

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020357/S006

Trade Name: GLUCOPHAGE TABLETS

Generic Name: METFORMIN HYDROCHLORIDE

Sponsor: BRISTOL-MYERS SQUIBB COMPANY

Approval Date: 11/6/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020357/S006

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Application Number: 020357/S006

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-357/S-006

NOV 6 1997

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

Dear Mr. Randolph:

We acknowledge your supplemental new drug application dated September 8, 1997, received September 9, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Glucophage (metformin hydrochloride) Tablets.

We acknowledge receipt of your submission dated October 8, 1997. The User Fee goal date for this application is March 8, 1998. This change was to be implemented immediately.

The supplemental application provides for changes to the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION sections of the package insert, and to Question #10 of the PATIENT INFORMATION ABOUT GLUCOPHAGE section, addressing potential risk factors for the development of lactic acidosis.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on October 8, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

NDA 20-357/S-006

Page 2

Sincerely yours,

/S/ 11/6/97

Solomon Sobel, M.D.

Director

Division of Metabolic and Endocrine Drug
Products (HFD-510)

Office of Drug Evaluation II

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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NDA 20-357/S-006

Page 3

cc: Original NDA 20-357

HFD-510/Div. files

HFD-510/RMisbin/JGueriguian/GFleming/MJohnston

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes

HFI-20/Press Office (with labeling)

Drafted by: Mjohnston10.22.97 (File: wpfiles/n20357/s06ap

Initialed by: Rmisbin11.3.97/GFleming11.3.97/EGalliers11.6.97/DHertig11.4.97/

Rsteigerwalt11.4.97/XYsern11.4.97/SMoore11.4.97

final: MJohnston11.6.97

APPROVAL (AP)

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357/S006

ADMINISTRATIVE DOCUMENTS

CSO REVIEW OF PACKAGE INSERT FINAL PRINTED LABELING

NDA 20-357/S-006

Glucophage (metformin hydrochloride)Tablets

Reviewed: October 22, 1997 by Michael F. Johnston, Project Manager

Labeling Pieces Reviewed: Comparison between FPL Package Insert (#P6369-01/Rev Oct 1997 submitted October 8, 1997) and approved draft (submitted September 19, 1997 via FAX) and last approved FPL (#NO18100/Rev June 1996). Note: The patient package insert is a section of the prescriber's package insert and contains changes also.

Changes Noted: This supplement makes changes to the WARNINGS, PRECAUTIONS/General:Monitoring of Renal Function, PRECAUTIONS/Geriatric Use, DOSAGE AND ADMINISTRATION/Specific Patient Populations sections of the package insert. In the patient package insert section, changes are made to Question #10.

All changes are noted in attachment #1. In a comparison to the previously approved FPL, no other changes were noted.

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT (1): Glucophage Labeling Outlining Revisions in comparison to current FPL.

**APPEARS THIS WAY
ON ORIGINAL**

REVIEWERS NOTE: Please sign below (in addition to routing slip)

NDA 20-357/S-006 Final Printed Labeling

GLUCOPHAGE (metformin hydrochloride) Tablets

/S/ 11/2/97
MO signature/date

/S/ 11/3/97
MO GpLdr signature/date

/S/ 11/2/97
Pharmacologist

/S/ 11/4/97
Pharmacology Tm/Leader

/S/ 4-NOV-1997
Chemist

/S/ 11/4/97
Chemistry Team Leader

/S/ 10/21/97
CSO-Reviewer/date

/S/ 11/6/97
SCSO/date

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT (1): Glucophage Labeling Outlining Revisions in comparison to current FPL

cc: Original NDA File: NDA 20-357
HFD-510: MJohnston

Redacted

b

pages of trade

secret and/or

confidential

commercial

information

OCT 8 1997

Medical Officer's Review

NDA Supplement, Sept 8, 1997

NDA 20-357

Glucophage

ref 006

NDA suppl for SLR

also ref submission of Septemebr 8, 1997

Cosmic trial

This change of label is the result of months of discussion between FDA and BMS and reflects new data from FDA's review of spontaneous reports of lactic acidosis, and preliminary results of the BMS cosmic trial. A summary of the sponteous reports is appended, in the form of a letter to the editor of the New England Journal of Medicine, and shows that a large proportion of patients with lactic acidosis had a history of congestive heart failure. The use of digoxin or furosemide also adversely affected recovery. Comparison to preliminary results of the Cosmic trial (prepared by Ananda Gubbi), demonstrated that a much higher of proportion of patients with lactic acidosis were 81 years old or older or were using digoxin or furosemide than patients in the Cosmic trial:

	Spontaneous Lact. acidosis	stable patient Cosmic trial	p value
furosemide	40%	6%	<0.0001
Digoxin	29%	7%	<0.0001
age > 80	17%	4%	0.0038

The new label would make congestive heart failure requiring drug treatment a contraindication.

