CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-545

Name: Metformin HCl Extended-release Tablets, 500mg

Sponsor: IVAX Pharmaceuticals, Inc.

Approval Date: October 28, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

APPROVAL LETTER

ANDA 76-545

OCT 28 2003

IVAX Pharmaceuticals, Inc.
Attention: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 25, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Metformin Hydrochloride Extended-release Tablets, 500 mg.

Reference is made to your amendments dated June 10, September 26, and October 21, 2003, and to your correspondence dated October 17, 2003, addressing patent issues associated with for this drug product.

The listed drug product (RLD) referenced in your application, Glucophage XR Extended-release Tablets, 500 mg, of Bristol Myers Squibb Company, is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 6,475,521, the '521 patent, is scheduled to expire on March 19, 2018. Your application contains a paragraph IV certification to the '521 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the '521 patent is invalid, unenforceable, or will not be infringed upon by your manufacture, use, or sale of Metformin Hydrochloride Extended-release Tablets, 500 mg. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA may be made effective immediately, unless an action is brought against IVAX Pharmaceuticals, Inc. (IVAX) for infringement of the '521 patent that was the subject of the paragraph IV certification. This action must be brought against IVAX prior to the expiration of forty-five (45) days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You

have notified the agency that IVAX complied with the requirements of Section 505(j)(2)(B) of the Act, and that no legal action for infringement of the '521 patent was brought against IVAX within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metformin Hydrochloride Extended-release Tablets, 500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Glucophage XR Extended-release Tablets, 500 mg, of Bristol Myers Squibb Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution testing should be conducted in 1000 mL of 0.05M Phosphate Buffer, pH 6.8, at 37°C using USP Apparatus 2 (paddle) at 100 rpm. Your Metformin Hydrochloride Extended-release Tablets, 500 mg, should meet the following "interim" dissolution specifications:

Time	Specification
1 hour	——— %
2 hours	——— %
6 hours	——— %
10 hours	Not less than —%

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" if no revisions are to be proposed to the "interim" specifications, or when the final specifications are tighter than the "interim" specifications. In all other instances, the data should be submitted in the form of a "Prior Approval Supplement."

With respect to 180-day generic drug exclusivity for this drug product, we have determined that IVAX Pharmaceuticals, Inc. (IVAX) was the first ANDA applicant to submit a substantially complete ANDA with paragraph IV certification to the '521 patent. Therefore, with this approval IVAX is eligible for 180-days of market exclusivity. This exclusivity will begin to run from the date IVAX begins commercial marketing of the drug product under this ANDA.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to this ANDA stating the date you commenced commercial marketing of this product.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 10/28/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-545
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-625/M.Shaikh/ 10/22/03

HFD-625/M.Smela/ 10/27/03

HFD-617/P.Chen/ 10/23/03

HFD-613/A.Payne/ 10/22/03

HFD-613/J.Grace/ 10/22/2003

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10/28/2003

F/T by

APPROVAL

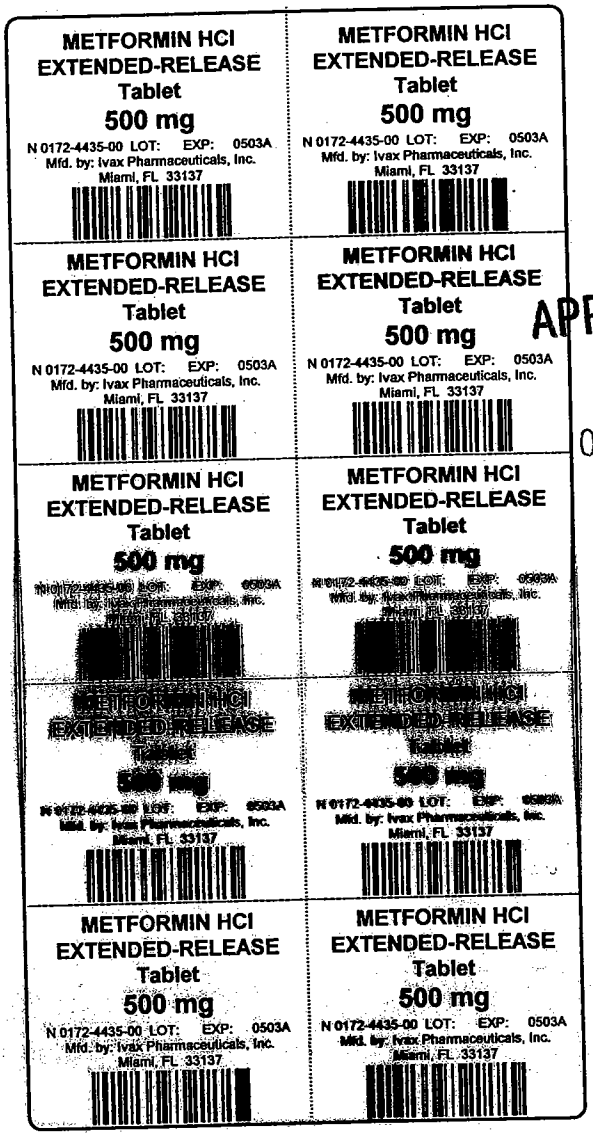
10/27/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

APPROVED LABELING



APPROVED

OCT 28 2003

NDC 0172-**4435**-60

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

500 mg

Rx only

100 TABLETS (White to Off-White)

IVAX *Pharmaceuticals, Inc.*

Each Extended-Release Tablet Contains:
Metformin hydrochloride 500 mg

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

0503A

Manufactured by:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137

N 3 0172-4435-60 5

LOT:

EXP:

NDC 0172-**4435**-70

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

500 mg

Rx only

500 TABLETS (White to Off-White)

IVAX *Pharmaceuticals, Inc.*

Each Extended-Release Tablet Contains:
Metformin hydrochloride 500 mg

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

0503A

Manufactured by:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137

N 3 0172-4435-70 4

LOT:

