cc: Jerry Phillips (PHILLIPSJ)
Cc: Sammie Beam (BEAMS)
Subject: NDA 21-202 (Glucophage XR)

Jena:

Thank you for the opportunity to comment on the latest labeling revisions for Glucophage XR. As discussed, we have reviewed the container labels that were submitted on 9/11/00 by Bristol-Myers Squibb, and have no objections.

Please let us know if you need further assistance.

Thanks,
Lauren

Electronic Mail Message

Date: 9/12/00 1_:19:03 AM
From: Mary T Peters (Mary.Peters@bms.com)
To: Jena Weber 301-827-6422 FAX 301-443 (WEBERJ@A1)
Subject: Re: carton LBL

Jena,

As requested, the container labels for Glucophage XR are attached.

Regards,
Mary

Jena Weber 301-827-6422 FAX 301-443-9282 wrote:

> Mary,
>
> When you get a chance, could you please send me an electronic copy of
> the carton labels that you fowarded tc Lauren Lee earlier today.
>
> Thanks,
> Jena

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 21-202
Glucophage®XR (metformin HCl extended release tablets)

June 30, 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 Glucophage®XR (metformin HCl extended release tablets), NDA 21-202. Reference is also made to a telephone conversation on June 2, 2000 between Dr. Lee (FDA, Office of Post-Marketing Drug Risk Assessment) and Ms. M. Brown (Bristol-Myers Squibb) concerning the draft bottle labels for the Glucophage® XR 500 mg tablets. In that conversation, Dr. Lee requested a pdf version of the labels. The pdf files were provided to Dr. Lee on June 14. Prior to sending the pdf files to Dr. Lee, Ms. M. Brown discussed some minor changes that have been made to the draft labels since the original NDA filing. This submission presents the revised labels provided to Dr. Lee.

Attachment I provides a copy of the email that Bristol-Myers Squibb sent on June 14, 2000.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the Glucophage®XR (metformin HCl extended release tablets) draft bottle labels that have been implemented since the November 12, 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)

From 6/30/00

Subject: Glucophage XR Labels
Date: Wed, 14 Jun 2000 08:40:45 -0400
From: Melody A Brown <Melody.Brown@bms.com>
Organization: Bristol-Myers Squibb
To: leel@cder.fda.gov

Dr. Lee,

As requested, please find the pdf files which contain the labels for the Glucophage XR (metformin HCl extended release tablets) 500 mg bottles. I have attached two files. One is for the 100 tablet count bottle and the other is for the 500 tablet count bottle. As we discussed, we have made some minor changes to the draft label that you previously reviewed. They are as follows:

1) The "extended release tablets" have been moved inside the parentheses instead of outside as previously submitted.
2) The word "hydrochloride" has been abbreviated to HCl.

These changes are made to make this label consistent with the marketed Glucophage (metformin hydrochloride tablets) and the Glucovance Tablets which are currently under review.

Please feel free to email me with any questions or phone me at (609) 818-3243.

Regards,

Melody A. Brown
Director, CMC Regulatory Sciences

N3484-00.pdf	**Name:** N3484-00.pdf **Type:** Acrobat (application/pdf) **Encoding:** base64 **Download Status:** Not downloaded with message

N3486-00.pdf	**Name:** N3486-00.pdf **Type:** Acrobat (application/pdf) **Encoding:** base64 **Download Status:** Not downloaded with message

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ON ORIGINAL

WITHHOLD 2 PAGE (S)

Draft

Labeling

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

OCT 5 2000

Fax: 609-252-6000

Reference: NDA 21-202, Glucophage XR (Metformin HCl Extended Release Tablets);
Revised PPI (patient package insert) completed by the Agency on October 4, 2000.

This information was sent to Warren Randolph on October 5 2000.

CLEARED FOR FAXING

/S/ 10-5-00

David Orloff, M.D.

/S/ 10/5/00

Jena Weber, RHPM

APPEARS THIS WAY
ON ORIGINAL

OCT 3 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Fax: 609-252-6000

Reference: NDA 21-202, Glucophage XR (Metformin HCl Extended Release Tablets); your fax dated October 2, 2000. Please remove the following sentences from the **Pharmacokinetics** subsection of the **CLINICAL PHARMACOLOGY** section of the package insert:

[ ]

This information was sent to Warren Randolph on October 3, 2000.

CLEARED FOR FAXING

/S/ 10-2-00

David Orloff, M.D.

/S/

Hae-Young Ahn, Ph.D.

/S/ 10/2/00

Jena Weber, RHPM

APPEARS THIS WAY
ON ORIGINAL

SEP 27 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Fax: 609-252-6000

Ref: NDA 21-202, Glucophage XR; original submission dated November 12, 1999 - **Patient Package Insert**

Attached you will find the patient package insert (PPI) as revised by The Division of Drug Marketing and Communications. We concur with their review, and request that you implement these changes to read as per their recommendations.

This information was faxed to Warren Randolph on September 27, 2000.

CLEARED FOR FAXING

/S/ 9-27-00

David Orloff, M.D.

/S/ 9/27/00

Jena Weber, RHPM

APPEARS THIS WAY
ON ORIGINAL

AUG 29 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs Fax: 609-252-6000

Ref: NDA 21-202, Glucophage XR (Metformin HCl Extended Release Tablets); original submission dated November 12, 1999.

This communication is being generated as a result of a request for consult from the reviewing Division to Office of Post-Marketing Drug Risk Assessment (OPDRA). Their revisions are for the 500 mg container label. Please provide your response in writing to your NDA file.

A. According to page 05, the proposed color for the strength, "500 mg," is purple ——— . However, the strength on the actual container label appears blue. As mentioned in our previous review, the color, blue, is already used in Glucophage 500 mg labels. Since both Glucophage XR and Glucophage overlap in strength and in order to prevent confusion between these two products, we recommend that similar colors not be used for the strength.

B. Although the design of the revised container labels for Glucophage XR appear different from Glucophage labels, the color, red, is used for the proprietary name in both Glucophage XR and Glucophage (1000 mg) container labels. In this case, we recommend that similar colors not be used for the proprietary name in order to prevent pharmacy dispensing errors in choosing the wrong drug from the shelf.

This information was faxed to Warren Randolph on August 29, 2000.

CLEARED FOR FAXING

/S/ for 8/29/00
John Jenkins, M.D.

/S/ 8/25/00
Saul Malozowski, M.D.

/S/
Robert Misbin, M.D.

