CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-202

ADMINISTRATIVE DOCUMENTS

~~CORRESPONDENCE~~

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-202/SE____-____

Drug METFORMIN HCl E-R Applicant BMS

RPM J. WEBER Phone 827-6422

☑ 505(b)(1)
☐ 505(b)(2) Reference listed drug ____

☐ Fast Track ☐ Rolling Review Review priority: ☑ S ☐ P

Pivotal IND(s) ____

Application classifications:
Chem Class 3
Other (e.g., orphan, OTC) S

PDUFA Goal Dates:
Primary 9/12/00
Secondary 11/12/00

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑ User Fee Paid # 3831
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☑ AP ☐ AE ☐ NA
- Labeling & Labels
  FDA revised labeling and reviews..... 10/12/00
  Original proposed labeling (package insert, patient package insert) 11/12/97
  Other labeling in class (most recent 3) or class labeling..... N/A
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels ..... See OPDRA reviews
  Nomenclature review ..... ~ 4/25/00
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☑ is not on the AIP.
  Exception for review (Center Director's memo)..... N/A
  OC Clearance for approval..... N/A

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments _____
  - Copy of Applicant's commitments _____

- Was Press Office notified of action (for approval action only)? ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper _____

- Patent
  - Information [505(b)(1)] ✓
  - Patent Certification [505(b)(2)] NA
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] _____

- Exclusivity Summary ✓

- Debarment Statement ✓

- Financial Disclosure
  - No disclosable information _____
  - Disclosable information – indicate where review is located ✓

- Correspondence/Memoranda/Faxes ✓

- Minutes of Meetings ✓
  - Date of EOP2 Meeting N/A
  - Date of pre NDA Meeting 5/24/99 CMC only
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting N/A
  - Date of Meeting _____
  - Questions considered by the committee _____
  - Minutes or 48-hour alert or pertinent section of transcript _____

- Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) 1/3/00 - Group Leader's memo
- Clinical review(s) and memoranda ✓ 9/28/00

Continued ⇨

- Safety Update review(s) ..... ✓ IN MOR REVIEW

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☑ Not Applicable

- Statistical review(s) and memoranda ..... _____

- Biopharmaceutical review(s) and memoranda..... ✓ 8/25/00

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... ✓

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... ✓ 6/7/00
  ☑ Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda ..... ✓ 9/25/00

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- DMF review(s) ..... ✓

- Environmental Assessment review/FONSI/Categorical exemption ..... ✓ CATEGORICAL EXEMPTION GRANTED

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report) Pending on 30-AUG-2000 AC 9/26/00
  Date completed ~~8/16/00~~ ..... ☑ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☑ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... ✓ 7/12/00

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

Fax 6/30/00
SUBMISSION

Introduction

This amendment presents updated draft labels for the Glucophage® XR 500 mg tablets packaged in 100- and 500-count bottles.

Reference is 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 presented in the original NDA (Volume 1.7, pages 145-147).

APPEARS THIS WAY
ON ORIGINAL

Labels

A copy of the updated draft labels for the Glucophage® XR 500 mg tablets packaged in 100- and 500-count bottles to include minor changes that have been made to the labels presented in the original NDA (Volume 1.7, pages 145-147) are being provided at this time on the following pages.

The minor changes made to the draft labels are summarized below:

- The "extended release tablets" have been moved inside the parentheses instead of outside the parentheses as previously presented in the original NDA.

- The word "hydrochloride" previously presented in the original NDA has been abbreviated to "HCl".

In addition, the color scheme of the draft labels is summarized below:

- The color of "*Glucophage®*" is Red.

- The color of "XR" is Purple.

- The color of "*500 mg*" is Purple.

- The color of all the remaining text is Black.

PATENT INFORMATION

The Glucophage® (metformin) formulation product described in Bristol-Myers Squibb Company's NDA No. 21-202 for which approval has been applied for November 12, 1999, is not covered by any patents.

In accordance with 21 CFR § 314.53(c)(2)(ii)(3) and § 314.53(d)(2)(D)(iii), certification of the fact that no patents claim the new Glucophage® formulation product described in this NDA is made on the attached sheet.

CERTIFICATION OF PATENT INFORMATION

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

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

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

Dated: November 12, 1999

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Checklist

NDA: 21-202				
Trade Name: GLUCOPHAGE XR				
Generic Name: METFORMIN HCl EXTENDED RELEASE TABLETS				
Applicant Name: BMS				
Division: 510				
Project Manager: J WEBER				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	✓	No	
b. Is it an effectiveness supplement?	Yes		No	✓
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	✓	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	3 YEARS			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes	✓	No	
If yes, NDA # 20-357				
Drug Name: Glucophage (METFORMIN) TABS				

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	Yes	✓	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	✓	No	

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

Drug Product GLUCOPHAGE (METFORMIN) TABLETS	
NDA # 20-357	
Drug Product	
NDA #	
Drug Product	
NDA #	

2. Combination product.	Yes		No	—
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	

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

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	

NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

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If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:	010 (Placebo controlled)			
Investigation #2, Study #:	036 (Placebo controlled)			
Investigation #3, Study #:	012 (active controlled)			
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	✓
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	✓
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the				