EXP:

NDC 0172-**4435**-80

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

500 mg

Rx only

1000 TABLETS (White to Off-White)

IVAX *Pharmaceuticals, Inc.*

Each Extended-Release Tablet Contains:
Metformin hydrochloride 500 mg

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

0503A

Manufactured by:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137

N 3 0172-4435-80 3

LOT:

EXP:

NDC 0172-**4435**-10

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

500 mg

Rx only

N 3 0172-4435-10 0

(10 x 10) 100 COUNT UNIT DOSE TABLETS

IVAX *Pharmaceuticals, Inc.*

NDC 0172-**4435**-10

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

500 mg

Rx only

For full prescribing information, see enclosed package insert

(10 x 10) 100 COUNT UNIT DOSE TABLETS

IVAX *Pharmaceuticals, Inc.*

Each Extended-Release Tablet Contains:
Metformin hydrochloride 500 mg

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

Store at 20°-25°C (68°-77°F) [See USP controlled room temperature].

PROTECT FROM LIGHT AND MOISTURE

Manufactured by:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137

0503A

OCT 28 2003

0270-01

METFORMIN HYDROCHLORIDE TABLETS

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

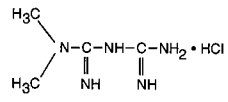
METFORMIN HYDROCHLORIDE TABLETS

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Rx only

DESCRIPTION

Metformin is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is as shown:



$C_4H_{11}N_5 \cdot HCl$ M.W. 165.63

Metformin hydrochloride is a white to off-white crystalline compound. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Metformin hydrochloride tablets contain 500 mg, 850 mg, or 1000 mg of metformin hydrochloride. Each tablet contains the following inactive ingredients: copovidone, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose and talc.

Metformin hydrochloride extended-release tablets contain 500 mg of metformin hydrochloride. Each tablet contains the following inactive ingredients: ethylcellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose and stearic acid.

System Components and Performance

Metformin hydrochloride extended-release tablets comprise a dual hydrophilic polymer matrix system. Metformin hydrochloride is combined with drug release controlling polymers. After administration, fluid from the gastrointestinal (GI) tract enters the tablet, causing the polymers to hydrate and swell. Drug is released slowly from the dosage form by a process of diffusion through the gel matrix that is essentially independent of pH. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

CLINICAL PHARMACOLOGY

Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Absorption and Bioavailability

The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin, however, the extent of absorption (as measured by AUC) is similar to metformin.

At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1,1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from metformin extended-release at a 2000 mg once-daily dose is similar to the same total daily dose administered as metformin tablets 1000 mg twice daily. After repeated administration of metformin extended-release, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from metformin extended-release is comparable to that with metformin.

Although the extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin extended-release.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1µg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see **Table 1**) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses.

The pharmacokinetics of metformin extended-release in patients with type 2 diabetes are comparable to those in healthy normal adults.

Renal Insufficiency

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see **Table 1**; also see **WARNINGS**).

Hepatic Insufficiency

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **Table 1**). Metformin and metformin hydrochloride extended-release tablets treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

Table 1
Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin Hydrochloride Tablets

Subject Groups: Metformin Hydrochloride Tablets dose[a] (number of subjects)	C_{max}[b] (mcg/mL)	T_{max}[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-Impaired adults:			
850 mg single dose			
Mild (CL_{cr}[g] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] All doses given fasting except the first 18 doses of the multiple dose studies
[b] Peak plasma concentration
[c] Time to peak plasma concentration
[d] Combined results (average means) of five studies: mean age 32 years (range 23-59 years)
[e] Kinetic study done following dose 19, given fasting
[f] Elderly subjects, mean age 71 years (range 65-81 years)
[g] CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

No pharmacokinetic data from studies of pediatric patients are currently available.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16).

Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride tablets was comparable in males and females.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

CLINICAL STUDIES

Metformin

In a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with metformin (up to 2550 mg/day) for 29 weeks resulted in significant mean net reductions in fasting and postprandial plasma glucose (PPG) and hemoglobin A_{1c} (HbA_{1c}) of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to the placebo group (see **Table 2**).

Table 2
Metformin vs. Placebo
Summary of Mean Changes from Baseline* in Fasting Plasma Glucose, HbA_{1c} and Body Weight, at Final Visit
(29-week study)

	Metformin (n=141)	Placebo (n=145)	p-Value
FPG (mg/dL)			
Baseline	241.5	237.7	NS**
Change at FINAL VISIT	-53.0	6.3	0.001
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS**
Change at FINAL VISIT	-1.4	0.4	0.001
Body Weight (lbs)			
Baseline	201.0	206.0	NS**
Change at FINAL VISIT	-1.4	-2.4	NS**

* All patients on diet therapy at Baseline
**Not statistically significant

A 29-week, double-blind, placebo-controlled study of metformin and glyburide, alone and in combination, was conducted in obese patients with type 2 diabetes who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see **Table 3**). Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG, and HbA_{1c} of 14 mg/dL, 3 mg/dL and 0.2%, respectively. In contrast, those randomized to metformin (up to 2500 mg/day) experienced a slight improvement, with mean reductions in FPG, PPG, and HbA_{1c} of 1 mg/dL, 6 mg/dL and 0.4%, respectively. The combination of metformin and glyburide was effective in reducing FPG, PPG, and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively.

Compared to results of glyburide treatment alone, the net differences with combination treatment were -77 mg/dL, -68 mg/dL and -1.9%, respectively (see **Table 3**).