/S/ 8/29/00
Jena Weber, RHPM

MESSAGE CONFIRMATION

08/29/00 08:41
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08/29 08:41	00'34"	609 252 6000	002 002	OK		0000

TELEFAX

TO: BMS - Att. Warren Randolph

REF: NDA 21-202

FAX: 609-252-6000

PHONE:

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

AUG 28 2000

Fax: 609-252-6000

Reference: NDA 21-202, Glucophage XR (Metformin HCl Extended Release Tablets); original submission dated November 12, 1999. Please address the following comments and requests in writing to your NDA.

LABELING COMMENT:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; indicates an explanation only and is not intended to be included in the labeling)

> Pharmacokinetics: Although the extent of metformin absorption from the GLUCOPHAGE XR tablet [redacted] increased by approximately [redacted] 50% when given [redacted] with food, there was no effect of food on Cmax and Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of GLUCOPHAGE XR. [redacted]

DISSOLUTION RECOMMENDATION:

> For the proposed dissolution specification, it is recommended that the 10 hour tolerance be changed to [redacted]

This information was sent to Warren Randolph on August 28, 2000.

CLEARED FOR FAXING

/S/ for 8/28/00
John Jenkins, M.D.

/S/
for Robert Shore, PharmD.

/S/
Hae-Young Ahn, Ph.D.

/S/ 8/28/00
Jena Weber, RHPM

MESSAGE CONFIRMATION

08/28/00 16:47
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08/28 16:46	00'33"	609 252 6000	002/002	OK		0000

TELEFAX

TO: BMS - Att. Warren Randolph

RE: NDA 21-202

FAX: 609-252-6000

PHONE:

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE HFD-510

AUG 25 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Fax: 609-252-6000

Reference: NDA 21-202, Glucophage XR (Metformin HCl Extended Release Tablets); original submission dated November 12, 1999. Please address the following comments and requests that apply to the insert labeling for this product.

Labeling Issues:

On page 2: Why are there no data about HbA1c reduction with Metformin XR? At a minimum, the comparison of Metformin XR to Glucophage IR at 24 weeks from study 012 should be included.

On page 4: The statement that [redacted] is based on just 3 patients who were given the higher dose after 12 weeks of 1500 mg. Given that 12 weeks is insufficient time to see the full effect on HbA1c, the small reduction that occurred with dose titration is not convincing. Study 036 showed that both 1500 mg and 2000 mg gave the same result.

On page 4: The effect on LDL is described as [redacted] and [redacted] but the rise in triglycerides is described as [redacted]. The label should be revised to include the data and remove the judgmental language.

This information was sent to Warren Randolph on August 25, 2000.

APPEARS THIS WAY
ON ORIGINAL

CLEARED FOR FAXING

/S/ 8/24/00

John Jenkins, M.D.

/S/ 8/24/00

Saul Malozowski, M.D.

/S/ 8/24/00

Robert Misbin, M.D.

/S/ 8/24/00

Jena Weber, RHPM

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

08/25/00 11:35
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08/25 11:35	00'36"	609 252 6000	003/003	OK		0000

TELEFAX

TO: Warren Randolph - RBMS

Ref NDA 21-202

FAX: 609-252-6000

PHONE:

FROM: Jena M. Weber, RHPM

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510

Electronic Mail Message

Date: 8/31/00 2:35:32 PM
From: Barbara Chong (CHONGB)
To: Jena Weber (WEBERJ)
Subject: Re: NDA 21-202

Jena,

My comments are attached. Additional comments on the PPI will be sent in a later attachment.

Barbara

>Barb,
>
>Just checking in; please let me know how your review of the Glucophage
>is coming along.
>
>Thanks,
>Jena

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 3 PAGE (S)

Electronic Mail Message

Date: 8/24/00 2:27:56 PM
From: Mary Dempsey (DEMPSEYM)
To: Jena Weber (WEBERJ)
Subject: NDA 21-202 Glucophage XR-----proprietary Trade Name Review

Jena,

FYI
This should also have been sent to you in Hard Copy.

Thanks,
MaryD

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Fax: 609-252-6000

Ref: NDA 21-202, Glucophage XR (Metformin HCl Extended Release Tablets); original submission dated November 12, 1999.

This communication is being generated as a result of the request for consult from the reviewing Division to Office of Post-Marketing Drug Risk Assessment (OPDRA). Their recommendations are as follows. Please provide your response in writing to your NDA file.

OPDRA has no objections to the use of the proprietary name, Glucophage XR. However, they recommend careful monitoring and sufficient education regarding the difference between Glucophage XR and Glucophage upon the launch of this product.

For the **Container Label** (500 mg): The container labels for Glucophage XR and Glucophage (500mg) are very similar in terms of their design and presentation. In order to prevent confusion between the two products, we recommend that the container label for Glucophage XR appear distinctively different than the label for Glucophage. Furthermore, the proposed colors for Glucophage XR container labels are purple and red. However, the colors purple and red are already used to differentiate Glucophage 850 mg and 1000 mg labels, respectively. We recommend that similar colors not be used for the Glucophage XR proposed labels.

For the **Patient Information Insert Labeling**: We recommend including the information regarding the difference between Glucophage and Glucophage XR in the patient insert in order to inform patients transferring from Glucophage or other agents to Glucophage XR.

This information was faxed to Warren Randolph on June 29, 2000.

CLEARED FOR FAXING

[/S/] 6/29/00
Jena Weber, RHPM

[/S/] 29-JUN-2000
Xavier Ysern, Ph.D.

[/S/] 6/29/00
Stephen Moore, Ph.D.

APPEARS THIS WAY ON ORIGINAL

511/ Weber

JAN 10 2000

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Fax: 609-252-6000

Ref: NDA 21-202, Metformin HCl; original submission dated November 12, 1999.

Based on our cursory review of this submission, we have the following comments and requests concerning the **clinical pharmacology and biopharmaceutics** portion of your application. Please provide your response in writing to the NDA file.

1. Please submit your proposed labeling in Word format on a 3.5" floppy disk.

2. According to the submission, two assays, both ——— were used for the quantitative determination of metformin in human plasma (Report number 910072436 for studies CV138-021, CV138-028, and CV138-035, and 910072436 for study CV138-031). Please provide any cross-validation data that may be available for these two assays, and a summary of differences between them.

3. The dissolution data submitted in Section 6 consists of two pages (vol. 1.8, page 025, 026), is very scant, and includes 2 batches that were manufactured in ——— (the commercial site is ——— ; these — batches were of ——— and ——— tablets total. The Office of Clinical Pharmacology and Biopharmaceutics would like to see data from 12 units from at least three different biobatches (biobatches should be — or greater than the proposed commercial production batch or at least ——— units, whichever is greater). Data for each unit as well as mean and CV% for all 12 units should also be submitted. In addition, you should provide data on dissolution in different media since the potential for pH dependence of drug release from a modified release drug product is well recognized.

