CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-460

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-460 SUPPL # ---
Trade Name Metaglip Generic Name glipizide/metformin HCl Tablets
Applicant Name Bristol-Myers Squibb, Inc. HFD-510
Approval Date October 21, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

      YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

THREE (3) YEARS

e) Has pediatric exclusivity been granted for this Active Moiety?
A pediatric written request was issued 6.18.02 for this combination drug product. However, pediatric exclusivity has been granted for metformin, one of the 2 active moieties in this product.

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.
Not applicable: combination drug product

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

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

NDA # 17-783 AP 05.08.84 [Glucotrol (glipizide) Tablets]

NDA # 20-329 AP 04.26.94 [Glucotrol (glipizide) XL]

NDA # 20-357 AP 03.03.95 [Glucophage (metformin) Tablets]

NDA # 21-202 AP 10.13.00 [Glucophage (metformin) XR]

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the

investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis 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 /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

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 # CV138-050

Investigation #2, Study # CV138-060

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1	
IND # _____ YES /_X_/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /_X_/	NO /___/ Explain: _____
	_____
	_____

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

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

{See appended electronic signature page}
James T. Cross, M.S.
Regulatory Project Manager

{See appended electronic signature page}
David G. Orloff, M.D.
Division Director

cc:
Archival NDA
HFD-510/Division File
HFD-510/J.Cross
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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/s/

James Cross
10/21/02 03:23:47 PM

David Orloff
10/21/02 03:35:22 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-460 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 21, 2001 Action Date: October 21, 2002

HFD-510 Trade and generic names/dosage form: Metaglip™ (glipizide/metformin HCl) Tablets

Applicant: Bristol-Myers Squibb, Inc. Therapeutic Class: oral anti-diabetic

Indication(s) previously approved: none.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

INDICATION #1: Initial therapy- as adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☑ Other: *Written request granted June 18, 2002 for Metaglip™ (glipizide/metformin HCl) under IND 57,453.*

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

James T. Cross, M.S.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

INDICATION #2: Second-line therapy- when diet, exercise, and first-line treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes.

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☑ **Other:** ***Written request granted June 18, 2002 for Metaglip™ (glipizide/metformin HCl) under IND 57,453.***

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies N/A

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies N/A

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

,ection D: Completed Studies N/A

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

James T. Cross, M.S.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze

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/s/

James Cross
10/24/02 03:12:15 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-460	Efficacy Supplement Type SE- n/a	Supplement Number n/a	
Drug: Metaglip (metformin/glipizide HCl) Tablets		Applicant: Bristol-Myers Squibb, Inc.	
RPM: James Cross		HFD-510	Phone # 301-827-6381
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	4
• Other (e.g., orphan, OTC)	n/a
❖ User Fee Goal Dates	Oct. 21, 2002
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A
❖ Exclusivity Summary (approvals only)	(✓) 3 years requested.
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	✓ **6.10.02; ADRA: N/A**

General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (✓) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**✓PM: 10.9.02; DDMAC: 9.13.02** **Tradename: 7.12.02, 9.18.02**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	✓
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	✓
• Documentation of discussions and/or agreements relating to post-marketing commitments	✓
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**✓ DMEDP Fax 10.10.02**
❖ Memoranda and Telecons	**✓ DMEDP Tcon memo 10.17.02**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	10.9.02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	10.02.02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	10.10.02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See p.27, 10.20.02 CMC review #1.
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (✓) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (✓) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

James Cross
10/25/02 02:39:14 PM

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

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

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Bristol-Myers Squibb
P.O. Box 4000
Princeton, New Jersey 08543-4000

2. TELEPHONE NUMBER *(Include Area Code)*

(609) 252-4000

3. PRODUCT NAME

Glucovance (glyburide and metformin HCl) Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4243

6. LICENSE NUMBER / NDA NUMBER

N021460

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

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

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

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Warren C. Randolph	Director, Regulatory Science	December 21, 2001

FORM FDA 3397 (5/98)

REGULATORY FILING REVIEW

NDA Number: 21-460
Requested Trade Name: Not provided.
Generic Name: Glipizide/Metformin hydrochloride
Dosage Form/Strengths: Tablets, 2.5 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg
Applicant: Bristol-Myers Squibb Company

Date of Application: December 21, 2001
Date of Receipt: December 21, 2001
Date of Filing Meeting: February 4, 2002
Filing Date: February 19, 2002

Indications requested:

First-line therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

Second-line therapy when diet, exercise, and first-line treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with type 2 diabetes.

Type of Application: Full NDA ✓ Supplement _____
(b)(1) ✓ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

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

Therapeutic Classifications: S ✓ P _____
Resubmission after a withdrawal or refuse to file N/A
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid ✓ Waived (e.g., small business, public health) ___
Exempt (orphan, pediatric supplement, government) _____
Form 3397 submitted: YES ✓ NO _____
User Fee ID# 4243
Clinical data? YES ✓ NO _____ Referenced _____
Date clock started after UN N/A

User Fee Goal date: October 21, 2002

Action Goal Date (optional) _____

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

- Does the submission contain an accurate comprehensive index? **YES** NO

- Form 356h included with authorized signature? **YES** NO

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

- If electronic NDA, does it follow the Guidance? **YES** NO

- Patent information included with authorized signature? **YES** NO

- Exclusivity requested? **YES**; If yes, 3 years NO

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

- Debarment Certification included with authorized signature? **YES** NO

If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

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

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

- Pediatric assessment of all ages? YES **NO**
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? NONE
  For what ages was a deferral requested? ALL AGES

- Financial Disclosure included with authorized signature? **YES** NO
  (Forms 3454 and/or 3455)

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

- All parts in English, or English translation? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? **YES** NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date_____ NO

If yes, distribute minutes before filing meeting.