Table 3
Combined Metformin/Glyburide (Comb) vs. Glyburide or Metformin Monotherapy: Summary of Mean Changes from Baseline* in Fasting Plasma Glucose HbA_{1c} and Body Weight, at Final Visit
(29-week study)

	Comb (n=213)	Glyburide (n=209)	Metformin (n=210)	p-values Glyburide vs. Comb	p-values Metformin vs. Comb	Metformin vs. Glyburide
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS**	NS**	NS**
Change at FINAL VISIT	-63.5	13.7	-0.9	0.001	0.001	0.025
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS**	NS**	0.007
Change at FINAL VISIT	-1.7	0.2	-0.4	0.001	0.001	0.001
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS**	NS**	NS**
Change at FINAL VISIT	0.9	-0.7	-8.4	0.011	0.001	0.001

* All patients on glyburide, 20 mg/day, at Baseline
**Not statistically significant

The magnitude of the decline in fasting blood glucose concentration following the institution of metformin hydrochloride tablets therapy was proportional to the level of fasting hyperglycemia. Patients with type 2 diabetes with higher fasting glucose concentrations experienced greater declines in plasma glucose and glycosylated hemoglobin.

In clinical studies, metformin, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol, and LDL cholesterol levels and had no adverse effects on other lipid levels (see **Table 4**).

Table 4
Summary of Mean Percent Change from Baseline of Major Serum Lipid Variables at Final Visit (29-week studies)

	Metformin vs. Placebo		Combined Metformin/Glyburide vs. Monotherapy		
	Metformin (n=141)	Placebo (n=145)	Metformin (n=210)	Metformin/ Glyburide (n=213)	Glyburide (n=209)
Total Cholesterol (mg/dL)					
Baseline	211.0	212.3	213.1	215.6	219.6
Mean % change at FINAL VISIT	-5%	1%	-2%	-4%	1%
Total Triglycerides (mg/dL)					
Baseline	236.1	203.5	242.5	215.0	266.1
Mean % change at FINAL VISIT	-16%	1%	-3%	-8%	4%
LDL-Cholesterol (mg/dL)					
Baseline	135.4	138.5	134.3	136.0	137.5
Mean % change at FINAL VISIT	-8%	1%	-4%	-6%	3%
HDL-Cholesterol (mg/dL)					
Baseline	39.0	40.5	37.2	39.0	37.0
Mean % change at FINAL VISIT	2%	-1%	5%	3%	1%

In contrast to sulfonylureas, body weight of individuals on metformin tended to remain stable or even decrease somewhat (see **Tables 2** and **3**).

A 24-week, double-blind, placebo-controlled study of metformin plus insulin versus insulin plus placebo was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone (see **Table 5**). Patients randomized to receive metformin plus insulin achieved a reduction in HbA_{1c} of 2.10%, compared to a 1.56% reduction in HbA_{1c} achieved by insulin plus placebo. The improvement in glycemic control was achieved at the final study visit with 16% less insulin, 93.0 U/day vs. 110.6 U/day, metformin plus insulin versus insulin plus placebo, respectively, p=0.04.

Table 5
Combined Metformin/Insulin vs. Placebo/Insulin
Summary of Mean Changes from Baseline in HbA_{1c} and Daily Insulin Dose

	Metformin/ Insulin n=26	Placebo/ Insulin n=28	Treatment difference Mean ± SE
Hemoglobin A_{1c} (%)			
Baseline	8.95	9.32	
Change at FINAL VISIT	-2.10	-1.56	-0.54 ± 0.43[a]
Insulin Dose (U/day)			
Baseline	93.12	94.64	
Change at FINAL VISIT	-0.15	15.93	-16.08 ± 7.77[b]

[a] Statistically significant using analysis of covariance with baseline as covariate (p=0.04)
Not significant using analysis of variance (values shown in table)
[b] Statistically significant for insulin (p=0.04)

A second double-blind, placebo-controlled study (n=51), with 16 weeks of randomized treatment, demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average HbA_{1c} of 7.46 ± 0.97%, the addition of metformin maintained similar glycemic control (HbA_{1c} 7.15 ± 0.61 versus 6.97 ± 0.62 for metformin plus insulin and placebo plus insulin, respectively) with 19% less insulin versus baseline (reduction of 23.68 ± 30.22 versus an increase of 0.43 ± 25.20 units for metformin plus insulin and placebo plus insulin, p<0.01). In addition, this study demonstrated that the combination of metformin hydrochloride tablets plus insulin resulted in reduction in body weight of 3.11 ± 4.30 lbs., compared to an increase of 1.30 ± 6.08 lbs. for placebo plus insulin, p=0.01.

Metformin Extended-Release

A 24-week, double-blind, placebo-controlled study of metformin extended-release, taken once daily with the evening meal, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA_{1c} 7.0 to 10.0%, FPG 126 to 270 mg/dL). Patients entering the study had a mean baseline HbA_{1c} of 8.0% and a mean baseline FPG of 176 mg/dL. After 12 weeks treatment, mean HbA_{1c} had increased from baseline by 0.1% and mean FPG decreased from baseline by 2 mg/dL in the placebo group, compared with a decrease in mean HbA_{1c} of 0.6% and a decrease in mean FPG of 23 mg/dL in patients treated with metformin extended-release 1000 mg once daily.

Subsequently, the treatment dose was increased to 1500 mg once daily if HbA_{1c} was ≥7.0% but <8.0% (patients with HbA_{1c} ≥8.0% were discontinued from the study). At the final visit (24-week), mean HbA_{1c} had increased 0.2% from baseline in placebo patients and decreased 0.6% with metformin hydrochloride extended-release tablets.

A 16-week, double-blind, placebo-controlled, dose-response study of metformin extended-release, taken once daily with the evening meal, or twice daily with meals, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA_{1c} 7.0 to 11%, FPG 126 to 280 mg/dL). Changes in glycemic control and body weight are shown in **Table 6**.