4. Study CV138-035 assessed pharmacokinetics and pharmacodynamics of metformin. Please specify if any attempt was made to develop a PK/PD relationship.

This information was faxed to Warren Randolph on January 10, 2000.

CLEARED FOR FAXING

/S/ 1/10/00
Jena Weber, CSO

/S/ 10-JAN-00
Acting TL
Robert Shore, Pharm.D.

ACTING AD
Hae-Young Ahn, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-202
HFD-510
HFD-510/RShore/HYAhn
HFD-511/JWeber

APPEARS THIS WAY
ON ORIGINAL

WEBER

MEMORANDUM OF MEETING

Meeting Date: Wednesday January 12, 2000; @ 1:30 pm, Room 1456

Application: BMS application for Metformin E-R Tablets, NDA 21-202.

Type of Meeting: Filing meeting

/S/ 1/13/00

Meeting Recorder and Chair: Jena Weber, PM

FDA Attendees

Saul Malozowski, M.D.	Team Leader, Medical Officer
Xavier Ysern, Ph.D.	Chemist
Ronald Steigerwalt, Ph.D.	Team Leader, Pharmacology
Roy Blay, Ph.D.	DSI
Robert Shore, Pharm.D.	Biopharmaceutics
Japo Choudhury, Ph.D.	Biometrics
William Koch, Ph.D.	PM
Jena Weber	RHPM

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

Pharmacology:	No issues, filable, but will have to review the proposed labeling.
Biopharmacology:	No issues, filable.
Chemistry (CMC):	No issues, filable.
Statistics:	No issues, filable.
MO:	No issues, filable.
DSI:	No issues, sites to be inspected will be determined.

Conclusions:

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

cc: NDA 21-202
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-511/JWeber/WKoch
HFD-510//RMisbin/SMalozowski/RShore/HYAhn/XYsern/SMoore/JChoudhury/TSahlroot
HFD-46/RBlay

Drafted by:Jweber 1/13/00
Final: Jweber 1/~~13~~/00

MEETING MINUTES

NDA 21-202

No Advisory Committee was assembled to discuss this application.

NDA 21-202

No Federal Register Notices were published for this Rx product.

APPEARS THIS WAY
ON ORIGINAL

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 21-202
Glucophage ®XR (metformin hydrochloride extended-release tablets)

October 6, 2000

David Orloff, 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. Orloff:

Reference is made to our pending New Drug Application for Glucophage XR (metformin hydrochloride extended-release tablets), NDA 21-202. Additional reference is made to the following:

- The Agency's facsimile transmission of October 3, 2000 which recommended removal of two sentences from the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section of the package insert (copy attached).

- The telephone conversations between John Bedard, of Bristol-Myers Squibb, and Dr. David Orloff, of the FDA on October 4, 2000. Dr. Orloff proposed revised text in the Recommended Dosing Schedule subsection of the 5DOSAGE AND ADMINISTRATION section of the package insert regarding BID dosage and upward titration of metformin hydrochloride if glycemic control is not obtained.

- The Agency's facsimile transmission of October 5, 2000 which recommended revised text for the patient package insert (PPI), copy attached.

We are now providing a revised draft of the professional package insert in which we have adopted the Agency's recommendation for the CLINICAL PHARMACOLOGY section. The suggested text for the Recommended Dosing Schedule subsection of the DOSAGE AND ADMINISTRATION section has also been adopted, except the phrase ——————— has been removed from the fourth

sentence of the third paragraph. In addition, the dosage instructions for Glucophage have been referenced to avoid confusion.

We are also providing a revised draft of the PPI which incorporates all of the text recommended by the Agency, to which some text from the current version of the PPI has been added for clarity.

For review purposes, separate, marked-up copies of the professional and patient package inserts are provided. Changes from the draft, professional package insert submitted on October 2, 2000 and changes to the PPI received from the Agency on October 5, 2000 are shown as strikeout (deleted text) or underline (added text). In addition, a merged, clean version of the package insert and PPI is included.

A Table of Contents, detailing the attachments contained in this submission, follows this letter. If there are any questions concerning this submission, please contact me at (609) 252-5228.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

Warren C. Randolph

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

WCR/JBS/HMK/dk
Attachments

Desk Copy: Ms. Jena Weber (2) (HFD-510, Room 14B04)

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 48 PAGE (S)

Draft

Labeling

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

ORIG AMENDMENT

DUPLICATE

bl

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

NDA 21-202
Glucophage ®XR (metformin hydrochloride extended-release tablets)

October 2, 2000

David Orloff, 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
500 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

Reference is made to our pending New Drug Application for Glucophage XR (metformin hydrochloride extended-release tablets), NDA 21-202. Additional reference is made to the facsimile transmission of the draft professional package insert for Glucophage XR to Bristol-Myers Squibb from Ms. Jena Weber on September 27, 2000 (copy attached).

As you are aware, the proposed patient package insert (PPI) is currently being discussed by DDMAC and the Division, and therefore it is not addressed herein. This submission provides proposed, draft labeling (professional package insert only) for Glucophage XR, which has been revised in response to FDA's comments of September 27. Both a clean copy and a copy showing (by strikeout/underline) changes from the draft labeling submitted to FDA via fax on September 12, 2000 are provided.

In most instances, changes proposed by FDA are incorporated in the attached draft. However, in some instances, alternatives to the FDA's proposed changes are provided; these are addressed below:

- First text paragraph following Table 6 and DOSAGE AND ADMINISTRATION: FDA proposed text to comment on [redacted] in DOSAGE AND ADMINISTRATION to suggest that twice daily dosing with Glucophage XR might be required to optimize glycemic control.

There are no data to demonstrate that divided doses of Glucophage XR have any advantage over divided doses of Glucophage. Therefore, we have added the following sentence to the DOSAGE AND ADMINISTATION section, ~~A reference to DOSAGE AND ADMINISTRATION has been added to the text following Table 6.~~

- ADVERSE REACTIONS: As noted by the Agency, the listing of adverse events became unwieldy. Therefore, we have revised both the tables and text in this section to include adverse reactions (as defined in the draft Guidance for Industry, Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics). Tables 10 and 11 now list adverse reactions in placebo-controlled trials with Glucophage and Glucophage XR respectively which occurred more frequently with drug than with placebo and had an incidence greater than 5%. The text following these tables lists those adverse reactions (again, for those occurring more frequently with drug than with placebo) that occurred in 1-5% of patients. References for the adverse reaction data follow:

  - Glucophage: NDA 20-357, Volume 1.105, Study Report for 87-1D-6023, Table 17.2

  - Glucophage XR: NDA 21-202, Volume 1.24, Study Report for CV138-010, Supplemental Table S.12.1.3A, and Volume 1.34, Study Report for CV138-036, Supplemental Table S.12.1.3A

We hope that review of the proposed, professional package insert can proceed in parallel with activities on the PPI. I will be following up with Ms. Weber to discuss the manner in which we can most efficiently move to approval.