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application or supplement that is essential to the approval (i.e., the investigations listed in #2 (c), less any that are not "new"):

Investigation #1	010
Investigation #2	012
Investigation #3	036

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 012	Yes	✓	No	
IND#: ———				
Explain: US SNDY				
Investigation #2 036	Yes	✓	No	
IND#: ———				
Explain: US + OVERSEAS SNDY				
Investigation #3 10	Yes		No	✓
IND#:				
Explain: OVERSEAS SNDY				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 N/A	Yes		No	
IND#:				
Explain:				
Investigation #2 N/A	Yes		No	
IND#:				
Explain:				
Investigation #3 N/A	Yes		No	
IND#: Sponsor conducted				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	—
If yes, explain:				

BACK TO TOP

Signature of PM/CSO [/S/] 8/1/00
Date:

APPEARS THIS WAY
ON ORIGINAL

Signature of Division Director [/S/]
Date: 10/13-00

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

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BACK TO TOP

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21202	**Trade Name:**	GLUCOPHAGE XR (METFORMIN HCL) 500MG ER T
Supplement Number:		**Generic Name:**	METFORMIN HCL
Supplement Type:		**Dosage Form:**	EXT
Regulatory Action:	PN	**Proposed Indication:**	For use in patients with type 2 diabetes who are not adequately controlled on diet and exercise alone.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

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

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENA WEBER

[/S/]

Signature

8/29/00

Date

APPEARS THIS WAY
ON ORIGINAL

GLUCOPHAGE XR

DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this New Drug Application.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN - 6 2000

Daniel A. Nadeau, M.D.
Diabetes Endocrine & Nutrition Center
905 Union Street, Suite 11
Bangor, Maine 04401

Dear Dr. Nadeau:

On April 18 and April 19, 2000, Mr. Garry Stewart, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocol #CV138-036-078) of Glucophage® (metformin hydrochloride extended release tablets) that you conducted for Bristol-Myers Squibb Pharmaceuticals. From our evaluation of the inspection report prepared by Mr. Stewart, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator Stewart during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY - 8 2000

Gregory A. Ledger, M.D.
St. John's Medical Research Group
1900 South National Avenue, Suite 2960
Springfield, MO 65804

Dear Dr. Ledger:

Between April 11 and April 13, 2000, Mr. Carl Montgomery, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocol # CV 138-012) of metformin that you conducted for Bristol-Myers Squibb. From our evaluation of the inspection report prepared by Mr. Montgomery, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Leslie J. Klaff, M.D.
Rainier Clinical Research Center, Inc.
4033 Talbot Road South
Renton, CA 98055

MAY - 8 2000

Dear Dr. Klaff:

Between April 10 and April 18, 2000, Mr. Carl Anderson, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocol # CV 138-012) of metformin that you conducted for Bristol-Myers Squibb. From our evaluation of the inspection report prepared by Mr. Anderson, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator Anderson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

SEP 12 2000

MEMORANDUM

DATE: September 11, 2000

FROM: John K. Jenkins, M.D.
Director
Office of Drug Evaluation II, HFD-102

/S/ 9/11/00

TO: NDA 21-202

SUBJECT: Overview of review issues

/S/ 10-13-00

Administrative

NDA 21-202 for Glucophage XR (metformin hydrochloride extended-release tablets) was submitted by Bristol-Myers Squibb on November 12, 1999. The application was assigned a standard review. The current user fee 10-month goal date for this application is September 12, 2000.

Clinical/Statistical

The proposed indication for Glucophage XR is the once daily treatment of Type 2 diabetes, either as monotherapy or in combination with a sulfonylurea or insulin. BMS is also the NDA holder for Glucophage (metformin hydrochloride tablets), which has been marketed in the US for several years, and Glucovance (glyburide and metformin hydrochloride tablets), which was approved on July 31, 2000. In support of the proposed indication for Glucophage XR, the sponsor submitted the results of three phase-3 trials. The first two trials (138-010 and 138-036) were randomized, double-blind, placebo-controlled, 24- and 16-week trials in patients with Type 2 diabetes who were not adequately controlled on diet and exercise alone. The third trial (138-012) was a randomized, double-blind, 24-week comparison of Glucophage 500 mg twice daily to Glucophage XR 1000 or 1500 mg once daily in patients previously treated with Glucophage 500 mg twice daily for at least 8 weeks who met certain criteria for adequate glycemic control. Please refer to the medical officer review prepared by Dr. Misbin and the statistical review prepared by Dr. Chowdhury for their comments and analyses on the clinical portion of this application.

In addition to the medical officer and statistical review for this NDA, I reviewed volumes 1.2 (application summary) and 1.28-1.31 (study report for study 138-012). The review of these volumes was necessary to clarify the design of study 138-012 with regard to inclusion criteria. Review of these volumes was also necessary and to better understand the results of this comparative study to support decisions regarding inclusion of the data in the Glucophage XR package insert. In particular, my review does not support the sponsor's proposed claim of clinical equivalence of Glucophage and Glucophage XR

when dosed at the same nominal total daily dose twice daily and once daily, respectively (see below).