Table 6
Summary of Mean Changes from Baseline* in HbA_{1c}, Fasting Plasma Glucose, and Body Weight at Final Visit (16-week study)

	Metformin Extended-Release					
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	Placebo
Hemoglobin A_{1c} (%)	(n=115)	(n=115)	(n=111)	(n=125)	(n=112)	(n=111)
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	-
FPG (mg/dL)	(n=126)	(n=118)	(n=120)	(n=132)	(n=122)	(n=113)
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	-
Body Weight (lbs)	(n=125)	(n=119)	(n=117)	(n=131)	(n=119)	(n=113)
Baseline	192.9	191.8	188.3	195.4	192.5	194.3
Change at FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value[a]	NS**	NS**	NS**	NS**	NS**	-

* All patients on diet therapy at Baseline
[a] All comparisons versus Placebo
**Not statistically significant

Compared with placebo, improvement in glycemic control was seen at all dose levels of metformin extended-release and treatment was not associated with any significant change in weight (see **DOSAGE AND ADMINISTRATION** for dosing recommendations for metformin and metformin extended-release).

A 24-week, double-blind, randomized study of metformin extended-release, taken once daily with the evening meal, and metformin, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes who had been treated with metformin 500 mg twice daily for at least 8 weeks prior to study entry. The metformin dose had not necessarily been titrated to achieve a specific level of glycemic control prior to study entry. Patients qualified for the study if HbA_{1c} was ≤8.5% and FPG was ≤200 mg/dL. Changes in glycemic control and body weight are shown in **Table 7**.

Table 7
Summary of Mean Changes from Baseline* in HbA_{1c}, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit
(24-week study)

	Metformin 500 mg twice daily	Metformin Extended-Release 1000 mg Once Daily	Metformin Extended-Release 1500 mg Once Daily
Hemoglobin A_{1c} (%)	(n=67)	(n=72)	(n=66)
Baseline	7.06	6.99	7.02
Change at 12 Weeks	0.14	0.23	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.14[a]	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dL)	(n=69)	(n=72)	(n=70)
Baseline	127.2	131.0	131.4
Change at 12 Weeks	12.9	9.5	3.7
(95% CI)	(6.5, 19.4)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)
Body Weight (lbs)	(n=71)	(n=74)	(n=71)
Baseline	210.3	202.8	192.7
Change at 12 Weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	0.9	1.1	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

*All patients on metformin 500 mg twice daily at Baseline
[a] n=68

After 12 weeks of treatment, there was an increase in mean HbA_{1c} in all groups; in the metformin extended-release 1000 mg group, the increase from baseline of 0.23% was statistically significant (see **DOSAGE AND ADMINISTRATION**).

Changes in lipid parameters in the previously described placebo-controlled dose-response study of metformin extended-release are shown in **Table 8**.

Table 8
Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (16-week study)

	Metformin Extended-Release					
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	Placebo
Total Cholesterol (mg/dL)	(n=120)	(n=113)	(n=110)	(n=126)	(n=117)	(n=110)
Baseline	210.3	218.1	214.6	204.4	208.2	208.6
Mean % change at FINAL VISIT	1.0%	1.7%	0.7%	-1.6%	-2.6%	2.6%
Total Triglycerides (mg/dL)	(n=120)	(n=113)	(n=110)	(n=126)	(n=117)	(n=110)
Baseline	220.2	211.9	198.0	194.2	179.0	211.7
Mean % change at FINAL VISIT	14.5%	9.4%	15.1%	14.9%	9.4%	10.9%
LDL-Cholesterol (mg/dL)	(n=119)	(n=113)	(n=109)	(n=126)	(n=117)	(n=107)
Baseline	131.0	134.9	135.8	125.8	131.4	131.9
Mean % change at FINAL VISIT	-1.4%	-1.6%	-3.5%	-3.3%	-5.5%	3.2%
HDL-Cholesterol (mg/dL)	(n=120)	(n=108)	(n=108)	(n=125)	(n=117)	(n=108)
Baseline	40.8	41.6	40.6	40.2	42.4	39.4
Mean % change at FINAL VISIT	6.2%	8.6%	5.5%	6.1%	7.1%	5.8%

* All patients on diet therapy at Baseline

Changes in lipid parameters in the previously described study of metformin and metformin extended-release are shown in **Table 9**.

Table 9
Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (24-week study)

	Metformin	Metformin Extended-Release	
	500 mg Twice Daily	1000 mg Once Daily	1500 mg Once Daily
Total Cholesterol (mg/dL)	(n=68)	(n=70)	(n=66)
Baseline	199.0	201.9	201.6
Mean % change at FINAL VISIT	0.1%	1.3%	0.1%
Total Triglycerides (mg/dL)	(n=68)	(n=70)	(n=66)
Baseline	178.0	169.2	206.8
Mean % change at FINAL VISIT	6.3%	25.3%	33.4%
LDL-Cholesterol (mg/dL)	(n=68)	(n=70)	(n=66)
Baseline	122.1	126.2	115.7
Mean % change at FINAL VISIT	-1.3%	-3.3%	-3.7%
HDL-Cholesterol (mg/dL)	(n=68)	(n=70)	(n=65)
Baseline	41.9	41.7	44.6
Mean % change at FINAL VISIT	4.8%	1.0%	-2.1%

*All patients on metformin 500 mg twice daily at Baseline

Pediatric Clinical Studies

In a double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 182.2 mg/dL), treatment with metformin (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 64.3 mg/dL, compared with placebo (see **Table 10**).