Th new label would prevent the use of metformin in patients, over 80 unless creatinine clearance had been measured and showed that renal function was not reduced. This includes almost all patients over 80.

Sepsis is added as a reason to discontinue metformin

Use of furosemide or digoxin is added to the Patient Information section as factors which can increase the risk of lactic acidosis.

Based on the series of spontaneous reports, I would estimate that

90% of all cases of metformin associated lactic acidosis and virtually all of the deaths would be prevented if physicians, pharmacists, and patients were to implement the warnings and precautions in this new label.

/S/

Robert I Misbin MD
Medical Officer
NDA 20,357
SRL 006

cc MISBIN/Heming/Johnston

Sub 1

/S/

9/29/97

FPL received dated 10/8/97

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

METFORMIN-ASSOCIATED LACTIC ACIDOSIS (MAL)

Since its introduction in the United States in May 1995, through June 30, 1996, the FDA received reports of 66 domestic cases of lactic acidosis associated with treatment with metformin. In 47 patients, the diagnosis was confirmed by lactates of 5.0 mM in accordance with established criteria(1,2). Details of the cases of confirmed MAL are shown in the table.

	DIED	RECOVERED
number (male/female)	20 (9/11)	27 (9/18)
age, mean \pm SEM	70.5 \pm 2.7	67.3 \pm 2.1
lactate, mM	15.9 \pm 1.9 *	11.2 \pm 1.3 *
pH	7.08 \pm 0.01 *	7.29 \pm 0.01 *
dose, mg/day	1259 \pm 145	1349 \pm 115
time to onset, days	64 \pm 26	56 \pm 18
creatinine > 1.4	16 **	7 **
creatinine < 1.5	1 **	8 **
furosemide YES	8 ***	5***
furosemide NO	3 ***	17***
digoxin YES	6 **	4**
digoxin NO	6 **	18 **

* p<0.05 by t test

** P<0.05 by exact permutation test

***P<0.01

Thirty of the 47 patients (64%) were known to have preexisting cardiac disease, including eighteen with histories of congestive heart failure. Thirteen patients (28%) had preexisting renal disease with two on dialysis, even though renal insufficiency is stated in the label to be a contraindication to the use of metformin. Three patients (6%) had chronic obstructive pulmonary disease with hypoxia. Eight patients (17%) were over the age of 80. We found only four patients who had no apparent risk factors for lactic acidosis when treatment with metformin was initiated. Specifically, these patients had normal creatinine levels, no history of heart disease or hypoxia, and were under 80 years of age. All four of these patients recovered. Two had only mild MAL (lactate 5.1, and 5.6 mM). One case was associated with severe ketoacidosis following discontinuation of insulin treatment, and one had E coli sepsis.

Of the 21 patients who did not meet our criteria for MAL, two were found not to have been taking metformin, three had no lactate reported, seven had lactate levels under 2.7 mM, which is the upper limit for stable diabetic patients on metformin (3), and seven had mild hyperlactatemia with levels between 2.7 to 4.9 mM. All patients with mild hyperlactatemia recovered. The remaining two patients probably had MAL but lactate was not measured initially.

Based on an estimate of 1 million Americans exposed to metformin, the reporting rate of MAL is about 5 per 100,000. However, the actual occurrence rate may be higher. From prescription and hospitalization data in Saskatchewan, Stang et al. found 18 per 100,000 diagnoses of MAL of which half had confirmatory lactates. (4)

Our data suggest that congestive heart failure should be included as a contraindication to the use of metformin. We also agree with Sulkin et al. that metformin should be withdrawn from acutely ill patients(5). Limiting the use of metformin to otherwise healthy diabetic outpatients under the age of 80 would undoubtedly decrease the incidence and mortality of MAL.