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

BACKGROUND

This NDA provides for a fixed dose combination of glipizide/metformin hydrochloride tablets. Fixed combination metformin/glipizide has been marketed in India in an oral dosage form. The application contains data from two pivotal studies CV138-050 (first-line therapy) and CV138-060 (second-line therapy) to support the use of two dose strengths of a fixed combination tablet (250/2.5 mg and 500/2.5 mg) as first line therapy, and one dose strength (500/5 mg) as second line therapy in patients with type 2 diabetes for whom monotherapy has been found to be inadequate. In addition, a rationale was provided for use of the 500/2.5 mg dosage strength as the starting dose in second line therapy.

Assigned Reviewers:

DISCIPLINE	REVIEWER
Medical:	Robert Misbin, M.D.
Statistical:	Lee-Ping Pian, Ph.D.
Pharmacology:	Herman Rhee, Ph.D.
Chemist:	Xavier Ysern, Ph.D.
Environmental Assessment (if needed):	Xavier Ysern, Ph.D.
Biopharmaceutcal:	Steven Johnson, Ph.D.
DSI:	Roy Blay
Project Manager:	James Cross

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

CLINICAL – File ✓ Refuse to file _____

- Clinical site inspection needed: YES_____ NO ✓

MICROBIOLOGY CLINICAL – File_____ Refuse to file_____

STATISTICAL – File ✓ Refuse to file _____

BIOPHARMACEUTICS – File ✓ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ✓

PHARMACOLOGY – File ✓ Refuse to file _____

CHEMISTRY –

- Establishment ready for inspection? YES ✓ NO____ File ✓ Refuse to file _____

505(b)(2)

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

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

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
Yes ____ No _____
(Normally, FDA will refuse-to-file such applications.)

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(2)

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

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

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

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

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

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

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

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

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

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity?

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

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

REGULATORY REQUIREMENTS/ORGANIZATION – CHECK ONE:

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

_____ The application is unsuitable for filing. Explain why.

Project Management

Copy of the labeling (PI, PPI) sent to DDMAC? YES **NO**
(DDMAC [B.Chong] was informed via email on 1-31-02 that the label was available through the Elec Document Room.)

Trade name/labeling sent to OPDRA? YES **NO**
(Trade name not provided, but firm indicated in coverletter that Trade name would be submitted shortly)
ADDENDUM: Proposed trade-name submitted 5-14-02; consult request sent to ODS.

Advisory Committee Meeting needed? YES **NO**

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A**
  YES_____ NO _____

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? **YES** **NO**

  If no, did sponsor submit a complete environmental assessment? **YES** **NO**

- EA consulted to Nancy Sager (HFD-357)? **YES** **NO**

- Establishment Inspection Request (EIR) package transmitted? **YES** **NO**

- Parenteral Applications Consulted to Sterile Products (HFD-805)? **YES** **NO**

{See appended electronic signature}

James T. Cross
Project Manager, HFD-510
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

James Cross
6/10/02 12:38:24 PM
CSO

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-510)
REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-460

Name of Drug: Metaglip™ (glipizide/metformin hydrochloride) Tablets, 2.5mg/250mg, 2.5mg/500mg, 5mg/500mg.

Applicant: Bristol-Myers Squibb, Inc.

Material Reviewed:

Proposed Physician Package Insert
Proposed Patient Package Insert
Proposed Carton/Container Labeling

Submitted: December 21, 2001
Received: December 21, 2001

Background and Summary

Metformin was first approved for the treatment of type 2 diabetes on March 3, 1995 (NDA 20-357) under the trade name, Glucophage®. Glipizide was first approved for the treatment of type 2 diabetes on May 8, 1984 (NDA 17-783) under the trade name, Glucotrol®. To date, the only fixed-dose combination product approved for the treatment of type 2 diabetes is metformin/glyburide, approved July 31, 2000 (NDA 21-178) under the trade name, Glucovance®.

This NDA provides for a new, fixed-dose combination product containing metformin and glipizide, in the treatment of Type 2 diabetes as (1) first-line therapy where hyperglycemia cannot be satisfactorily managed with diet and exercise alone, and (2) second-line therapy when diet, exercise, and first-line treatment with a sulfonylurea or metformin do not result in adequate glycemic control.

Review

The proposed patient and physician package inserts for Metaglip™ were compared with those currently approved for Glucovance®. The format of the proposed PI and PPI for Metaglip™ is similar to that of Glucovance, although discrepancies in the scientific content of the labels exist. It should be noted that these discrepancies may result from differences in the design of the pivotal clinical trials between the two applications, and because glipizide and glyburide are different moieties with potentially different pharmacokinetic/pharmacodynamic properties.

Conclusions

The proposed Metaglip™ labeling should be approved if no deficiencies warranting an approvable or not approvable action are identified in the chemistry, biopharmaceutics, or clinical reviews prepared by Dr. Ysern, Dr. Johnson, and Dr. Misbin, respectively.