Table 10
Metformin vs. Placebo (Pediatrics[a]) Summary of Mean Changes from Baseline* in Plasma Glucose and Body Weight at Final Visit

	Metformin	Placebo	p-Value
FPG (mg/dL)	(n=37)	(n=38)	
Baseline	162.4	192.3	
Change at FINAL VISIT	-42.9	21.4	<0.001
Body Weight (lbs)	(n=39)	(n=38)	
Baseline	205.3	189.0	
Change at FINAL VISIT	-3.3	-2.0	NS **

[a] Pediatric patients mean age 13.8 years (range 10 to16 years)
* All patients on diet therapy at Baseline
**Not statistically significant

INDICATIONS AND USAGE

Metformin Hydrochloride Tablets and Metformin Hydrochloride Extended-Release Tablets, as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin Hydrochloride Tablets are indicated in patients 10 years of age and older, and Metformin Hydrochloride Extended-Release Tablets are indicated in patients 17 years of age and older. Metformin or metformin extended-release may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

CONTRAINDICATIONS

Metformin Hydrochloride Tablets and Metformin Hydrochloride Extended-Release Tablets are contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS** and **PRECAUTIONS**).
2. Congestive heart failure requiring pharmacologic treatment.
3. Known hypersensitivity to metformin hydrochloride.
4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin and metformin extended-release should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see also **PRECAUTIONS**).

WARNINGS

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin or metformin extended-release; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. 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. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin or metformin extended-release and by use of the minimum effective dose of metformin or metformin extended-release. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin or metformin extended-release 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. In addition, metformin and metformin extended-release should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin and metformin extended-release should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin or metformin extended-release, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin and metformin extended-release should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also **PRECAUTIONS**).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also **PRECAUTIONS**). Metformin and metformin extended-release should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin or metformin extended-release, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin or metformin extended-release do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling (see also **PRECAUTIONS**).

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin or metformin extended-release, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see also **CONTRAINDICATIONS** and **PRECAUTIONS**).

PRECAUTIONS

General

Monitoring of Renal Function

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. In patients with advanced age, metformin and metformin extended-release should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, metformin and metformin extended-release should not be titrated to the maximum dose (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Before initiation of metformin or metformin extended-release therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin or metformin extended-release discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS, Drug Interactions**), should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials (For Example, Intravenous Urogram, Intravenous Cholangiography, Angiography, and Computed Tomography (CT) Scans with Intravascular Contrast Materials)

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, metformin or metformin extended-release should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin or metformin extended-release therapy, the drug should be promptly discontinued.

Surgical Procedures

Metformin or metformin extended-release therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving metformin or metformin extended-release.

Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, metformin or metformin extended-release should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin or metformin extended-release and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS, Laboratory Tests**).

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes previously well controlled on metformin or metformin extended-release who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, metformin or metformin extended-release must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin or metformin extended-release alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin or metformin extended-release and temporarily administer insulin. Metformin or metformin extended-release may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either metformin or metformin extended-release or sulfonylurea monotherapy, combined therapy with metformin or metformin extended-release and sulfonylurea may result in a response. Should secondary failure occur with combined metformin/sulfonylurea therapy or metformin extended-release/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

Information for Patients

Patients should be informed of the potential risks and benefits of metformin or metformin extended-release and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections, should be explained to patients. Patients should be advised to discontinue metformin or metformin extended-release immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of metformin or metformin extended-release, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving metformin or metformin extended-release.

Metformin alone does not usually cause hypoglycemia, although it may occur when metformin or metformin extended-release is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

Patients should be informed that metformin hydrochloride extended-release tablets must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

(See **Patient Information** printed below).

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also **DOSAGE AND ADMINISTRATION**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

Drug Interactions (Clinical Evaluation of Drug Interactions Conducted with Metformin)

Glyburide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see **DOSAGE AND ADMINISTRATION, Concomitant Metformin or Metformin Extended-Release and *Oral Sulfonylurea Therapy***).

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin or metformin extended-release and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin or metformin extended-release, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin or metformin extended-release, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, metformin and metformin extended-release should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with metformin or metformin extended-release. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If metformin or metformin extended-release is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and effectiveness of metformin for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of metformin in this age group is supported by evidence from adequate and well-controlled studies of metformin in adults with additional data from a controlled clinical study in pediatric patients ages 10 to 16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults (see **CLINICAL PHARMACOLOGY, Pediatric Clinical Studies**). In this study, adverse effects were similar to those described in adults (see **ADVERSE REACTIONS, Pediatric Patients**). A maximum daily dose of 2000 mg is recommended (see **DOSAGE AND ADMINISTRATION, Recommended Dosing Schedule, *Pediatrics***).

Safety and effectiveness of metformin extended-release in pediatric patients have not been established.

Geriatric Use

Controlled clinical studies of metformin and metformin extended-release did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin and metformin extended-release should only be used in patients with normal renal function (see **CONTRAINDICATIONS, WARNINGS**, and **CLINICAL PHARMACOLOGY, Pharmacokinetics**). Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin or metformin extended-release (see also **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

In a U.S. double-blind clinical study of metformin in patients with type 2 diabetes, a total of 141 patients received metformin therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin than placebo-treated patients, are listed in **Table 11**.

Table 11
Most Common Adverse Reactions (>5.0%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

	Metformin Monotherapy n=141	Placebo n=145
Adverse Reaction	**% of Patients**	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

* Reactions that were more common in metformin than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 6% of patients treated with metformin. Additionally, the following adverse reactions were reported in ≥1.0 to ≤5.0% of metformin patients and were more commonly reported with metformin than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

In worldwide clinical trials over 900 patients with type 2 diabetes have been treated with metformin extended-release in placebo- and active-controlled studies. In placebo-controlled trials, 781 patients were administered metformin extended-release and 195 patients received placebo. Adverse reactions reported in greater than 5% of the metformin extended-release patients, and that were more common in metformin extended-release than placebo-treated patients, are listed in **Table 12**.