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

WCR/ls/dk
Attachments

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

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

NDA AMENDMENT - RESPONSE TO FDA QUESTION

NDA 21-202
Glucophage®XR (metformin HCl extended release tablets)

September 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:

Please refer to our pending New Drug Application for Glucophage®XR (metformin HCl extended release tablets), NDA 21-202. Reference is also made to a communication from the FDA, dated August 28, 2000 concerning the Biopharmaceutic Team's comments to NDA 21-202; specifically, the comment regarding the proposed tablet dissolution specification.

This submission provides a copy of the correspondence received from the Agency on August 28, 2000 in Attachment I.

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

Comment:

Tablet Dissolution Specification
For the proposed dissolution specification, it is recommended that the 10 hour tolerance be changed to [redacted]

Response:

We accept the Agency's comment to change the tablet dissolution specification for the 10 hour tolerance to ———— Consequently, the specifications for Glucophage® XR (metformin HCl extended release tablets) 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 Glucophage® XR (metformin HCl extended release tablets) drug substance and product sections which have been implemented since the November 12, 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)
Dr. R. Shore (HFD-870, 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
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Glucophage XR™ (Metformin HCl Extended Release Tablets)

August 25, 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 Glucophage XR (metformin HCl extended release tablets), NDA 21-202, submitted November 12, 1999. Additional reference is made to an August 8, 2000 facsimile transmission from Dr. Japobrata Choudhury (copy attached) in which he requested clarifications concerning previously submitted information.

Provided herein are responses to Dr. Choudhury's requests. Please contact me at (609) 252-5228 with any questions.

Sincerely,

Warren C. Randolph

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

WCR/ls/dk
Attachment(s)
Desk Copies: Dr. Japobrata Choudhury (HFD-715, Room 9B07)
Ms. Jena Weber (HFD-510, Room 14B04)

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

NDA AMENDMENT

NDA 21-202
Glucophage®XR (metformin HCl extended release tablets)

August 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 Glucophage®XR (metformin HCl extended release tablets), NDA 21-202. Reference is also made to a communication from the FDA, dated June 29, 2000 concerning recommendations for the container labels from the Office of Post-Marketing Drug Risk Assessment (OPDRA). OPDRA indicated that the container labels for Glucophage® XR and Glucophage® (500 mg) are similar in terms of their design and presentation and then recommended that the container labels for Glucophage® XR appear distinctively different than the label for Glucophage®; specifically, OPDRA recommended that similar colors not be used for the Glucophage® XR proposed labels. This submission presents the revised draft labels that reflect the recommendations from OPDRA.

Attachment I provides a copy of the communication from the FDA, dated June 29, 2000.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the Glucophage®XR (metformin HCl extended release tablets) product sections that have been implemented since the November 12, 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 5400 Princeton, NJ 08543-5400 609 818-3000

ORIGINAL

NDA AMENDMENT ~~NDA SUPP AMEND~~

NDA 21-202
Glucophage®XR (metformin HCl extended release tablets)

August 11, 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 Glucophage®XR (metformin HCl extended release tablets), NDA 21-202. Reference is also made to a telephone conversation on August 2, 2000 between Dr. Robert Shore (FDA) and myself (Bristol-Myers Squibb) concerning the additional data requested by the Agency at a pre-NDA meeting to justify the proposed —— dissolution methodology for Glucophage®XR tablets. A pre-NDA CMC meeting was held between Bristol-Myers Squibb and FDA on May 24, 1999 to discuss the chemistry, manufacturing and controls development program and the information to be included in the Glucophage®XR New Drug Application. At the meeting, the FDA participants questioned the proposed —— dissolution method and requested additional data to justify using the —— rpm paddle rotation speed. Consequently, the additional data were submitted in an amendment to IND ——— on October 1, 1999. As a result of the phone conversation between Dr. Robert Shore and myself, the additional data are being submitted to the NDA at this time.

This amendment presents the additional data to justify the use of —— rpms as the paddle rotation speed in the dissolution method for Glucophage®XR (metformin HCl extended release tablets).

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the Glucophage®XR (metformin HCl extended release tablets) product sections that have been implemented since the November 12, 1999 filing of the NDA.

DA 21-202 August 11, 2000

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)
Dr. R. Shore (HFD-870, Room 14B04
Ms. J. Weber (HFD-510, Room 14B04)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY

ORIGINAL

ORIG AMENDMENT

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

BS

Warren C. Randolph
Director
Diabolic/Endocrine Products
Comparison and Global Strategy Unit
Regulatory Science

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Glucophage XR™ (Metformin HCl Extended Release Tablets)

August 10, 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 Glucophage XR (metformin HCl extended release tablets), NDA 21-202, submitted November 12, 1999. Additional reference is made to the following:

- April 10, 2000 facsimile transmission from Dr. Japobrata Choudhury, providing requests for additional information pertaining to NDA 21-202 (Attachment 1).
- May 24, 2000 teleconference between Dr. Choudhury and BMS representatives, at which certain of Dr. Choudhury's requests were discussed and clarified.
- Dr. Choudhury's request of May 24, 2000 for a listing of mean changes in HbA1c by site.
- Our June 29, 2000 submission, providing responses to a portion of Dr. Choudhury's requests.
- Our July 10, 2000 submission of the statistical sections of NDA 21-202 in pdf format on CD-ROM.
- Our July 19, 2000 submission of responses to outstanding requests from Dr. Choudhury.

Attachment 1
Response

- My July 20, 2000 telephone discussion with Dr. Choudhury, in which he requested that BMS provide responses in WORD format, as well as in pdf.

- July 21, 2000 telephone conversation between Dr. Choudhury and myself, in which he indicated that responses to the request numbered 11 in Attachment 1 (pertaining to Study CV138-012) would be needed, though BMS was not making claims of equivalence.

- My July 25, 2000 telephone conversation with Dr. Robert Misbin, concerning the analyses for CV138-012 that would be needed for his review. Dr. Misbin indicated that BMS should provide analyses for HbA1c and FPG and for any other parameters that would appear to be of interest, based upon review of the study data.

At this time we are providing analyses as requested in item 11, both in paper and electronic format. The electronic review aid consists of two diskettes, each containing one file, and is included in the Archival copy submitted to the Division as well as Dr. Choudhury's desk copy. The total size of diskette #1 (WORD format) is 87.0KB; diskette #2 (.pdf format) is 67.7KB in size. The files were screened for known viruses on August 10, 2000 with Norton Antivirus Software, Version — for Windows NT 4.0 (Symantec) and no viruses were detected.