1 Misbin, RI, Phenformin-associated lactic acidosis: pathogenesis and treatment. Ann Int Med 1977;87:591-5

2 Stacpoole PW, Harman EM, Misbin RI, Treatment of lactic acidosis with dichloroacetate. N Engl J Med 1983; 309: 390-6

3 DeFronzo RA, Goodman AM, Multicenter Metformin Study Group. Efficacy of metformin in patients with NIDDM. N Engl J Med 1995, 333:541-9

4 Stang MR, LueckL, Wysowski DK, Downey W, Butler-Jones D Metformin and Lactic Acidosis. Canadian Pharmacoepidemiology Forum, April 1997

5 Sulkin TH, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. Diabetes Care 1997, 20:925-8

Presented at the Congress of the International Diabetes Federation, July 20, 1997, Helsinki Finland

R Misbin, L Green, B Stadel, J Gueriguian, A Gubbi and A Fleming Food and Drug Administration, Rockville, Maryland USA (The views expressed here are those of the authors and do not necessarily represent the official position of the FDA.)

Robert I Misbin MD

Lanh Green

Bruce Stadel MD

**APPEARS THIS WAY
ON ORIGINAL**

John Gueriguian MD

Ananda Gubbi

**APPEARS THIS WAY
ON ORIGINAL**

G Alexander Fleming MD

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020357/S006

CORRESPONDENCE

NDA NO. _____ REF. NO. 006

NDA SUPPL FOR 006

ORIGINAL

NDA SUPPLEMENT

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08545-4000
609 252 5228 Fax: 609 252 6000

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



NDA 20-357 Glucophage® (metformin hydrochloride) Tablets

September 8, 1997

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

Handwritten: N/S
14 09/1997

Handwritten: Notice
N/S
9-20-1997

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Additional reference is made to the following:

- June 5, 1997 telephone conversation between Dr. Robert Misbin and myself, in which he addressed problems which have been associated with the labeled prohibition for the use of certain contrast media for 48 hours after the last metformin dose and asked that we consider a change to address them.
- July 31, 1997 telephone conversation, also between Dr. Misbin and myself, at which time Dr. Misbin suggested that BMS change the Glucophage® package insert to address potential risk factors for the development of lactic acidosis, as discussed in a draft letter submitted to NEJM (copy provided herein).

At this time we are submitting revised, draft labeling in which changes are proposed to address potential risk factors identified in the draft NEJM letter. These changes are summarized as follows:



A Bristol-Myers Squibb Company

- Congestive heart failure
Added to CONTRAINDICATIONS: "Patients with decompensated congestive heart failure or congestive heart failure stabilized by treatment and with serum creatinine levels ≥ 1.5 mg/dl (males) or ≥ 1.4 mg/dl (females) or abnormal creatinine clearance.

- Age greater than 80 years
Added to Black Box Warnings: "In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis."
 - Added to Monitoring of Renal Function in PRECAUTIONS: "For patients ≥ 80 years of age, see WARNINGS"

 - Added to Geriatric Use in PRECAUTIONS: "See also Warnings and DOSAGE AND ADMINISTRATION" (underlined section added).

 - Added to Specific Patient Populations in DOSAGE AND ADMINISTRATION: "Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See WARNINGS).

 - Under Q10 in PATIENT INFORMATION (other risk factors for lactic acidosis): "You are ≥ 80 years of age and have NOT had your kidney function tested."

We have not as yet obtained sufficient information from reported cases of lactic acidosis to permit us to conclude if the concomitant administration of furosemide or digoxin constitutes a risk factor in and of itself, or if the use of these drugs is connected to another condition which actually increases the risk. The proposed contraindication pertaining to congestive heart failure would eliminate patients at risk due to their condition, some of whom would also be likely to be receiving these drugs. We will continue to evaluate the lactic acidosis reports to determine if additional changes are needed for patients who may be receiving furosemide and digoxin.

We are not proposing a change at this time to the current wording which addresses the use of iodinated contrast materials, as we continue to evaluate how best to provide adequate protection to patients who have need for diagnostic procedures, while providing flexibility where such procedures are urgently needed. We plan to discuss this unresolved issue with the Agency in the near future.