Table 12
Most Common Adverse Reactions (>5.0%) in Placebo-Controlled Studies of Metformin Extended-Release*

	Metformin Extended-Release n=781	Placebo n=195
Adverse Reaction	**% of Patients**	
Diarrhea	9.6	2.6
Nausea/Vomiting	6.5	1.5

*Reactions that were more common in metformin extended-release than placebo-treated patients

Diarrhea led to discontinuation of study medication in 0.6% of patients treated with metformin extended-release. Additionally, the following adverse reactions were reported in ≥1.0% to ≤5.0% of metformin extended-release patients and were more commonly reported with metformin extended-release than placebo: abdominal pain, constipation, distention abdomen, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance.

Pediatric Patients

In clinical trials with metformin in pediatric patients with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

OVERDOSAGE

Hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin, although lactic acidosis has occurred in such circumstances (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with metformin hydrochloride or metformin hydrochloride extended-release or any other pharmacologic agent. Dosage of metformin hydrochloride or metformin hydrochloride extended-release must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of metformin hydrochloride is 2550 mg in adults and 2000 mg in pediatric patients (10 to 16 years of age); the maximum recommended daily dose of metformin hydrochloride extended-release in adults is 2000 mg.

Metformin hydrochloride should be given in divided doses with meals while metformin hydrochloride extended-release should generally be given once daily with the evening meal. Metformin hydrochloride or metformin hydrochloride extended-release should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see **Recommended Dosing Schedule**), fasting plasma glucose should be used to determine the therapeutic response to metformin hydrochloride or metformin hydrochloride extended-release and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. **The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of metformin hydrochloride or metformin hydrochloride extended-release, either when used as monotherapy or in combination with sulfonylurea or insulin.**

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of metformin hydrochloride or metformin hydrochloride extended-release may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Metformin hydrochloride extended-release tablets must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of metformin hydrochloride extended-release will be eliminated in the feces as a soft, hydrated mass (see **Patient Information** printed below).

Recommended Dosing Schedule

Adults

In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of metformin hydrochloride tablets is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, metformin hydrochloride may be given to a maximum daily dose of 2550 mg per day. Doses above 2000 mg may be better tolerated given three times a day with meals.

The usual starting dose of metformin hydrochloride extended-release tablets is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on metformin hydrochloride extended-release 2000 mg once daily, a trial of metformin hydrochloride extended-release 1000 mg twice daily should be considered. If higher doses of metformin are required, metformin hydrochloride should be used at total daily doses up to 2550 mg administered in divided daily doses, as described above (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

In a randomized trial, patients currently treated with metformin hydrochloride were switched to metformin hydrochloride extended-release. Results of this trial suggest that patients receiving metformin hydrochloride treatment may be safely switched to metformin hydrochloride extended-release once daily at the same total daily dose, up to 2000 mg once daily. Following a switch from metformin hydrochloride to metformin hydrochloride extended-release, glycemic control should be closely monitored and dosage adjustments made accordingly (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Pediatrics

The usual starting dose of metformin hydrochloride is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses. Safety and effectiveness of metformin hydrochloride extended-release in pediatric patients have not been established.

Transfer From Other Antidiabetic Therapy

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to metformin hydrochloride or metformin hydrochloride extended-release, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant Metformin Hydrochloride or Metformin Hydrochloride Extended-Release and Oral Sulfonylurea Therapy In Adult Patients

If patients have not responded to four weeks of the maximum dose of metformin hydrochloride or metformin hydrochloride extended-release monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing metformin hydrochloride or metformin hydrochloride extended-release at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide).

With concomitant metformin hydrochloride or metformin hydrochloride extended-release and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant metformin hydrochloride or metformin hydrochloride extended-release and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea.)

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of metformin hydrochloride or metformin hydrochloride extended-release and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without metformin hydrochloride or metformin hydrochloride extended-release.

Concomitant Metformin Hydrochloride or Metformin Hydrochloride Extended-Release and Insulin Therapy in Adult Patients

The current insulin dose should be continued upon initiation of metformin hydrochloride or metformin hydrochloride extended-release therapy. Metformin hydrochloride or metformin hydrochloride extended-release therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of metformin hydrochloride or metformin hydrochloride extended-release should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose is 2500 mg for metformin hydrochloride and 2000 mg for metformin hydrochloride extended-release. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and metformin hydrochloride or metformin hydrochloride extended-release. Further adjustment should be individualized based on glucose-lowering response.

Specific Patient Populations

Metformin hydrochloride or metformin hydrochloride extended-release are not recommended for use in pregnancy. Metformin hydrochloride is not recommended in patients below the age of 10 years. Metformin hydrochloride extended-release is not recommended in pediatric patients (below the age of 17 years).

The initial and maintenance dosing of metformin hydrochloride or metformin hydrochloride extended-release should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of metformin hydrochloride or metformin hydrochloride extended-release.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly (see **WARNINGS**).

HOW SUPPLIED

Metformin Hydrochloride Tablets are available as white, oval-shaped, unscored, film-coated tablets, debossed "∑" and "4331" on one side and "500" on the other side containing 500 mg metformin hydrochloride packaged in bottles of 90, 100, 500, 1000 and 2000 tablets and unit-dose boxes of 100 tablets.

Metformin Hydrochloride Tablets are available as white, oval-shaped, unscored, film-coated tablets, debossed "∑" and "4330" on one side and "850" on the other side containing 850 mg metformin hydrochloride packaged in bottles of 100, 500 and 1000 tablets and unit-dose boxes of 100 tablets.

Metformin Hydrochloride Tablets are available as white oval-shaped, scored on both sides, film-coated tablets, debossed "∑" and "4432" on one side and "1000" on the other side containing 1000 mg metformin hydrochloride packaged in bottles of 100, 500 and 1000 tablets and unit-dose boxes of 100 tablets.

Metformin Hydrochloride Extended-Release Tablets are available as white to off-white, oval-shaped, beveled-edged, unscored, compressed tablets, debossed "∑" and "4435" on one side and "500" on the other side containing 500 mg metformin hydrochloride packaged in bottles of 100, 500 and 1000 tablets and unit-dose boxes of 100 tablets.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 20°-25°C (68° -77°F) [See USP controlled room temperature].