{See appended electronic signature page}

James T. Cross, M.S.
Regulatory Project Manager, HFD-510

Drafted: J.Cross/10.9.2002
Initialed: K.Johnson/10.9.2002
Finalized: J.Cross/10.9.2002

CSO LABELING REVIEW

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/s/

James Cross
10/9/02 05:09:53 PM
CSO

MEMORANDUM OF TELECON

DATE: October 16, 2002
APPLICATION: NDA 21-460, Metaglip™ (metformin HCl/glipizide) Tablets

BETWEEN:

Name: Eileen Connolly, CMC Regulatory Affairs
Phone: 609-818-4388
Representing: Bristol-Myers Squibb, Inc.

AND

Name: James T. Cross, Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Biopharmaceutics Postmarketing (Phase 4) Study Commitment

BACKGROUND

This application was submitted and received on December 21, 2001, to market a fixed dose combination of glipizide/metformin HCl, 2.5mg/250mg, 2.5mg/500mg, and 5mg/500mg, as initial- and second-line therapy based on data presented from 2 pivotal studies (Study CV138-050 and Study CV138-060).

Dr. Steven Johnson's biopharmaceutics NDA review, dated October 10, 2002, identified that, as specified in biopharmaceutic FDA guidance documents, dissolution media for multipoint dissolution data should fall within the pH range of 1.2 to 6.8, unless there is compelling evidence to warrant otherwise. Bristol-Myers Squibb, Inc. provided data having used a dissolution medium of pH 7.5. Consequently, Dr. Johnson, on behalf of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), has requested that the firm agree to a postmarketing commitment to conduct and submit a study report for dissolution study for release lots of each of the to-be-marketed strengths (2.5mg/250mg, 2.5mg/500mg, and 5mg/500mg). This study must use dissolution media at pH 6.8 and a study report must be submitted within 6 months of NDA approval.

BMS sent a fax today in which the firm committed to conduct a dissolution study at pH 6.8, as requested by the Division in a fax to the firm dated October 10, 2002.

TODAY'S CALL

I contacted Ms. Connolly to explain that the firm's amendment in which they would commit to conduct the aforementioned study needed to specify that, in addition to studying tablets from stability lots, Metaglip™ tablets from release lots must be studied. Ms. Connolly stated that the firm would commit to this and acknowledge this commitment in an amendment to the NDA.

{see appended electronic signature page}

James T. Cross, M.S.
Regulatory Project Manager

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/s/

James Cross
10/17/02 11:39:04 AM
CSO

WITHHOLD 4 PAGE (S)

MEMORANDUM OF TELECON

DATE: January 30, 2002

APPLICATION NUMBER: NDA 21-460, Glipizide/metformin hydrochloride Tablet

BETWEEN:

Name: Warren Randolph, Director, Regulatory Science
Phone: 609-252-5228
Representing: Bristol-Myers Squibb

AND

Name: James Cross, Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Submission date extended for 4-month Safety Update.

Bristol-Myers Squibb submitted a new drug application (NDA) dated December 21, 2001, for glipizide/metformin hydrochloride tablets. An amendment dated January 23, 2002, was submitted to request an extension on the submission of the 4-month safety update from April 2002, to mid-July 2002. According to the firm, such an extension would permit the inclusion of all safety information from the

Today the firm was notified that this request was acceptable. No written correspondence is being sent to the firm, however the firm was notified that a memo documenting the conversation would be recorded in our division file for this NDA.

{see appended electronic signature page}

James T. Cross
Regulatory Project Manager, HFD-510

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/s/

James Cross
1/30/02 12:37:34 PM
CSO

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: July 11, 2002	**DUE DATE:** September 13, 2002	**DMETS CONSULT #:** 02-0112-1

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: James Cross
Regulatory Project Manager
HFD-510

PRODUCT NAME:	**NDA SPONSOR:**
Metaglip (Glipizide/Metformin Hydrochloride Tablets) 2.5 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg **NDA #** 21 - 460	Bristol-Myers Squibb

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "Metaglip", to determine the potential for confusion with approved proprietary and established names as well as pending names.

METS RECOMMENDATION: DMETS has no objection to the use of the proprietary name, "Metaglip". DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. DMETS recommends that the Division of Surveillance, Research and Communication Support (ODS/DSRCS) be consulted to review the Patient Information section of the Package Insert.

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 or established names from the signature date of this document.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

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

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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

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
Fred T. Fiedorek, M.D.	Vice-President, Metabolics Clinical Development and Life Cycle Management
FIRM/ORGANIZATION	
Bristol-Myers Squibb Company	
SIGNATURE	DATE
Fred T. Fiedorek	12 December 2001

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)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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 Protocol CV138-060 (*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
Fred T. Fiedorek, M.D.	Vice-President, Metabolics Clinical Development and Life Cycle Management
FIRM/ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE Fred T. Fiedorek MD	DATE 12 December 2001

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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 CV138-060, -073, -074 (*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
Fred T. Fiedorek, M.D.	Vice-President, Metabolics Clinical Development and Life Cycle Management
FIRM/ORGANIZATION Bristol-Myers Squibb Company	
SIGNATURE Fred T. Fiedorek, MD	DATE 12 December 2001

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

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Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 21-460
Document Type:	Minutes
Document Group:	
Document Name:	NDA Filing Meeting Minutes
Shortcut ID Code:	
COMIS Decision:	
Drafted by:	J.Cross/3-1-02
Revised by:	K.Johnson/3-22-02
Initialed by:	
Finalized:	J.Cross/3-28-02
Filename:	
DFS Key Words:	
Notes:	
Linking Instructions:	

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **September 13, 2002**

NDA NUMBER: **21-460**

NAME OF DRUG: **Metaglip**
(Glipizide/Metformin Hydrochloride Tablets)
2.5 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg

NDA SPONSOR: **Bristol-Myers Squibb**

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name Metaglip. The sponsor had previously submitted the name "Zyphage" as their first choice for this combination product. DMETS evaluated the first choice, but did not recommend the use of the proprietary name "Zyphage". DMETS also reviewed the container label, and insert labeling.