Studies 138-010 and 138-036, the placebo-controlled studies, demonstrated the effectiveness of Glucophage XR versus placebo in patients with Type 2 diabetes not adequately controlled on diet and exercise alone. Study 138-036 was a dose comparison study of Glucophage XR doses ranging from 500 to 2000 mg once daily as well as 1000 mg twice daily. This study showed an increasing ordering of HBA1C response from 500 to 1500 mg once daily, but did not show any difference between 1500 and 2000 mg once daily in this patient population. Of note, the 1000-mg twice-daily group showed better HBA1C response than the 2000-mg once-daily group (mean change from baseline to week 12 of –1.17% and –0.95%, respectively). This observation may be a reflection of more consistent plasma levels of metformin over the 24-hour dosing cycle in the 1000-mg twice-daily group than the 2000-mg once-daily group (see comments below under Clinical Pharmacology and Biopharmaceutics). While Glucophage XR has been shown to be effective when given once daily in these two studies, it appears that additional lowering of HBA1C may be achieved when the drug is given in divided doses twice daily. These data should be included in the package insert to inform physicians of this option.

Study 138-012 was an active-controlled trial with no concurrent placebo group. Patients who entered this trial were previously treated with 500 mg twice daily of Glucophage and met certain criteria for adequate glycemic control. However, no attempt was made to titrate patients who entered the study to a certain goal of glycemic control on Glucophage before they were randomized to Glucophage 500 mg twice daily, Glucophage XR 1000 mg once daily, or Glucophage XR 1500 mg once daily. The statistical analysis plan for this study only specified analysis of the mean change from baseline in HBA1C within each group, no between group analyses were planned. The design and analysis plan of this study limit the interpretation of the data obtained. The failure to titrate patients to a desired target glycemic control on Glucophage twice daily at baseline in a rigorous manner increased the likelihood that any true differences in the effectiveness of the two regimens may not have been detected during the relatively short primary treatment comparison (i.e., 12 weeks). In other words, the study did not have much sensitivity to detect any true differences between the two regimens. The study also was not powered as a non-inferiority study, in fact no between group comparisons were specified in the plan.

Despite the limitations of the study design, it is of interest that the only group in study 138-012 that demonstrated a significant increase from baseline in HBA1C was the Glucophage XR 1000-mg once-daily group (0.23%, 95% CI 0.10-0.37 at 12 weeks). While all three groups demonstrated a mean increase in HBA1C during the study, the results suggest that at equal nominal total daily doses Glucophage twice daily may be more effective than Glucophage XR once daily. This result seems consistent with the observations in study 138-036 that Glucophage XR twice daily may be more effective than Glucophage XR once daily at the same nominal total daily dose.

The differences noted above in study 138-012 in HBA1C were not reflected in fasting-plasma glucose (FPG) at 12 weeks. In this study, the Glucophage 1000-mg once-daily dose was administered with the evening meal and the Glucophage 500-mg twice-daily doses were administered with the morning and evening meals. It is likely that the plasma levels of metformin were more similar between the Glucophage and Glucophage XR groups in the morning than they were just prior to the evening meal given the known pharmacokinetic profiles of these two formulations (no PK data were collected in study 138-012). The PK profile, combined with the overnight fast, would likely result in similar AM FBG values.

Unfortunately, the study design did not include plasma glucose measurements at the end of the Glucophage XR dosing interval (i.e., before the evening meal). Patients were asked to measure their serum blood glucose (SBG) four times daily during the study (pre-morning meal, 1-hour post-morning meal, pre-evening meal, and 1-hour post-evening meal). The mean of average daily SBG values correlated well with the findings noted above for HBA1C; i.e., all groups showed a small increase in mean average SBG by week 12 and 24 with the largest increase occurring in the Glucophage XR 1000-mg once-daily group. The mean changes in average daily SBG at 12 weeks were 6.09, 9.31, and 2.38 mg/dL for Glucophage 500 mg twice daily, Glucophage XR 1000 mg once daily, and Glucophage 1500 mg once daily, respectively. The mean SBG at the four different times during the day generally supported a conclusion that Glucophage XR 1000 mg once daily may be less effective at the end of the dosing interval compared to Glucophage 500 mg twice daily. For example, at week 12 the mean change from baseline in SBG 1-hour post-evening meal was 3.99, 13.93, and 6.57 mg/dL for Glucophage 500 twice daily, Glucophage XR 1000 once daily, and Glucophage XR 1500 once daily, respectively.

The clinical significance of the small increases in HBA1C, average SBG, and end-of-dosing interval SBG is not clear from this study since clinical endpoints of diabetes complications were not measured and the study was not of adequate duration. However, given the current goal of closely controlling HBA1C and fluctuations of blood glucose during the day (i.e., postprandial fluctuations), dosing Glucophage XR once daily may not provide the optimum glycemic control in some patients. It may be that the optimum approach to clinical use of Glucophage XR is to dose the drug twice daily, as was suggested by the results of study 138-036.

It will be important to include in the package insert the results from study 138-012 along with appropriate caveats about the study design. The package insert should also include text recommending that patients switched from Glucophage to Glucophage XR at the same nominal daily doses be monitored for a change in their glycemic control so that the appropriate adjustments in the Glucophage XR dose, either an increase in mg of the once daily dose or a change to twice daily dosing, can be made to optimize glycemic control.