Please contact me at (609) 252-5228 with any questions concerning this submission. As proposed by Dr. Misbin and discussed with Mr. Johnston on August 18, BMS representatives will be available at 10:00 a.m. on September 22 to discuss the proposed labeling changes, if such discussion is needed.

REVIEWS COMPLETED	
CSO ACTION: AP Ltr	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/	11-6-97
CSO INITIALS	DATE

Sincerely,

Warren C. Randolph

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

Attachments

Desk Copies: Dr. R. Misbin (HFD-510, PKLN 14B-04)
Mr. M. Johnston (HFD-510, PKLN 14B-04)

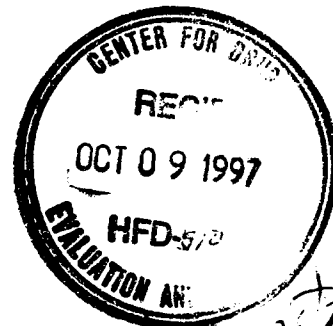
**APPEARS THIS WAY
ON ORIGINAL**

Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08545-4000
609 252-5228 Fax: 609 252-6000

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

Changes Being Effectuated



NDA 20-357/S-006
Glucophage® (metformin hydrochloride) Tablets

October 8, 1997

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

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Glucophage® (metformin hydrochloride) Tablets, NDA 20-357. Additional reference is made to the following:

- Our submission of draft Glucophage® labeling, dated September 8, 1997 (S-006), which contained proposed revisions to address potential risk factors for the development of lactic acidosis.
- A facsimile transmission from Dr. Misbin dated September 10, 1997, which suggested additional changes to the Glucophage® package insert.
- The September 10, 1997 teleconference between Dr. Misbin and representatives of Bristol-Myers Squibb, which focused on appropriate wording to address potential risk with the use of Glucophage® in patients with congestive heart failure (CHF), particularly those treated with furosemide and/or digoxin.
- Our September 19, 1997 facsimile transmission of a revised version of the package insert and the telephone conversations with Dr. Misbin in which he suggested



additional changes. Bristol-Myers Squibb agreed to all of the proposed changes and Dr. Misbin agreed to our submission of the final printed insert as "Changes Being Effected."

At this time we are submitting fourteen copies of the revised, final printed package insert (code P6369-01). Eight copies are mounted to heavy weight paper and six copies are enclosed in an envelope. A side-by-side rendition of the package insert, showing each of the changes, is also included. The changes are summarized as follows:

- Congestive heart failure

Added to CONTRAINDICATIONS: "Congestive heart failure requiring pharmacologic treatment."

Added to Black Box Warnings: "Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis."

Added under Q10 in PATIENT INFORMATION (other risk factors for lactic acidosis):
"● You have congestive heart failure which is treated with medications, e.g., digoxin (Lanoxin[®]) or furosemide (Lasix[®])."

- Age greater than 80 years

Added to Black Box Warnings: "In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage treatment should not be initiated in patients \geq 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis."

Added to Monitoring of Renal Function in PRECAUTIONS: "For patients \geq 80 years of age, see WARNINGS."

Added to Geriatric Use in PRECAUTIONS: "See also WARNINGS and DOSAGE AND ADMINISTRATION" (underlined section added).

Added to Specific Patient Populations in DOSAGE AND ADMINISTRATION: "Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See WARNINGS)."

Added under Q10 in PATIENT INFORMATION: "You are \geq 80 years of age and have NOT had your kidney function tested."

- Other Changes

Added to Black Box Warnings: Sepsis has been added as a condition when Glucophage[®] should be promptly withheld.

Added under Q10 in PATIENT INFORMATION: "You should discuss your risk with your physician."

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

REVIEWS COMPLETED
CSO ACTION: AP Ltr
<input checked="" type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
/S/ 11-6-97
CSO INITIALS DATE

Sincerely,

Warren C. Randolph

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

APPEARS THIS WAY
ON ORIGINAL

WCR/HMK/lp
Attachments
Desk Copies:

Dr. R. Misbin (HFD-510, PKLN 14B-04)
Mr. M. Johnston (HFD-510, PKLN 14B-04)

*labeling change
can be implemented*

APPEARS THIS WAY
ON ORIGINAL

/S/

10/23/97