PRODUCT INFORMATION

Metaglip contains the active ingredients glipizide and metformin hydrochloride. Metaglip is indicated as first line therapy to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise. Usual doses of Metaglip are shown in the dosing table below with the maximum recommended daily dose of glipizide/2000 mg metformin. Metaglip will be supplied bottles of 100 tablets in the following strengths: 2.5 mg/250 mg, 2.5 mg, 500 mg, and 5 mg/500 mg. The use of Metaglip is contraindicated in patients who have known hypersensitivity to glipizide or metformin hydrochloride, in patients with congestive heart failure requiring pharmacologic treatment, renal disease or renal dysfunction which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. In addition, Metaglip should not be used in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Starting Doses of Metaglip

Patients whose hyperglycemia is not satisfactorily managed with diet and exercise alone	2.5 mg/250 mg once a day with a meal
	2.5 mg/500 mg once a day with a meal
Patients not controlled on glipizide or metformin alone	2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meal *
Patients previously treated with combination therapy of glipizide plus metformin	2.5 mg/500 mg or 5 mg/500 mg o

* The starting dose of Metaglip should not exceed the daily doses of glipizide or metformin already being taken.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Metaglip" 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 trademark electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Metaglip". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel Discussion (EPD) did not identify any drug names that were thought to have potential for confusion with Metaglip. One DMETS member stated that the order in which the prefixes, "Meta" and "Glip" are combined might confuse some prescribers since the proprietary name Metaglip is a combination of prefixes of the active ingredients for this product. However, the established name for this combination product is expressed in the reverse order as Glipizide and Metformin Tablets. Therefore, health professionals could be confused between the expression of the strength and the name.

2. DDMAC did not have concerns about the name with regard to promotional claims.

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[1] MICROMEDEX Healthcare Intranet Series, 2002, 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.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).

[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.

[3] The Drug Product Reference File [DPR], Established Evaluation System [EES], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.

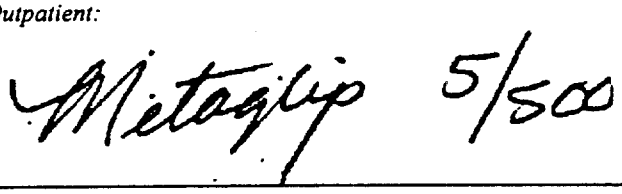
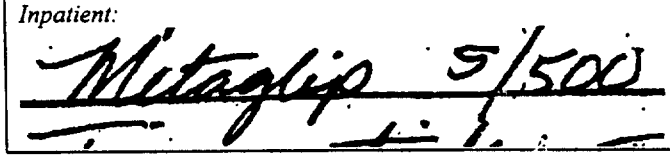
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

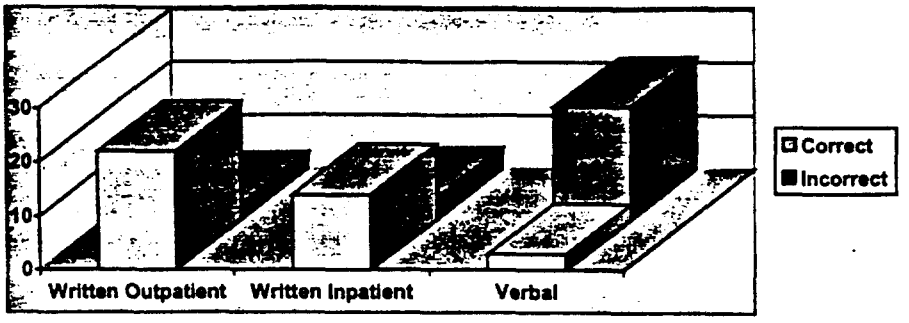
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Metaglip with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Metaglip. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient:  	*Outpatient:* Metaglip 5/500 mg Number 30 She is to take 1 every day.
Inpatient:  	

2. Results

Results of the Metaglip exercises are summarized below:

Study	No. of participants	# of responses (%)	"Metaglip" response	Other response
Written: Outpatient	39	25 (64%)	22 (88%)	3 (12%)
Inpatient	32	18 (56%)	14 (78%)	4 (22%)
Verbal: Outpatient	35	24 (69%)	3 (13%)	21 (88%)
Total:	106	67 (63%)	39 (58%)	28 (42%)



Among participants in the written outpatient prescription study, 22 of 25 respondents (88%) interpreted the name correctly. The only incorrect interpretation submitted by the respondents was Metaglix (3).

Among participants in the written inpatient prescription study, 14 of 18 respondents (78%) interpreted the name correctly. Incorrect interpretations included Metaglup (1), Metaslip (1), Metaglix (1) and Metaclid (1).

Among participants in the verbal outpatient prescription study, 3 of 24 respondents (13%) interpreted the name correctly. Incorrect interpretations included Metaclid (1), Medigri (1), Medigrip (4), Metagrip (3), Mediglip (5), Metaglib (1), Mediglit (1), Medicalith (1), Mediglib (2), Metoglipzide (1) and Medagrip (1).