The approved indication for Glucophage includes combination use with a sulfonylurea or insulin. These indications were originally approved based on adequate and well-controlled trials in which Glucophage was added to either a sulfonylurea or insulin in

patients not adequately controlled on the single agent therapy alone. The sponsor has requested that these indications "carry over" to Glucophage XR despite the fact that no clinical trials of the combination of Glucophage XR and a sulfonylurea or insulin have been conducted. I believe that it is appropriate to grant these indications to Glucophage XR without need for specific new combination trials. There is no basis to conclude that Glucophage XR would not be effective in improving glycemic control in patients not adequately controlled on a sulfonylurea or insulin alone and there is no safety concern regarding the combination of these agents. This decision is consistent with previous agency actions on approval of extended-release products.

No new safety signals were detected in the clinical trials for Glucophage XR. Gastrointestinal adverse events (nausea, vomiting, and diarrhea) remained the most common drug-related adverse events, with no clear trend of a clinically significant difference between Glucophage and Glucophage XR. The maximum dose of Glucophage XR studied was 2000 mg/day. There were no cases of documented drug-related lactic acidosis in the clinical trials.

This application is approvable from a clinical/statistical perspective. The draft labeling submitted by the sponsor on September 1, 2000, requires significant revisions to more accurately reflect the results of the submitted studies and to better direct physicians in the use of Glucophage XR. The significant changes include presentation of the major efficacy findings from the three studies, presentation of the adverse events from the three studies, and changes to the dosing an administration section to address switching patients from Glucophage to Glucophage XR. In addition, there are numerous minor edits that need to be made in the entire labeling (see labeling comment that were faxed to the sponsor on September 8, 2000). Labeling negotiations are continuing at present with the sponsor.

No phase 4 clinical commitments have been requested from the sponsor. The sponsor will be reminded in the action letter of the requirement to submit a pediatric plan to address use of Glucophage XR in pediatric patients in compliance with the 1998 Pediatric Rule. Submission of pediatric data will be deferred until after approval of Glucophage XR in adults, consistent with the agency's stated approach to implementation of the 1998 Pediatric Rule.

[ ]

The sponsor will be encouraged to pursue these studies, but they will not be requested as phase 4 commitments since these issues will be addressed in labeling instructions for use.

Pharmacology/Toxicology

No preclinical studies were included in the NDA and none were required given the previous approval and marketing history of Glucophage and the nature of the inactive ingredients included in Glucophage XR.

This application is approvable from a pharmacology/toxicology perspective. No significant changes from the current Glucophage package insert are required in the preclinical sections of the labeling.

Chemistry, Manufacturing, and Controls

The sponsor proposes to market tablets containing 500 mg of metformin hydrochloride in an extended release tablet. Please refer to the reviews prepared by Dr. Ysern for a detailed analysis of the data submitted by the sponsor in support of this new tablet. The sponsor has adequately addressed all CMC issues; however, two foreign establishment inspections are still pending at this time.

This application is approvable from a CMC perspective pending receipt of satisfactory recommendations from the Office of Compliance regarding the two outstanding establishment inspections.

Clinical Pharmacology and Biopharmaceutics

Please refer to the review prepared by Dr. Shore for a detailed analysis of the clinical pharmacology and biopharmaceutics data submitted by the sponsor in support of Glucophage XR. Compared to Glucophage, Glucophage XR has a delayed Tmax (median 7 hours versus 3 hours), a Cmax that is reduced by 20-30%, and a similar AUC. The single-dose and steady state pharmacokinetic profiles of Glucophage XR are very similar. In both single-dose and steady state, there is a very wide fluctuation between peak and trough plasma levels of metformin, which may explain the findings noted above with regard to end-of-dosing interval efficacy. As was seen with Glucophage, plasma concentrations of metformin increase in less than a dose proportional manner after increasing doses of Glucophage XR. This observation appears to be related to decreased absorption at higher doses rather than any change in metformin elimination. Dr. Shore recommended a change in the dissolution specifications for Glucophage XR. The sponsor accepted the recommended change in their submission dated September 5, 2000.

This application is approvable from a biopharmaceutics and clinical pharmacology perspective with appropriate changes to the labeling as reflected in the fax labeling comments sent to the sponsor on September 8, 2000.

Data Integrity/Financial Disclosure

The Division of Scientific Investigations audited three clinical sites involved in the conduct of the phase 3 studies of Glucophage XR submitted in support of this application. All sites were rated as NAI and no Form 483 was issued at any site.

The sponsor has provided the appropriate certifications with regard to financial disclosure for investigators and financial arrangements between BMS and the study investigators.

There are no apparent financial conflicts of interest that raise questions about the integrity of the studies submitted in support of this application.

Labeling and Nomenclature

The sponsor has proposed the tradename Glucophage XR for this product. The sponsor currently markets an immediate-release metformin product under the tradename Glucophage and also markets a combination of glyburide and metformin under the tradename Glucovance. The proposed tradename, Glucophage XR is acceptable to the Division and OPDRA. The XR suffix has been used previously to differentiate extended-release products and is appropriate since it makes reference to the product formulation and not to any implied claim of superiority.