PATIENT INFORMATION

METFORMIN HYDROCHLORIDE TABLETS and METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Read this information carefully before you start taking this medicine and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What are Metformin and Metformin Extended-Release?

Metformin and metformin extended-release are used to treat type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus. People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots. Before you take metformin or metformin extended-release, try to control your diabetes by exercise and weight loss. While you take your diabetes medicine, continue to exercise and follow the diet advised for your diabetes. No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.

Metformin and metformin extended-release have the same active ingredient. However, metformin extended-release works longer in your body. Both of these medicines help control your blood sugar in a number of ways. These include helping your body respond better to the insulin it makes naturally, decreasing the amount of sugar your liver makes, and decreasing the amount of sugar your intestines absorb. Metformin and metformin extended-release do not cause your body to make more insulin. Because of this, when taken alone, they rarely cause hypoglycemia (low blood sugar), and usually do not cause weight gain. However, when they are taken with a sulfonylurea or with insulin, hypoglycemia is more likely to occur, as is weight gain.

WARNING: A small number of people who have taken metformin have developed a serious condition called lactic acidosis. Lactic acidosis is caused by a buildup of lactic acid in the blood. This happens more often in people with kidney problems. Most people with kidney problems should not take metformin or metformin extended-release. (See "What Are the Side Effects of Metformin and Metformin Extended-Release?")

Who Should Not Take Metformin Or Metformin Extended-Release?

Some conditions increase your chance of getting lactic acidosis, or cause other problems if you take either of these medicines. Most of the conditions listed below can increase your chance of getting lactic acidosis.

Do Not Take Metformin or Metformin Extended-Release if You:

- have kidney problems
- have liver problems
- have heart failure that is treated with medicines, such as Lanoxin® (digoxin) or Lasix® (furosemide)
- drink a lot of alcohol. This means you binge drink for short periods or drink all the time
- are seriously dehydrated (have lost a lot of water from your body)
- are going to have an x-ray procedure with injection of dyes (contrast agents)
- are going to have surgery
- develop a serious condition, such as heart attack, severe infection, or a stroke
- are 80 years or older and you have NOT had your kidney function tested

Tell your doctor if you are pregnant or plan to become pregnant. Metformin and metformin extended-release may not be right for you. Talk with your doctor about your choices. You should also discuss your choices with your doctor if you are nursing a child.

Can Metformin or Metformin Extended-Release Be Used In Children?

Metformin has been shown to effectively lower glucose levels in children (ages 10 to 16 years) with type 2 diabetes. Metformin has not been studied in children younger than 10 years old. Metformin has not been studied in combination with other oral glucose-control medicines or insulin in children. If you have any questions about the use of metformin in children, talk with your doctor or other healthcare provider.

Metformin extended-release has not been studied in children.

How Should I Take Metformin or Metformin Extended-Release?

Your doctor will tell you how much medicine to take and when to take it. You will probably start out with a low dose of the medicine. Your doctor may slowly increase your dose until your blood sugar is better controlled. You should take metformin or metformin extended-release with meals.

Your doctor may have you take other medicines along with metformin or metformin extended-release to control your blood sugar. These medicines may include insulin shots. Taking metformin or metformin extended-release with insulin may help you better control your blood sugar while reducing the insulin dose.

Continue your exercise and diet program and test your blood sugar regularly while taking metformin or metformin extended-release. Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally. There is no evidence that metformin or metformin extended-release causes harm to the liver or kidneys.

Tell your doctor if you

- have an illness that causes severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal. These conditions can lead to severe dehydration (loss of water in your body). You may need to stop taking metformin or metformin extended-release for a short time.
- plan to have surgery or an x-ray procedure with injection of dye (contrast agent). You may need to stop taking metformin for a short time.
- start to take other medicines or change how you take a medicine. Metformin and metformin extended-release can affect how well other drugs work, and some drugs can affect how well metformin and metformin extended-release work. Some medicines may cause high blood sugar.

Metformin extended-release must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of metformin extended-release may be eliminated as a soft mass in your stool that may look like the original tablet; this is not harmful and will not affect the way metformin extended-release works to control your diabetes.

What Should I Avoid While Taking Metformin or Metformin Extended-Release?

Do not drink a lot of alcoholic drinks while taking metformin or metformin extended-release. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase the chance of getting lactic acidosis.

What Are the Side Effects of Metformin and Metformin Extended-Release?

Lactic Acidosis

In rare cases, metformin and metformin extended-release can cause a serious side effect called lactic acidosis. This is caused by a buildup of lactic acid in your blood. This build-up can cause serious damage. Lactic acidosis caused by metformin is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking metformin over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the people who develop it.

It is also important for your liver to be working normally when you take metformin or metformin extended-release. Your liver helps remove lactic acid from your blood.

Make sure you tell your doctor before you use metformin or metformin extended-release if you have kidney or liver problems. You should also **stop using metformin or metformin extended-release and call your doctor right away if you have signs of lactic acidosis. Lactic acidosis is a medical emergency that must be treated in a hospital.**

Signs of Lactic Acidosis Are:

- feeling very weak, tired, or uncomfortable
- unusual muscle pain
- trouble breathing
- unusual or unexpected stomach discomfort
- feeling cold
- feeling dizzy or lightheaded
- suddenly developing a slow or irregular heartbeat

If your medical condition suddenly changes, stop taking metformin or metformin extended-release and call your doctor right away. This may be a sign of lactic acidosis or another serious side effect.

Other Side Effects

Common side effects of metformin and metformin extended-release include diarrhea, nausea, and upset stomach. These side effects generally go away after you take the medicine for a while. Taking your medicine with meals can help reduce these side effects. Tell your doctor if the side effects bother you a lot, last for more than a few weeks, come back after they've gone away, or start later in therapy. You may need a lower dose or need to stop taking the medicine for a short period or for good.