None of the misinterpreted names is a currently marketed drug product within the United States.

B. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name no products in the U.S. marketplace were identified as having potential for name confusion with Metaglip. The prescription analysis studies did not yield any responses that might raise concern.

During the Expert Panel Discussion one DMETS member stated that the order in which the prefixes, "Meta" and "Glip" are combined might confuse some prescribers since the proprietary name Metaglip is a combination of prefixes of the active ingredients for this product. However; the established name for this combination product is expressed in the reverse order as Glipizide and Metformin Tablets. Therefore, health professionals could be confused between the expression of the strength and the name. Intuitively, one would assume Metaglip 2.5 mg/ 500 mg would indicate the strength of Metformin as 2.5 mg and Glipizide as 500 mg. However, Metaglip 2.5 mg/500 mg actually represents the strength of Glipizide as 2.5 mg and Metformin as 500 mg. Although this may cause some confusion among healthcare professionals and patients, DMETS does not have any evidence of safety related issues caused by an apparent reversal of prefixes to create the proprietary name with relationship to the expression of strength of the active ingredients.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS has reviewed the proposed container label, and package insert labeling. DMETS has focused on safety issues to prevent possible medication errors. Areas of possible improvement have been identified, in the interest of minimizing potential user error and patient safety.

A. CONTAINER LABEL (2.5mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg)
The two areas of possible improvement listed below have previously been reported in the original consult for this combination product (ODS consult 02-0112). The proposed label does not demonstrate the recommended revisions.

1. The [redacted] color for the 2.5 mg/250 mg and 5 mg/500 mg strengths are very similar and may increase the potential for error due to color confusion and side-by-side proximity on the pharmacy shelf. We recommend differentiating one of the strengths (2.5 mg/250 mg or 5 mg/500 mg) with a completely different contrasting color scheme.

2. In order to avoid strength and dosing confusion the statement on each container label describing the amount of each active ingredient in one tablet should be revised to read " [redacted]

B. PACKAGE INSERT LABELING

1. The "Dosage and Administration" section contains a large amount of information. Although this information is valuable and pertinent, it may be beneficial to extract information and create a dosing table or tables. This would provide the health professional with a more visual and concise reference. A cursory example of a table is listed below.

Starting Doses of Metaglip

Patients whose hyperglycemia is not satisfactorily managed with diet and exercise alone	2.5 mg/250 mg once a day with a meal
[redacted]	2.5 mg/500 mg once a day with a meal
Patients not controlled on glipizide or metformin alone	2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meal *
Patients previously treated with combination therapy of glipizide plus metformin	2.5 mg/500 mg or 5 mg/500 mg [redacted]

- The starting dose of Metaglip should not exceed the daily doses of glipizide or metformin already being taken.

2. A review of the wording and information contained in the Patient Information section led to a brief discussion with Karen Lechter, Social Science Analyst OPSS/ODS/DSRCS. Karen Lechter recommended the Division of Surveillance, Research and Communication Support be consulted to review the wording and content found in the Patient Information section of the Package Insert.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Metaglip.

2. DMETS recommends the above labeling revisions to encourage the safest possible use of the product.

3. DMETS recommends that the Division of Surveillance, Research and Communication Support (DSRCS) be consulted to review the Patient Information section of the Package Insert.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Scott Dallas
9/17/02 08:47:44 AM
PHARMACIST

Carol Holquist
9/18/02 01:43:15 PM
PHARMACIST

Jerry Phillips
9/18/02 02:17:56 PM
DIRECTOR

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 5/20//02	DUE DATE: 7/19/02	ODS CONSULT: 02-0112

TO:

David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

James Cross
Project Manager
HFD-510

PRODUCT NAME:	**NDA SPONSOR:**
Zyphage (Glipizide/Metformin Hydrochloride Tablets) 2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg **NDA #:** 21-460	Bristol-Myers Squibb

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Zyphage" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS does not recommend the use of the proprietary name, Zyphage. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 10, 2002

NDA NUMBER: 21-460

NAME OF DRUG: **Zyphage** (Glipizide/Metformin Hydrochloride Tablets)
2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg

NDA HOLDER: Bristol-Myers Squibb

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the tradename "Zyphage", regarding potential name confusion with other proprietary and established drug names.

PRODUCT INFORMATION

Zyphage is the proposed proprietary name for Glipizide/Metformin Hydrochloride Tablets. Zyphage is indicated as first-line therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes whose hyperglycemia cannot be adequately managed with diet and exercise alone. The dosage of Zyphage must be individualized on the basis of effectiveness and tolerance. Usual doses of Zyphage are shown in the dosing table below with the maximum recommended daily dose of [redacted] glipizide/2000 mg metformin. Zyphage will be supplied bottles of 100 tablets in the following strengths: 2.5 mg/250 mg, 2.5 mg, 500 mg, and 5 mg/500 mg. The use of Zyphage is contraindicated in patients who have known hypersensitivity to glipizide or metformin hydrochloride, in patients with congestive heart failure requiring pharmacologic treatment, renal disease or renal dysfunction which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. In addition, Zyphage should not be used in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Dosing Table - Zyphage

Patients whose hyperglycemia is not satisfactorily managed with diet and exercise alone	2.5 mg /250 mg once a day
[redacted]	2.5 mg/500 mg once a day
Patients not controlled on glipizide or metformin alone	2.5 mg/500 mg or 5 mg/500 mg twice daily
Patients previously treated with combination therapy of glipizide plus metformin	2.5 mg/500 mg or 5 mg/500 mg once a day