The package insert and patient package insert require further revision from the draft submitted by the sponsor on September 1, 2000. Comments on this submission were faxed to the sponsor on September 8, 2000, and we are currently awaiting the sponsor's reply. OPDRA made some suggestions regarding the carton and container labeling in their July 28, 2000, review. The sponsor has changed the carton and container labeling to be consistent with these recommendations in their August 24, 2000, submission and they are now acceptable.

Conclusions

This NDA should be APPROVED once the sponsor submits an acceptable draft package insert and patient package insert. In addition, satisfactory recommendations must be received from the Office of Compliance regarding the two manufacturing sites where the inspection results are pending.

cc:
NDA 21-202
HFD-510/Division File
HFD-510/Weber
HFD-102/Jenkins

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

/S/

Memorandum

AUG 29 2000

Date: 8/28/00

From: Saul Malozowski, MD, PhD
Medical Team Leader, Division of Metabolic and Endocrine Drug Products, HFD-510

Subject: Glucophage XR, NDA 21-202. Team leader recommendations

To: John Jenkins, MD
Acting Director, DMEDP, HFD-510
Director, Office of Drug Evaluation II, HFD-102

This memo is to concur with the recommendations of the primary reviewer, Dr. Misbin, to approve the Glucophage XR submission. The studies performed by the sponsor support the efficacy and effectiveness of this new formulation. No new safety signals emerged from the studies. Minor, labeling modifications are needed. These have been sent to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

MEMO

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum
Date: 07-JAN-00

NDA:	**21-202/N-000**	**Sponsor:**	**Bristol-Myers Squibb Co.**
IND:	—		
Brand Name:	Glucophage® XR	**Priority Classification:**	3S
Generic Name:	Metformin HCL extended release tablet	**Indication(s):**	Type 2 DM (alone or with SU or insulin)
Drug Class:	Biguanide	**Date of Submission:**	12-NOV-99
Dosage Form:	500mg tablet	**Route of Admin.:**	Oral
Dosing Regimen:	QD in PM upto 2gm	**Due Date of Review:**	20-JUN-00 (to TL) 20-AUG-00 (to PM)
Division:	DPE2	**Medical Division:**	DMEDP
Reviewer:	Robert M. Shore	**Team Leader:**	Hae-Young Ahn

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		Diskette
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies			
Mass Balance Study		X	
BA Studies			
Absolute BA		X	
Relative BA	X		
BE Studies		X	
Average BE			
Population BE			
Individual BE			
Food-Drug Interaction	X		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)		X	
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies			
PK, and Initial Safety and Tolerability in Healthy Volunteers		X	
Single Dose	X		
Multiple Dose	X		
PK, and Initial Safety and Tolerability in Patient Volunteers			
Single Dose	X		
Multiple Dose	X		

Dose Proportionality			
Single Dose	X		
Multiple Dose	X		
PK in Population Subsets to Evaluate Effects of Intrinsic Factors			
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors			
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies	X		
PK/PD studies in Volunteers		X	
PK/PD studies in patients	X		
Individual Datasets for all PK and PK/PD studies in electronic format	X		
Other			
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

Volumes submitted to Section 6: 1.1 - 1.3, 1.8-1.17. The data sets from the Section 6 studies are available in SAS electronic format; the rest of Section 6 of this NDA is available only in paper format.

Study synopses for the 4 studies submitted to Section 6 are provided on paper.

CV138-021: Pharmacokinetics and bioavailability of [redacted] metformin tablets relative to Glucophage® - Single dose of prototype formulations.

CV138-028: Steady state pharmacokinetics of metformin [redacted] tablet – Single and multiple dose PK/dose proportionality of [redacted] tablet.

CV138-031: Evaluation of the effect of food on the pharmacokinetics of metformin [redacted] tablet – Effect of fasting, high- and low-fat meal on single dose of [redacted] tablet.

CV138-035: The pharmacokinetics and pharmacodynamics of the [redacted] controlled release versus immediate release metformin tablet in type 2 diabetics – Multiple dose.

Assay methods and validation are included in the submission.

This application is X is not ___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)
Is exposure to metformin comparable between the IR and MR formulations?
Is there a food effect with the MR formulation?
Are the pharmacokinetics of the MR dosages proportional?
Is the dissolution method/spec acceptable?

Requests/Comments are _X__ are not ___ to be sent to firm. If any was sent, indicate the date of FDA letter.

Comments to be sent to Sponsor:
1. Please submit proposed labeling in Word format on 3.5" floppy diskette.

2. According to the submission two assays, both ——— were used for the quantitative determination of metformin in human plasma (Report No. 910062324 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 provided a summary of differences between them.

3. Dissolution data submitted in Section 6 consists of two pages (Vol. 1,8, p. 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 be submitted. Also, the sponsor should submit 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. Was any attempt made by the sponsor to develop a PK/PD relationship.