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

APPEARS THIS WAY
ON ORIGINAL

WCR/ls/dk
Attachment(s)

Desk Copies: Dr. Japobrata Choudhury (HFD-715, Room 9B07) (w/ disks)
Ms. Jena Weber (HFD-510, Room 14B04)

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

ORIG AMENDMENT
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NDA AMENDMENT

NDA 21-202
Glucophage®XR (metformin HCl extended release tablets)

August 4, 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 Glucophage®XR (metformin HCl extended release tablets), NDA 21-202. 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 —-month expiry period. As a result of the phone conversation, in support of a —-month expiry period for the tablets, additional stability data are being provided at this time.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the Glucophage®XR (metformin HCl extended release tablets) product sections that have been implemented since the November 12, 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)
Mr. W. 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

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Glucophage XR™ (Metformin HCl Extended Release 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:

Reference is made to our pending New Drug Application for Glucophage XR (metformin HCl extended release tablets), NDA 21-202, submitted November 12, 1999. Additional reference is made to the following:

- April 10, 2000 facsimile transmission from Dr. Japobrata Choudhury, providing requests for additional information pertaining to NDA 21-202 (Attached).

- May 24, 2000 teleconference between Dr. Choudhury and BMS representatives, at which certain of Dr. Choudhury's requests were discussed and clarified.

- Our submissions on June 29, July 10 and July 19, 2000 which provided responses to Dr. Choudhury's requests.

- My telephone conversation with Dr. Choudhury on July 20, 2000 in which he requested electronic copies of the aforementioned submissions in Microsoft (MS) Word format to aid in his review.

Dr. Choudhury had also asked that the information requested in MS Word be provided in pdf format for Archival purposes. However, for NDA 21-202 the Archival copy is in paper so the materials provided to aid the review are provided only in MS Word, which is identical to the paper Archival copy.

At this time we are providing the requested electronic copies, in MS Word format, of our responses included in our submissions of June 29, July 10 and July 19. The files are located in folders named by date of submission.

- The 29Jun00 folder contains the responses to questions 1, 2, 6, 7, 8, 9 and 10.
- The 10Jul00 folder contains the response to question 13, previously provided in pdf format, and a copy of the Application Summary for NDA 21-202 (paper Archival copy is located in Volume 1.2 of the NDA) containing the requested pages 93, 94 and 95.
- The 19Jul00 folder contains the responses to questions 3, 4, 5, 11, 12 as well as the listings of mean changes in HbA1c by site, as Appendix 10.1. for each study (CV138-010, CV138-012 and CV138-036).

We have compared the MS word files contained in this submission to the paper Archival files which were submitted to the NDA and the content is identical to the paper Archival files. Formatting may vary when comparing the paper Archival pages to the electronic pages in MS Word, even though the content is identical.

This submission consists of 11 files and seven folders on one CD-ROM which is enclosed in the Archival copy submitted to the Division. An additional copy of the CD-ROM is provided to Dr. Choudhury as a desk copy. The total size of the electronic submission is approximately 7.1 MB. The files were screened for known viruses on July 24, 2000 with Norton Antivirus Software, Version — for Windows NT 4.0 (Symantec) and no viruses were detected. Depending on the desktop computer environment, an MS Word macro message may appear when opening a file. The message will prompt for a response to either "enable" or "disable" macros. If the macros are enabled, the format of the original document will be retained; if the macros are disabled, some of the formatting may change, but the content will remain the same.

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

Sincerely,

Warren C. Randolph

APPEARS THIS WAY
ON ORIGINAL

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

Desk Copies: Dr. Japobrata Choudhury, HFD-715, Rm. 9B07
Ms. Jena Weber, (letter only) HFD-510, Rm. 14B04

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

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ORIG AMENDMENT
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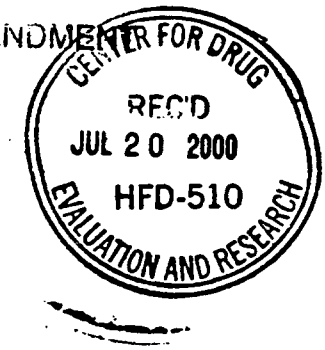

Warren C. Randolph
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Glucophage XR™ (Metformin HCl Extended Release Tablets)

July 19, 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 Glucophage XR (metformin HCl extended release tablets), NDA 21-202, submitted November 12, 1999. Additional reference is made to the following:

- April 10, 2000 facsimile transmission from Dr. Japobrata Choudhury, providing requests for additional information pertaining to NDA 21-202 (Attachment 1).
- May 24, 2000 teleconference between Dr. Choudhury and BMS representatives, at which certain of Dr. Choudhury's requests were discussed and clarified.
- Dr. Choudhury's request of May 24, 2000 for a listing of mean changes in HbA1c by site.
- Our June 29, 2000 submission, providing responses to a portion of Dr. Choudhury's requests.
- Our July 10, 2000 submission of the statistical sections of NDA 21-202 in pdf format on CD-ROM.

At this time we are providing responses to the outstanding requests from Dr. Choudhury. In order to facilitate linking of responses to specific items in Dr. Choudhury's request, we have assigned a number to each item and have so annotated the copy of the April 10 communication herein. Please refer to these annotations to identify the responses, which are similarly numbered in the section identified as "Responses". Appendices supporting the responses are provided as the second and third volumes of this submission.

Since the request for mean changes in HbA1c by site was made separate from the April 10 communication, these data are provided in Attachment 2, separate from the other responses.

Three diskettes (one each for studies CV138-010, CV138-012 and CV138-036) are provided to support the response identified as item 12. Each of the diskettes contain 2 files. The files were screened for known viruses on July 19, 2000 with Norton Antivirus Software, Version — for Windows NT 4.0 (Symantec) and no viruses were detected.

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. Japobrata Choudhury, HFD-715, Rm. 9B07
Ms. Jena Weber, (letter only) HFD-510, Rm. 14B04

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

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 21-202
Glucophage XR (Metformin HCl Extended Release Tablets)

July 11, 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 Glucophage XR (metformin HCl extended release tablets), NDA 21-202, submitted November 12, 1999. Additional reference is made to my July 5, 2000 telephone conversation with Ms. Jena Weber, in which she relayed Dr. Misbin's request for hospital records for Subject 009/007, who developed lactic acidosis and died while receiving extended release metformin.

At this time we are submitting the requested records. 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

WCR/ls/dk
Attachment(s)

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

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Glucophage XR (Metformin HCl Extended Release Tablets)

July 10, 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
Rockvilie, MD 20857

Dear Dr. Jenkins:

Reference is made to our pending New Drug Application for Glucophage XR (metformin HCl extended release tablets), NDA 21-202, submitted November 12, 1999. Additional reference is made to an April 10, 2000 facsimile transmission from Dr. Japobrata Choudhury, providing requests for additional information pertaining to NDA 21-202 (copy, with annotations, attached).