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names that sound-alike or look-alike to "Zyphage" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Zyphage". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Zyphage. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Zyphage	Glipizide/Metformin Hydrochloride Tablets 2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg	Varies among individual patients - See dosing table on page 2	
Zyprexa	Olanzapine, Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg Orally Disintegrating Tablets: 5 mg, 10 mg, 15 mg, 20 mg	Schizophrenia: 5 mg - 10 mg/day Bipolar Mania: 10 mg - 15 mg/day	L/A
Zyvox	Linezolid Tablets: 400 mg, 600 mg Oral Suspension: 20 mg/mL (150 mL) Infusion: 200 mg (100 mL), 400 mg (200 mL), 600 mg (300 mL)	VRE: 600 mg q12h x 14-28 days Nosocomial Pneumonia, Complicated Skin Infection: 600 mg q12h x 10-14 days Uncomplicated Skin Infection: 400 mg q12h x 10-14 days	S/A
Zyflo	Zileuton Tablets: 600 mg	One 600 mg tablet four times a day	S/A
Glucophage and Glucophage XR	Metformin Tablets: 500 mg, 850 mg, 1000 mg Metformin Extended-Release Tablets: 500 mg	Metformin: 500 mg 2x/day or 850 mg 1x/ day or Metformin Extended-Release: 500 mg/day	L/A, S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

[1] MICROMEDEX Healthcare Intranet Series, 2002, 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.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).
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[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Zyphage with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Zyphage (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

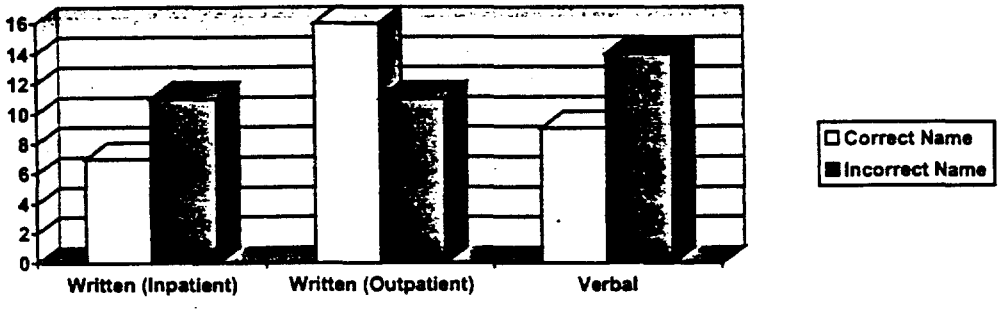
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient RX: ℞ Zyphage 5/500 1 p.o. q.d. #30	Zyphage 5/500 Take one tablet by mouth daily. Dispense thirty.
Inpatient RX: Zyphage 5/500 mg QD	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted Zyphage	Incorrectly Interpreted
Written Inpatient	33	18 (55%)	7 (39%)	11 (61%)
Written Outpatient	39	27 (69%)	16 (59%)	11 (41%)
Verbal Outpatient	36	23 (64%)	9 (39%)	14 (61%)
Total	108	68 (63%)	26 (38%)	36 (53%)



Among the verbal outpatient Zyphage prescriptions, 14 of 23 (61%) respondents interpreted the name incorrectly. Many of the incorrect name interpretations were misspelled/phonetic variations of "Zyphage". Incorrect interpretations included Zyphase, Xiphage, Ziphage, Xyphage, Ziphase, Zyphaze, Zypace, and Zyvase.

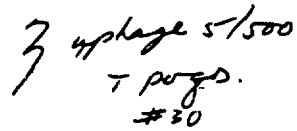
When examining the interpretations from the written inpatient prescriptions, 11 of 18 (61%) respondents interpreted the name incorrectly. Respondents incorrectly interpreted the name to be Zyphagr, Zlyphage, Zyphaga, Zlyphag, ZOyphagi, Zoyphagi, Zephagr, and Zyphagi.

In addition, 11 of 27 (41%) respondents from the written outpatient prescriptions interpreted the name incorrectly. Incorrect interpretations included Zuphage, Zaphage, Uhage, and Uphage. One respondent incorrectly interpreted the name to be Glucophage, a drug product currently marketed in the United States.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Zyphage", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Zyphage were Zyprexa, Zyvox, and Zyflo.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Zyphage could be confused with Glucophage. One study respondent from the outpatient handwriting study interpreted the name to be Glucophage, a currently marketed drug product in the United States. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with these drug products. The following is the outpatient handwriting sample provided in the studies for this drug name:



While the two drug names do not hold a strong look-alike or sound-alike similarity, both drug products contain the active ingredient metformin. Glucophage is the brand name for metformin, a drug indicated for the treatment of type II diabetes. Both Glucophage and Zyphage are indicated for the treatment of type II diabetes, contain the active ingredient metformin, are tablets for oral administration, have a 500 mg strength, and have a twice daily dosing regimen for the 500 mg strength tablet.

The inadvertent administration of Glucophage (metformin) instead of Zyphage (glipizide and metformin) in a diabetes patient normalized on Zyphage may lead to an increase in blood sugar due to the lack of glipizide. In this situation a patient may experience hyperglycemia associated with extreme thirst, excessive hunger, frequent urination, fatigue, nausea, vomiting, and abdominal pain. Likewise, the inadvertent administration of Zyphage instead of Glucophage may increase the risk of hypoglycemia because Zyphage also contains glipizide, another type of glucose lowering agent. Another possible scenario involves the inadvertent administration of Glucophage in combination with Zyphage which may increase a patients risk for unintentional hypoglycemia. This risk may be especially significant because it includes the addition of glipizide to the two metformin doses. Symptoms associated with hypoglycemia include

tachycardia, palpitations, shakiness, sweating, inability to concentrate, dizziness, hunger, blurred vision, and even impairment of motor function, seizure, or coma.