Sign/Date /S/ 07-JAN-00
Robert M. Shore, Pharm.D., Reviewer

/S/ 1/7/00
Hae-Young Ahn, Ph.D., Team Leader

CC: NDA 21-202/N-000, HFD-850(Electronic Entry or Lee), HFD-510(Weber, Misbin, Ysern, Steigerwalt), HFD-870(AhnH, HuangSM), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21202/000
Stamp: 12-NOV-1999
Regulatory Due: 12-SEP-2000
Applicant: BRISTOL MYERS SQUIBB
4000
PRINCETON, NJ 085434000
Priority: 3S
Org Code: 510

Action Goal:
District Goal: 14-JUL-2000
Brand Name: GLUCOPHAGE XR (METFORMIN HCL) 500MG ER T
Estab. Name:
Generic Name: METFORMIN HCL

Dosage Form: (EXTENDED-RELEASE TABLET)
Strength: 500-MG

Application Comment:
FDA Contacts: X. YSERN (HFD-510) 301-827-6420 , Review Chemist

Overall Recommendation:
Establishment: 2627673
BRISTOL LABORATORIES INC DIV BRISTOL MYERS CO
FOREIGN TRADE ZONE #7 RD #114
MAYAGUEZ, PR 00680
DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	30-NOV-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	01-DEC-1999	GMP			MTORRES
INSPECTION SCHEDULED	14-DEC-1999		15-JAN-2000		MTORRES
INSPECTION PERFORMED	24-MAR-2000		21-MAR-2000		MTORRES
PACKAGING / RELEASE TESTING ONLY.					
DO RECOMMENDATION	24-MAR-2000			ACCEPTABLE INSPECTION	MTORRES
PACKAGING/RELEASE TESTING ONLY.					
OC RECOMMENDATION	27-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: 1819504
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD EXPY
EVANSVILLE, IN 477210001
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TTR OAI Status: NONE
Estab. Comment: DRUG PRODUCT MANUFACTURE, PACKAGING AND TESTING (STABILITY AND RELEASE) AND IT IS ALSO A TESTER/CONTROL FACILITY FOR THE DRUG SUSBSTANCE (on 29-NOV-1999 by X. YSERN (HFD-510) 301-827-6420)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	30-NOV-1999	10D			FERGUSONS
DO RECOMMENDATION	30-NOV-1999			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO
GMP & PAI DATED 10/25-11/10/1999 REPORTED NO DEVIATIONS AND NO FDA-483 WAS ISSUED.					
OC RECOMMENDATION	01-DEC-1999			ACCEPTABLE	FERGUSONS

DISTRICT RECOMMENDATION

Establishment: 9611716
BRISTOL MYERS SQUIBB PHARMACEUTICAL LTD
L 46 1QW
MORETON, WIRRAL, MERSEYSIDE, , UK
DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: INSPECTION TO TAKE PLACE 9/11/00. INVESTIGATOR HAS BEEN TOLD TO FAX SOMETHING ASAP. (on 07-AUG-2000 by M. GARCIA (HFD-322) 301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	01-DEC-1999	10D			EGASM
ASSIGNED INSPECTION '	03-DEC-1999	GMP			EGASM
INSPECTION SCHEDULED	07-AUG-2000		13-SEP-2000		RKIMMEL

Establishment: [redacted]
DMF No: AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	01-DEC-1999	GMP			EGASM
ASSIGNED INSPECTION '	03-DEC-1999	GMP			EGASM
INSPECTION SCHEDULED	16-AUG-2000		18-SEP-2000		IRIVERA

Establishment: [redacted]
DMF No: AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
OC RECOMMENDATION	01-DEC-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities:
Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	30-NOV-1999	GMP			FERGUSONS
DO RECOMMENDATION	30-NOV-1999			ACCEPTABLE BASED ON FILE REVIEW	DPAGANO
PHI-DO CONDUCTED A GMP INSPECTION 9/99 AND WAS CLASSIFIED NAI.					
OC RECOMMENDATION	01-DEC-1999			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: [redacted]
DMF No: AADA:
Responsibilities:
Profile: TTR OAI Status: NONE
Estab. Comment: ESTABLISHMENT CHANGED NAME TO [redacted] EFF.2/9/99. CFN AND LABELER CODE REMAIN THE SAME.
(on 01-DEC-1999 by M. TORRES IRIZARRY (HFR-SE550) 787-729-6728)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	30-NOV-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	01-DEC-1999	GMP			MTORRES
INSPECTION SCHEDULED	14-DEC-1999		15-FEB-2000		MTORRES
INSPECTION PERFORMED	27-JAN-2000		21-JAN-2000		MTORRES
DO RECOMMENDATION	27-JAN-2000			ACCEPTABLE INSPECTION	MTORRES
OC RECOMMENDATION	28-JAN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: [redacted]
DMF No: AADA:
Responsibilities:
Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
OC RECOMMENDATION	30-NOV-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 2623458
SQUIBB MANUFACTURING INC
STATE RD #3 KM775
HUMACAO, PR 00791