The last item in Dr. Choudhury's request (number 13 on the attached, annotated copy) was for statistical sections of NDA 21-202 in pdf format on a CD-ROM. We are now providing the requested information.

The electronic portion of this submission consists of 25 files and nine folders on one CD-ROM which is enclosed in the Archival copy submitted to the Division. The total size of the electronic submission is approximately 14.5MB. The file was screened for known viruses on July 6, 2000 with Norton Antivirus Software, Version —— for Windows NT 4.0 (Symantec) and no viruses were detected.

An additional copy of the CD-ROM has been provided to Dr. Choudhury as a desk copy. The attached table provides comments which describe the files in the electronic submission.

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

WCR/JBS/pak

Desk Copies: Dr. Japobrata Choudhury, HFD-715, Rm. 9B07
Ms. Jena Weber, HFD-510, Rm. 14B04

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

ORIG AMENDMENT

ORIGINAL

NDA AMENDMENT

NDA 21-202
Glucophage®XR (metformin HCl extended release tablets)

June 30, 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 Glucophage®XR (metformin HCl extended release tablets), NDA 21-202. Reference is also made to a telephone conversation on June 2, 2000 between Dr. Lee (FDA, Office of Post-Marketing Drug Risk Assessment) and Ms. M. Brown (Bristol-Myers Squibb) concerning the draft bottle labels for the Glucophage® XR 500 mg tablets. In that conversation, Dr. Lee requested a pdf version of the labels. The pdf files were provided to Dr. Lee on June 14. Prior to sending the pdf files to Dr. Lee, Ms. M. Brown discussed some minor changes that have been made to the draft labels since the original NDA filing. This submission presents the revised labels provided to Dr. Lee.

Attachment I provides a copy of the email that Bristol-Myers Squibb sent on June 14, 2000.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the Glucophage®XR (metformin HCl extended release tablets) draft bottle labels that have been implemented since the November 12, 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

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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BS

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

RESPONSE TO FDA REQUEST FOR INFORMATION

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

NDA 21-202
Metformin Hydrochloride Extended Release Tablets

June 29, 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 extended release tablets, NDA 21-202, submitted November 12, 1999. Additional reference is made to the following:

- April 10, 2000 facsimile transmission from Dr. Japobrata Choudhury, providing requests for additional information pertaining to NDA 21-202. (Attachment 1)

- May 18, 2000 facsimile transmission from BMS to Dr. Choudhury (Attachment 2) which included a concept sheet and hardcopy samples of materials provided in the electronic submission for NDA 21-202.

- May 24, 2000 teleconference between Dr. Choudhury and BMS representatives, at which certain of Dr. Choudhury's requests were discussed and clarified.

- May 24, 2000 telephone conversation between Dr. Choudhury and myself (following the aforementioned teleconference) in which Dr. Choudhury indicated that BMS should provide mean changes in HbA1c, by site, to supplement the data which had been submitted electronically in appendices 10.1 to the study reports.

In order to facilitate linking of specific items in Dr. Choudhury's request to our responses, we have assigned a number to each and have so annotated the copy of the April 10 communication herein. Please refer to these annotations to identify the responses, listed by item number, in the Table of Contents for Attachment 3.

At this time we are providing a partial set of responses, as Dr. Choudhury requested that we submit those responses that have been completed as soon as they become available. Responses to items 1, 2, 6, 7, 8, 9 and 10 are provided in this submission. The remainder of the responses will be provided in the near future. Additionally, Dr. Choudhury agreed that a response to item 11 was not required, since Bristol-Myers Squibb is not making a claim of equivalence between the two dose forms, designated as IR and XR in the request.

If you have any questions, 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. Japobrata Choudhury (HFD-715, PKLN 9B-07)
Ms. Jena Weber (HFD-510, PKLN 14B-04)

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 21-202
Metformin Hydrochloride Modified Release Tablets

June 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
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 modified release tablets, NDA 21-202. Reference is also made to a telephone conversation on March 16, 2000 between Dr. X. Ysern and myself (Bristol-Myers Squibb) discussing a change to the Chemistry, Manufacturing and Controls (CMC) section of the NDA that Bristol-Myers Squibb would like to submit. This change involved the addition of a ——— bottle presentation (sample packs only).

Since that phone conversation, other minor changes have been made that Bristol-Myers Squibb is submitting in this amendment as well. These changes involve the addition of ——— ——— DMF page references for all the ——— ——— procedures.

Reference is also made to a telephone conversation on April 11, 2000 between Dr. X Ysern and myself (Bristol-Myers Squibb) concerning the location (page references) of the information for the ———) in the Drug Master Files listed in the NDA. A summary of the action required by Bristol-Myers Squibb based on Dr. X. Ysern's request was faxed on April 12, 2000. In addition, the fax made reference to the amendment that Bristol-Myers Squibb was planning to file and summarized the information that would be included.

Reference is also made to a telephone conversation on April 17, 2000 between Dr. X Ysern and myself (Bristol-Myers Squibb) concerning whether he received the Drug Master File page references from the vendors for the ——————————————— that he requested. As a result of the conversation, the information requested by Dr. X. Ysern was faxed by Bristol-Myers Squibb on April 24.

Attachments I and II provide copies of the faxes that Bristol-Myers Squibb sent on April 12 and 24, 2000, respectively.

In accordance with 21 CFR 314.60, this NDA is being amended to present changes/updates to the metformin hydrochloride modified release drug product sections which have been implemented since the November 12, 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 of the hard copy or the bookmarks within the electronic version.

The total size of the electronic submission is less than 4 MB. There are 27 files and 12 folders. The files have been checked for viruses on 6-13-00 with Norton Antivirus Software (Version —— 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.

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)

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

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Metformin Hydrochloride Extended Release Tablets

April 12, 2000

Mr. R. Andros
Supervisory Investigator
District Office
U.S. Food and Drug Administration
22201 23rd Dr. SE
Bothell, WA 98021

Dear Mr. Andros:

Please refer to our pending New Drug Application for Metformin Hydrochloride Extended Release Tablets, NDA 21-202. Additional reference is made to the request of FDA Investigator Carl Anderson for monitoring reports of ——— for Dr. Leslie Klaff's investigational site. This request was conveyed to Bristol-Myers Squibb by the study coordinator, ———

At this time we are providing monitoring reports of ——— for Dr. Klaff's site. These documents contain proprietary information and are considered confidential.