While we believe that a practitioner would question the use of Glucophage and Zyphage together before dispensing or verify a prescription for Zyphage 500 mg as either the 2.5 mg/500 mg or 5 mg/500 mg strength, we believe that the consequences of a medication error with these two drugs are serious and potentially life threatening providing a reason for concern regarding the marketing of the two drug names together.

Zyprexa (Olanzapine) is an antipsychotic medication used in the treatment of the manifestations of psychotic disorders. Zyprexa is available as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg oral tablets as well as 5 mg, 10 mg, 15 mg, and 20 mg orally disintegrating tablets. The usual dose of Zyprexa in the treatment of schizophrenia is 5 mg to 10 mg once daily. In the treatment of bipolar mania, the usual starting dose of Zyprexa is 10 mg to 15 mg daily. Zyprexa can look-alike to Zyphage in that each name contains the similar letter combination "zyp" and contains an ending without any upstroke or downstroke letters. In addition, the letters "h" and "r" can look alike if the letter "h" is scripted with a shortened, non-looped upstroke.

zyprexa 2.5mg zyprexa 2.5mg zyprexa zyphage

In addition to the look-alike similarities, Zyprexa and Zyphage share many other commonalties. Both medications share overlapping strengths (2.5 mg and 5 mg) and dosing schedules (once daily). Similarly, both Zyprexa and Zyphage are tablets for oral administration. Another important fact to keep in mind is that both Zyphage and Zyprexa will be located in close proximity to one another in pharmacies that alphabetize medications by brand names. The close storage proximity, in addition to the overlapping strengths, dosage form, route of administration, and daily dosing schedule, may increase the potential for confusion and error in the dispensing process.

In addition, Zyprexa has been identified through post-marketing surveillance as having confusion and mix-up errors with Zyrtec. Even though Zyrtec and Zyprexa do not contain obvious look-alike or sound-alike similarities (two syllables vs. three syllables, completely different endings "rtec" vs. "prexa"), the two drugs share many similarities that can and have caused confusion among practitioners. Both Zyrtec and Zyprexa are tablets for oral administration, share overlapping strengths (5 mg and 10 mg), are stored in close proximity to one another on the pharmacy shelf, and have once daily dosing. Thus, even though we would expect that the two names would have minimal name confusion, confusion has occurred because of the numerous commonalties that exist between the two drug products. DMETS believes that the addition of another tradename with a significant amount of similarities to Zyprexa may lead to more confusion and error. While we believe that many scenarios may result in the verification of a prescription order with the respective prescriber, we question whether it is appropriate to introduce a proprietary drug name that may potentially generate confusion in an area already burdened by confusion, error, and patient safety concerns.

Zyvox (Linezolid) is an antibiotic used in the treatment of vancomycin-resistant *Enterococcus faecium* (VRE) infections, nosocomial pneumonia caused by *Staphylococcus aureus*, skin and skin structure infections, and community-acquired pneumonia. Zyvox is a prescription medication available as 400 mg and 600 mg tablets, a 20 mg/mL (150 mL) oral suspension, and 200 mg (100 mL), 400 mg (200mL), and 600 mg (300 mL) infusions. The usual dosage of Zyvox in the treatment of VRE infections is 600 mg every 12 hours for 14 to 28 days. Zyvox can be dosed as 600 mg every 12 hours for 10 to 14 days for the treatment of nosocomial

pneumonia and complicated skin infections. Uncomplicated skin infections are normally dosed as 400 mg every 12 hours for 10 to 14 days. Zyvox and Zyphage have sound-alike similarities to one another. Zyvox and Zyphage each have two syllables and contain the prefix letters ("zy"). However, Zyvox and Zyphage have different indications for use (antibiotic vs. diabetes). Both drugs have several different strengths that do not overlap (400 mg and 600 mg vs. 2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg). In addition, Zyvox is available in tablet, suspension, and infusion dosage forms while Zyphage will only be available as a tablet. Thus, the potential for confusion between these two drug names is minimal.

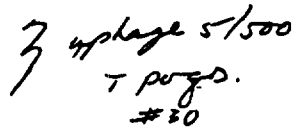
Zyflo (Zileuton) is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. Zyflo is available as a 600 mg oral tablet. The recommended dosage of Zyflo is one tablet four times a day. Zyflo is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal. Zyflo and Zyphage have similar sound-alike characteristics. Each name contains two syllables and has the prefix "zy". Likewise, the endings "flo" and "phage" are similar in that the letter "f" is prominent when the second syllable is pronounced. However, there are several differences that may help to limit confusion between the two drugs. Zyflo and Zyphage have completely different strengths (600 mg vs. 2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg) and indications for use (asthma vs. diabetes). In addition, Zyflo is dosed four times a day while Zyphage is to be given once or twice a day. Thus, the risk of confusion between the two drug names is minimal.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proposed proprietary name, Zyphage.