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
SUBMITTED TO DO	30-NOV-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	01-DEC-1999	GMP			MTORRES
INSPECTION SCHEDULED	14-DEC-1999		15-MAR-2000		MTORRES
INSPECTION PERFORMED	15-MAR-2000		16-FEB-2000		MTORRES
OBSERVATION NOTED WAS CORRECTED DURING EI.					
DO RECOMMENDATION	15-MAR-2000			ACCEPTABLE INSPECTION	MTORRES
VALIDATION COVERED AND FOUND ADEQUATE.					
OC RECOMMENDATION	15-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-NOV-1999				YSERNX
OC RECOMMENDATION	30-NOV-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21202/000** Priority: **3S** Org Code: **510**
Stamp: **12-NOV-1999** Regulatory Due: **12-SEP-2000** Action Goal: District Goal: **14-JUL-2000**
Applicant: **BRISTOL MYERS SQUIBB 4000 PRINCETON, NJ 085434000**
Brand Name: **GLUCOPHAGE XR (METFORMIN HCL) 500MG ER T**
Established Name:
Generic Name: **METFORMIN HCL**
Dosage Form: **EXT (EXTENDED-RELEASE TABLET)**
Strength: **500-MG**

FDA Contacts: **X. YSERN (HFD-510) 301-827-6420 , Review Chemist**

Overall Recommendation:

Establishment: **2627673**
BRISTOL LABORATORIES INC DIV B
FOREIGN TRADE ZONE #7 RD #114
MAYAGUEZ, PR 00680
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE PACKAGER**
FINISHED DOSAGE RELEASE TESTER

Establishment: **1819504**
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD EXPY
EVANSVILLE, IN 477210001
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: **9611716**
BRISTOL MYERS SQUIBB PHARMAC
L 46 1QW
MORETON, WIRRAL, MERSEYSIDE,
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **INSPECTION SCHEDULED**
Milestone Date: **07-AUG-2000**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment:
DMF No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

AADA No:

[redacted]

Profile: CSN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 03-DEC-1999

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

[redacted]

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-DEC-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-DEC-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

[redacted]

Profile: TTR OAI Status: NONE Responsibilities: _____
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-NOV-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: 2623458
SQUIBB MANUFACTURING INC
STATE RD #3 KM775
HUMACAO, PR 00791

DMF No:
AADA No:

Profile: TTR OAI Status: NONE Responsibilities: FINISHED DOSAGE PACKAGER
Last Milestone: OC RECOMMENDATION FINISHED DOSAGE RELEASE TESTER
Milestone Date: 15-MAR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE Responsibilities: _____
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-NOV-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

APPEARS THIS WAY ON ORIGINAL

Establishment Information

The "Establishment Information" for this amendment is the same as that provided in the original NDA 21-202 filed November 12, 1999.

) **MEMORANDUM** **OFFICE OF POST-MARKETING DRUG RISK ASSESSMENT**

CENTER FOR DRUG EVALUATION AND RESEARCH
HFD-400; Rm 15B-03

CONSULT#: 00-0102

DATE: July 28, 2000

FROM: Lauren Lee, Pharm.D., Safety Evaluator
Medication Error Prevention, HFD-400

THROUGH: Jerry Phillips, R.Ph., Associate Director
Medication Errors Prevention, HFD-400

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

SUBJECT: NDA No. 21-202; Glucophage XR
(Metformin HCL Extended Release Tablets)

I. INTRODUCTION:

This memorandum is in response to a request received on July 20, 2000, from the Division of Metabolic and Endocrine Drug Products, to review the revised container labels for Glucophage XR.

According to a letter dated June 30, 2000, Bristol-Myers Squibb Company stated that on June 2, 2000, OPDRA requested colored copies of the labels and labeling. However, the pdf files containing Glucophage XR container labels were received after the completion of the review. The final copy of the review was signed and sent to the Division on June 6, 2000, and the revised labels were received on June 14, 2000.

II. BACKROUND:

The proposed proprietary name, Glucophage XR, was previously reviewed by the Office of Post-Marketing and Drug Risk Assessment (OPDRA) on June 6, 2000. We had no objections to the use of the proprietary name, Glucophage XR. However, we recommended careful monitoring and sufficient education regarding the difference between Glucophage XR and Glucophage upon the launch of this product. Furthermore, as part of the consult, OPDRA reviewed the proposed container labels and the package insert labeling for possible interventions in minimizing medication errors. In reference to the proposed container labels,

OPDRA recommended the following:

The container labels for Glucophage XR and Glucophage (500 mg) 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 Glucophage XR proposed labels.

III. REVISED CONTAINER LABEL (500 mg)

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.

IV. CONCLUSION

OPDRA recommends the above revisions for the container labels that might lead to the safer use of the product.

If you have further questions or need clarification, please contact Lauren Lee, Pharm.D. at 301-827-3243.

Lauren Lee, Pharm.D.