Copies of this letter and the monitoring reports are also enclosed, in a separate envelope, labeled "Forward to Carl Anderson, FDA Investigator, regarding review of Dr. Klaff's investigational site." A desk copy of these materials is also being provided to Dr. Roy Blay, Division of Scientific Investigations, and this letter will be provided to NDA 21-202.

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

Sincerely,

Warren C. Randolph

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

WCR/ls/dk
Attachments

Desk Copies: Dr. Roy Blay (HFD-46, Room 107)
Ms. Jena Weber (HFD-510, Room 14B04)
(2 copies – letter only) for NDA 21-202

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

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
(metformin hydrochloride extended release tablets)

March 27, 2000

Roy Blay, Ph.D.
Good Clinical Practices, Branch I
Division of Scientific Investigations
Office of Medical Policy, Room 107
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Dear Dr. Blay:

Reference is made to our pending New Drug Application for metformin hydrochloride extended release tablets, NDA 21-202. Additional reference is made to our telephone conversation of March 13, 2000 in which you requested information pertaining to 3 investigators (listed below) that participated in the Phase III double-blind trials included in NDA 21-202:

- Dr. Gregory Ledger (participated in study CV138-012 – site No. 036);
- Dr. Leslie Klaff (participated in study CV138-012 – site No. 018); and
- Dr. Daniel Nadeau (participated in study CV138-036 – site No. 078).

The information requested for each investigator follows:

- Copy of signed Form FDA 1572
- Protocol and cover letters for revisions
- Tabular listings of:
  - Number of subjects who entered and completed each arm

  - Number who dropped out and reasons
  - Number of protocol violations and descriptions
  - Primary efficacy listings by patient
  - Listing of all serious AEs
  - Listing of concomitant medications
  - Listing of laboratory abnormalities
- Randomization list
- Blank case report form (CRF)
- One randomly-selected, completed CRF (for a subject who completed the study)
- Beginning and end date for study at site

In a separate volume, the following items were requested:

- Protocol numbers for sites to be inspected (i.e. – CV138-012 or CV138-036)
- Numbers for sites being inspected
- Names of investigators at sites being inspected and their addresses
- Name, address and title of monitoring organization for each site to be inspected
- Names of individual monitors and dates each site was monitored
- Yes/no answer as to whether original subject records were reviewed during monitoring visits
- Monitoring SOP for each site, with amendments and site applicability
- Copies of monitoring logs

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 21-202. If you have any questions regarding this submission, I can be reached at (609) 252-5228.

Sincerely,

Warren C. Randolph

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

WCR/HMK/dk
Attachments

Desk Copy: Ms. Jena Weber (2 copies - letter only) for NDA 21-202
(HFD-510, Room 14B04)

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6228 Fax: 609 252-6000

ORIGINAL
NEW [redacted] SEQ
SV

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 13 2000
HFD-510

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

FOUR MONTH SAFETY UPDATE

NDA 21-202
Metformin Hydrochloride Extended Release Tablets

March 10, 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

No review needed 3-27-00 /S/
/S/ 3/29/00 3/27/00

Dear Dr. Jenkins:

Reference is made to our pending New Drug Application for metformin hydrochloride extended release tablets, NDA 21-202. 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 214 MB and has been provided on 1 CD-ROM disk to the Central Document Room. There are approximately 182 files and 65 folders.

The files have been checked for viruses on March 9, 2000 with Norton Antivirus Software (Version —— for Windows NT 4.0) and no viruses were detected.

If there are any questions, please call 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/HMK/dk

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

Warren C. Randolph

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Metformin Hydrochloride Extended Release Tablets

February 23, 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 extended release tablets, NDA 21-202. Additional reference is made to our phone conversations on February 3 and 15, 2000 in which you requested the following information pertaining to the Phase III double-blind trials in our NDA 21-202:

- 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.

Attached to this letter is a table containing the requested information. The table is sorted by study number and alphabetically by investigator last name.

Two copies of the cover letter for this submission are being provided (as desk copies to Ms. Weber) for NDA 21-202. 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, Metabolic/Endocrine Products
FDA Liaison and Global Strategy
Regulatory Science

WCR/HMK/dk
Attachments

Desk Copy: Ms. Jena Weber (2 copies - letter only) for NDA 21-202
(HFD-510, Room 14B04)

Bristol-Myers Squibb
Pharmaceutical Research Institute

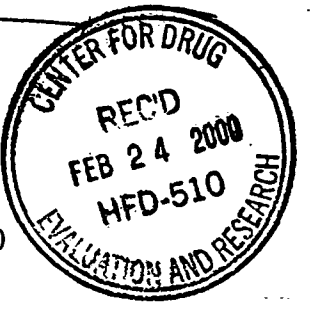
P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

ORIGINAL

52

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

RESPONSE TO FDA REQUEST FOR INFORMATION



NDA 21-202
Metformin Hydrochloride Extended Release Tablets

February 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 metformin hydrochloride extended release tablets, NDA 21-202. Reference is also made to the FDA facsimile of January 10, 2000 (attached) which contained four requests for additional material and information. We are now providing the responses to that facsimile.

Please refer to the table of contents for the location of each of our responses. For the convenience of the reviewer, the comments from the FDA facsimile have been reproduced and followed by the response.

Item 1 requested a floppy disk containing the proposed labeling. Contained within Ms. Weber's desk copy of this submission is a 3.5" floppy disk containing the proposed package insert as two Word 97 files. One file presents the insert showing the changes made to the Glucophage®insert, while the other displays the insert with all changes incorporated. A printout of each file is also provided.

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

Sincerely,

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

WCR/HMK/dk
Attachment

Desk copy with floppy disk: Ms. J. Weber (HFD-510, Room 14B04)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

RESPONSE TO FDA REQUEST FOR INFORMATION

NDA 21-202
Metformin Hydrochloride Extended Release Tablets

November 24, 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 Extended Release Tablets, NDA 21-202. Additional reference is made to our pending New Drug Application for Metformin Hydrochloride/Glyburide Tablets, NDA 21-178 and the teleconference of October 22, 1999 with Dr. Lee Ping Pian of the FDA.

During the teleconference, Dr. Pian requested additional data sets from those contained in our initial NDA submission for NDA 21-178. Dr. Pian also expressed that she would be interested in obtaining the same type of information for the NDA 21-202 filing.

We are now providing a CD-ROM disk containing the requested data sets for the efficacy studies contained in our initial NDA submission for NDA 21-202. Details of the additional data sets are as follows:

1. Inclusion of a single variable that identifies patients in analysis and supplemental data sets included in the initial submission that did not yet contain this patient identifier.