In reviewing the proprietary name "Zyphage", the primary concern raised was related to a sound-alike, look-alike name that already exists in the U.S. marketplace. The product considered having the greatest potential for name confusion with Zyphage was Zyprexa. In addition, one respondent from the DMETS written oupatient handwriting study interpreted the name to be Glucophage, a drug product currently marketed in the United States.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Zyphage could be confused with Glucophage. One study respondent from the outpatient handwriting study interpreted the name to be Glucophage, a currently marketed drug product in the United States. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with these drug products. The following is the outpatient handwriting sample provided in the studies for this drug name:

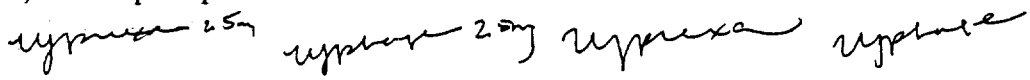


While the two drug names do not hold a strong look-alike or sound-alike similarity, both drug products contain the active ingredient metformin. Glucophage is the brand name for metformin, a drug indicated for the treatment of type II diabetes. Both Glucophage and Zyphage are indicated for the treatment of type II diabetes, contain the active ingredient metformin, are tablets for oral administration, have a 500 mg strength, and have a twice daily dosing regimen for the 500 mg strength tablet.

The inadvertent administration of Glucophage (metformin) instead of Zyphage (glipizide and metformin) in a diabetes patient normalized on Zyphage may lead to an increase in blood sugar due to the lack of glipizide. In this situation a patient may experience hyperglycemia associated with extreme thirst, excessive hunger, frequent urination, fatigue, nausea, vomiting, and abdominal pain. Likewise, the inadvertent administration of Zyphage instead of Glucophage may increase the risk of hypoglycemia because Zyphage also contains glipizide, another type of glucose lowering agent. Another possible scenario involves the inadvertent administration of Glucophage in combination with Zyphage which may increase a patients risk for unintentional hypoglycemia. This risk may be especially significant because it includes the addition of glipizide to the two metformin doses. Symptoms associated with hypoglycemia include tachycardia, palpitations, shakiness, sweating, inability to concentrate, dizziness, hunger, blurred vision, and even impairment of motor function, seizure, or coma.

While we believe that a practitioner would question the use of Glucophage and Zyphage together before dispensing or verify a prescription for Zyphage 500 mg as either the 2.5 mg/500 mg or 5 mg/500 mg strength, we believe that the consequences of a medication error with these two drugs are serious and potentially life threatening providing a reason for concern regarding the marketing of the two drug names together.

Zyprexa (Olanzapine) is an antipsychotic medication used in the treatment of the manifestations of psychotic disorders. Zyprexa is available as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg oral tablets as well as 5 mg, 10 mg, 15 mg, and 20 mg orally disintegrating tablets. The usual dose of Zyprexa in the treatment of schizophrenia is 5 mg to 10 mg once daily. In the treatment of bipolar mania, the usual starting dose of Zyprexa is 10 mg to 15 mg daily. Zyprexa can look-alike to Zyphage in that each name contains the similar letter combination "zyp" and contains an ending without any upstroke or downstroke letters. In addition, the letters "h" and "r" can look alike if the letter "h" is scripted with a shortened, non-looped upstroke..



In addition to the look-alike similarities, Zyprexa and Zyphage share many other commonalties. Both medications share overlapping strengths (2.5 mg and 5 mg) and dosing schedules (once daily). Similarly, both Zyprexa and Zyphage are tablets for oral administration. Another important fact to keep in mind is that both Zyphage and Zyprexa will be located in close proximity to one another in pharmacies that alphabetize medications by brand names. The close storage proximity, in addition to the overlapping strengths, dosage form, route of administration, and daily dosing schedule, may increase the potential for confusion and error in the dispensing process.

Furthermore, Zyprexa has been identified through post-marketing surveillance as having confusion and mix-up errors with Zyrtec. Even though Zyrtec and Zyprexa do not contain obvious look-alike or sound-alike similarities (two syllables vs. three syllables, completely different endings "rtec" vs. "prexa"), the two drugs share many similarities that can and have caused confusion among practitioners. Both Zyrtec and Zyprexa are tablets for oral administration, share overlapping strengths (5 mg and 10 mg), are stored in close proximity to one another on the pharmacy shelf, and have once daily dosing. Thus, even though we would expect that the two names would have minimal name confusion, confusion has occurred because of the numerous commonalties that exist between the two drug products. DMETS believes that the addition of another tradename with a significant amount of similarities to Zyprexa may lead to more confusion and error. While we believe that many scenarios may result in the verification of a prescription order with the respective prescriber, we question whether it is appropriate to introduce a proprietary drug name that may potentially generate confusion in an area already burdened by confusion, error, and patient safety concerns.

In addition, DMETS has reviewed the container label and insert labeling and has identified several areas of possible improvement which might minimize potential user error.

A. CONTAINER LABEL (2.5 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg - 100 tablets)

1. The [redacted] color for the 2.5 mg/250 mg and 5 mg/500 mg strengths are very similar and may increase the potential for error due to color confusion and side-by-side proximity on the pharmacy shelf. We recommend differentiating one of the strengths (2.5 mg/250 mg or 5 mg/500 mg) with a completely different contrasting color scheme.

2. In order to avoid strength and dosing confusion the statement on each container label describing the amount of each active ingredient in one tablet should be revised to read [redacted]

B. INSERT LABELING

No comments at this time.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name, Zyphage.

B. DMETS recommends the labeling revisions as outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS 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 Sammie Beam, project manager, at 301-827-3242.

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/s/

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