APPEARS THIS WAY
ON ORIGINAL

Concur:

Jerry Phillips, RPh

APPEARS THIS WAY
ON ORIGINAL

CC:

NDA: 21-202
Office Files
HFD-510; DivFiles; Jena Weber, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-042, Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Jennie Chang, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management
(Electronic Only)

APPEARS THIS WAY
ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Postmarketing Drugs, Atten. Jerry Philips, HFD-400			FROM: Jena Weber/Xavier Ysern, HFD-510	
3/24/00	IND NO.	NDA NO.21-202	TYPE OF DOCUMENT original NDA	DATE OF DOCUMENT: 11/12/99
NAME OF DRUG GLUCOPHAGE®XR Metformin Hcl Extended Release Tablets, 500 mg	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG: Oral Hypoglycemic	DESIRED COMPLETION DATE: 7/31/00
NAME OF FIRM: BMS				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*: + Secondary Review per PDC 3/24/00

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review and comment on the proprietary name Metformin Hydrochoride Extended Release. This consult is for assessment of a Trademark for a proposed drug product. Any questions, call Jena at 827-6422.
UFGD is 9/12/00

SIGNATURE OF REQUESTER /S/ 3/24	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER /S/	SIGNATURE OF DELIVERER

BEST POSSIBLE COPY

73243 Jan

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

DATE RECEIVED: 3/24/2000	DUE DATE: 6/3/2000	OPDRA CONSULT #: 00-0102

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

THROUGH:
Jena Weber
Project Manager
(HFD-510)

PRODUCT NAME:	**MANUFACTURER:**
Glucophage XR (Metformin HCL Extended Release Tablets) **NDA #:** 21-202	Bristol-Myers Squibb Company

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Glucophage XR. However, we recommend careful monitoring and sufficient education regarding the difference between Glucophage XR and Glucophage upon the launch of this product. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

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

PROPRIETARY NAME REVIEW

DATE RECEIVED: March 24, 2000

NDA#: 21-202

NAME OF DRUG: Glucophage XR (Metformin HCL Extended Release Tablets)

NDA HOLDER: Bristol-Myers Squibb Company

I. INTRODUCTION:

This consult is in response to a March 24, 2000 request by the Division of Metabolic and Endocrine Drug Products, to review the proposed proprietary drug name, Glucophage XR, regarding potential name confusion with other proprietary/generic drug names. The container label and the insert labeling were reviewed for possible interventions in minimizing medication errors.

Glucophage is an approved drug product under NDA 20-357. On 3/3/95, 500 mg and 850 mg tablets were approved. On 11/5/98, 1 g strength was also approved. The firm has submitted NDA 21-202 for approval of an extended release formulation, Glucophage XR.

PRODUCT INFORMATION
Glucophage XR is an oral antihyperglycemic agent used in the management of patients with type 2 diabetes mellitus. It improves glucose tolerance and lowers both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, intestinal absorption of glucose, and improves insulin sensitivity. Glucophage XR as monotherapy is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. It may also be used concomitantly with a sulfonylurea or insulin. The usual starting dose of Glucophage XR is 500 mg once daily with evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2 g once daily. Glucophage XR is supplied as 500 mg tablets.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound-alike or

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

look-alike Glucophage XR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches

A. EXPERT PANEL DISCUSSION

[The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC)].

1. According to the expert panel, the modifier, "XR," is part of many approved drug names for extended release formulations. However, there is an overlapping strength between Glucophage and Glucophage XR.

2. DDMAC – no comments.

B. SAFETY EVALUATOR RISK ASSESSMENT

There are many approved proprietary names containing the modifier "XR" for extended release formulations, including Tegretol XR, Voltaren XR, Dilacor XR, and Effexor XR. Similarly, Glucophage XR is an extended release formulation. However, there is a safety concern involving the overlapping strength (500 mg) between Glucophage and Glucophage XR. If these two formulations are confused for one another, significant adverse events could occur, including hypoglycemia, lactic acidosis, hyperglycemia, and other events.

Overlapping strengths also exist between the extended release and non-extended release formulations for Tegretol XR/Tegretol and Effexor XR/Effexor. According to a search in the Adverse Event Reporting System (AERS), four medication error reports of confusion between Effexor and Effexor XR were identified *(none for Tegretol XR)*. In three of these four cases, Effexor XR was given instead of Effexor.

Despite the safety concern regarding the overlapping strength, there is insufficient evidence to render the name objectionable. Therefore, careful monitoring and sufficient education regarding the difference between Glucophage XR and Glucophage may be warranted upon the launch of this product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label and insert labeling of Glucophage XR, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container label and the insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (500 mg)

The container labels for Glucophage XR and Glucophage (500 mg) 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

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

1000 mg labels, respectively. We recommend that similar colors not be used for Glucophage XR proposed labels.

B. 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.

IV. RECOMMENDATIONS:

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

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

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

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

Concur:

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

APPEARS THIS WAY
ON ORIGINAL

CC:

NDA: 21-202
Office Files
HFD-510; DivFiles; Jena Weber, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-042, Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Jennie Chang, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management (Electronic Only)

APPEARS THIS WAY
ON ORIGINAL

NDA 21-202

NOV 17 1999

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

Dear Mr. Randolph:

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

Name of Drug Product:	Metformin Hydrochloride Extended Release Tablets, 500 mg
Therapeutic Classification:	Standard (S)
Date of Application:	November 12, 1999
Date of Receipt:	November 12, 1999
Our Reference Number:	NDA 21-202

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 11, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 12, 2000, and the secondary user fee goal date will be November 12, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not

granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

[/S/] 11.16.99

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-202
HFD-510/Div. Files
HFD-510/J. Weber
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/November 16, 1999
Initialed by: Galliers 11.16.99
final: DK 11.16.99
filename: 21202ACK

ACKNOWLEDGEMENT (AC)