2. Addition of a treatment variable to the data set Dispstx.xpt for studies CV138-010, CV138-036 and CV138-012.

3. New data sets containing one record for each patient at each protocol-specified visit for each efficacy variable. One data set is provided per study. The data sets should contain:

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

   b) For each time point, the measurement value or the last prior measurement in case no measurement was taken (i.e., last observation carried forward approach). This type of information is contained in variable LOCF.

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

Sincerely,

Warren C. Randolph

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

WCR/JBS/AG/jh

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

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 21-202
Metformin Hydrochloride Extended Release Tablets

November 12, 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 an extended release tablet dose form of metformin hydrochloride, NDA 21-202. As background to this application, 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 an extended release dose form of Metformin were discussed.

- Our December 23, 1997 submission of plans for a steady-state study of dose proportionality and intra-subject variability with the extended release product and for three trials of the safety and efficacy of this product. In this submission we also proposed that additional studies should not be required to support the use of the extended release product with sulfonylureas.

- My January 30, 1998 telephone conversation with Dr. Misbin, in which he provided comments on the clinical trial plans submitted December 23, 1997.

- February 25, 1998 teleconference between BMS representatives and Dr. Misbin, in which the designs of the safety and efficacy trials with the extended release product were further discussed.

- My July 30, 1998 telephone conversation with Ms. Jena Weber, in which she indicated that reviewers had noted "NAI" (no action indicated) by the text in our December 23, 1997 submission which proposed that no additional studies should be required to support the use of the extended release product with sulfonylureas.

- August 11, 1998 teleconference between BMS representatives and Drs. Ahn and Fossler, concerning the design proposed by BMS for a food effect study. In this discussion it was agreed that certain departures from FDA's guidance on such studies were appropriate, such as designing the trial around the evening meal and having a six hour fast (post-lunch), for the study of food effects on this product.

- Our May 28, 1999 submission of the proposed tradename, "Glucophage —', for the extended release product and my telephone conversation of July 13, 1999, in which Dr. Ysern indicated that the Labeling Committee had no objection to this tradename.

- My October 3, 1999 telephone conversation with Ms. Peggy Hair, in which she assigned the number 21-202 to this NDA.

The bioavailability and pharmacokinetic characteristics of the extended release product, including the effects of food, dose proportionality and intra-subject variability, are described in three studies provided in this application. In addition, data from a study of the pharmocodynamics and pharmacokinetics of the extended release product in type 2 diabetics are included.

Three double-blind, controlled, randomized trials were conducted to demonstrate the safety and efficacy of the extended release product, administered once daily. Two placebo-controlled trials were conducted in type 2 diabetic subjects who had inadequate glycemic control with diet and exercise; one of these examined the effects of a range of doses of the extended release product. The third study was conducted in subjects with good to moderate glycemic control on a regimen of Glucophage®, 500mg BID, who were then randomized to either continue on Glucophage® or receive one of two doses of the extended release, given once daily.

Results of these clinical trials showed the following with the extended release product, dosed once daily:

- Highly significant improvement in glycemic control, compared to placebo;

- Maintenance of clinically equivalent glycemic control in subjects switched from Glucophage®; and

- Safety profile similar to that for Glucophage.

Via this submission, we wish to propose a different tradename from that previously submitted for consideration for the extended release product. The tradename for which we are seeking approval is:

Glucophage ® XR

We would appreciate a decision concerning this tradename as soon as possible, so that we can move forward with labeling for the product.

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

The total size of the electronic submission is approximately 298 MB. There are approximately 325 files and 112 folders.

The files have been checked for viruses on November 5, 1999 with Norton Antivirus Software (Version ——— for Windows NT 4.0) and are virus free.

The electronic submission has been provided on one CD-ROM disk 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.

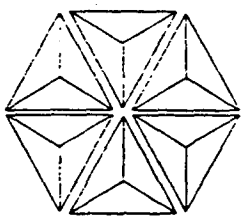
Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Science

WCR/ls/dk

Desk Copies: Dr. Robert Misbin – Vol. 1.1 – 1.3 (HFD-510, Room 14B04)
Dr. L. P. Pian – Vol. 1.1 – 1.3 (HFD-714, Room 14B18)
Ms. Jena Weber - Vol. 1.1 – 1.3 (HFD-510, Room 14B04)
Dr. Xavier Ysern (cover letter only) (HFD-510, Room 14B04)



BRISTOL-MYERS SQUIBB
PHARMACEUTICAL RESEARCH INSTITUTE

METFORMIN MODIFIED RELEASE TABLETS
FINANCIAL DISCLOSURE INFORMATION

CONTENTS **PAGE**

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

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
[signature]	Nov 10, 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

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

WITHHOLD 50 PAGE (S)

Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND 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 CV138-012 and/or CV138-036 (*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.

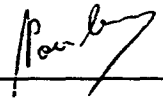
☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ 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
	NOV 10, 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

FORM FDA 3455 (3/99)

Created by Electronic Document Services/USDHHS: (301) EF

WITHHOLD 2 PAGE (S)

Information Request after a Preliminary Look at the Responses

Mr. Warren C. Randolph
Director, US Regulatory Liaison
Bristol-Myers Squibb Company
P.O. Box 40
Princeton, NJ 08543-4000 Phone: (609) 252-5228 Fax: (609) 252-6000

Subject: Request for clarification from the Statistical Reviewer,
Japo Choudhury Phone: (301) 827- 3110 Fax: (301) 443-9279

Reference: NDA #21-202 Glucophage® XR (metformin hydrochloride extended release tablets)

Thank you for the review aids.

I need clarification on the following:

1. Study 036 - Vol. 1.32, p.109 shows that 13 patients dropped out of the 500mg QD group due to inadequate glycemic control. In such patients, one would expect the change from baseline in HbA_{1c} to be positive. However, the graph for such changes provided on p.53 of the 6-29-00 submission shows 11 patients for whom the respective means before dropout were positive and 4 dropouts whose mean changes was negative.

Also, there were in all 27 dropouts from the above treatment group. In the above graph, only 15 patients were represented. Were there no measurements for the remaining patients?

In the same graph, why there is no representation of placebo completers?

2. Page 63 of your 7-19-00 submission states, "Gender, duration of diabetes, and use of prior anti-hyperglycemic medication were the only variables found to show a significant effect at the $\alpha = 0.10$ level in the Simple Augmented Models."

Page 107 of the same submission states, "In augmented models, the effects of use of prior anti-hyperglycemic medication, baseline HDL-cholesterol, body mass index, baseline fructosamine, and duration of diabetes are significant at the 0.10 level."

In the first instance, all covariates/factors were to be investigated. In the second, specifically, those with baseline imbalances were to be investigated, although other covariates/factors clearly affecting the response could be included as well. Kindly explain the above two apparently mis-matching statements.