About 3 out of every 100 people who take metformin or metformin extended-release have an unpleasant metallic taste when they start taking the medicine. It lasts for a short time.

Metformin and metformin extended-release rarely cause hypoglycemia (low blood sugar) by themselves. However, hypoglycemia can happen if you do not eat enough, if you drink alcohol, or if you take other medicines to lower blood sugar.

General Advice about Prescription Medicines

If you have questions or problems, talk with your doctor or other healthcare provider. You can ask your doctor or pharmacist for the information about metformin and metformin extended-release that is written for health care professionals. Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use metformin or metformin extended-release for a condition for which it was not prescribed. Do not share your medicine with other people.

Manufactured by
Ivax Pharmaceuticals, Inc.
Miami, FL 33137

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METFORMIN HYDROCHLORIDE TABLETS

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

PATIENT INFORMATION

METFORMIN HYDROCHLORIDE TABLETS
and
METFORMIN HYDROCHLORIDE
EXTENDED-RELEASE TABLETS

0271-01

Read this information carefully before you start taking this medicine and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What are Metformin and Metformin Extended-Release?
Metformin and metformin extended-release are used to treat type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus. People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots. Before you take metformin or metformin extended-release, try to control your diabetes by exercise and weight loss. While you take your diabetes medicine, continue to exercise and follow the diet advised for your diabetes. No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.

Metformin and metformin extended-release have the same active ingredient. However, metformin extended-release works longer in your body. Both of these medicines help control your blood sugar in a number of ways. These include helping your body respond better to the insulin it makes naturally, decreasing the amount of sugar your liver makes, and decreasing the amount of sugar your intestines absorb. Metformin and metformin extended-release do not cause your body to make more insulin. Because of this, when taken alone, they rarely cause hypoglycemia (low blood sugar), and usually do not cause weight gain. However, when they are taken with a sulfonylurea or with insulin, hypoglycemia is more likely to occur, as is weight gain.

APPROVED

WARNING: A small number of people who have taken metformin have developed a serious condition called lactic acidosis. Lactic acidosis is caused by a buildup of lactic acid in the blood. This happens more often in people with kidney problems. Most people with kidney problems should not take metformin or metformin extended-release. (See "What Are the Side Effects of Metformin and Metformin Extended-Release?")

Who Should Not Take Metformin Or Metformin Extended-Release?
Some conditions increase your chance of getting lactic acidosis, or cause other problems if you take either of these medicines. Most of the conditions listed below can increase your chance of getting lactic acidosis.

Do Not Take Metformin or Metformin Extended-Release If You:
- have kidney problems
- have liver problems
- have heart failure that is treated with medicines, such as Lanoxin® (digoxin) or Lasix® (furosemide)
- drink a lot of alcohol. This means you binge drink for short periods or drink all the time
- are seriously dehydrated (have lost a lot of water from your body)
- are going to have an x-ray procedure with injection of dyes (contrast agents)
- are going to have surgery
- develop a serious condition, such as heart attack, severe infection, or a stroke
- are 80 years or older and you have NOT had your kidney function tested

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Tell your doctor if you are pregnant or plan to become pregnant. Metformin and metformin extended-release may not be right for you. Talk with your doctor about your choices. You should also discuss your choices with your doctor if you are nursing a child.

Can Metformin or Metformin Extended-Release Be Used In Children?
Metformin has been shown to effectively lower glucose levels in children (ages 10 to 16 years) with type 2 diabetes. Metformin has not been studied in children younger than 10 years old. Metformin has not been studied in combination with other oral glucose-control medicines or insulin in children. If you have any questions about the use of metformin in children, talk with your doctor or other healthcare provider.

Metformin extended-release has not been studied in children.

How Should I Take Metformin or Metformin Extended-Release?
Your doctor will tell you how much medicine to take and when to take it. You will probably start out with a low dose of the medicine. Your doctor may slowly increase your dose until your blood sugar is better controlled. You should take metformin or metformin extended-release with meals.

Your doctor may have you take other medicines along with metformin or metformin extended-release to control your blood sugar. These medicines may include insulin shots. Taking metformin or metformin extended-release with insulin may help you better control your blood sugar while reducing the insulin dose.

Continue your exercise and diet program and test your blood sugar regularly while taking metformin or metformin extended-

release. Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally. There is no evidence that metformin or metformin extended-release causes harm to the liver or kidneys.

Tell your doctor if you

- have an illness that causes severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal. These conditions can lead to severe dehydration (loss of water in your body). You may need to stop taking metformin or metformin extended-release for a short time.
- plan to have surgery or an x-ray procedure with injection of dye (contrast agent). You may need to stop taking metformin for a short time.
- start to take other medicines or change how you take a medicine. Metformin and metformin extended-release can affect how well other drugs work, and some drugs can affect how well metformin and metformin extended-release work. Some medicines may cause high blood sugar.

Metformin extended-release must be swallowed whole and never crushed or chewed. Occasionally, the inactive of metformin extended-release may be eliminated as a soft mass in your stool that may look like the original tablet; this is not harmful and will not affect the way metformin extended-release works to control your diabetes.

What Should I Avoid While Taking Metformin or Metformin Extended-Release?

Do not drink a lot of alcoholic drinks while taking metformin or metformin extended-release. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase the chance of getting lactic acidosis.

What Are the Side Effects of Metformin and Metformin Extended-Release?

Lactic Acidosis

In rare cases, metformin and metformin extended-release can cause a serious side effect called lactic acidosis. This is caused by a buildup of lactic acid in your blood. This build-up can cause serious damage. Lactic acidosis caused by metformin is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking metformin over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the people who develop it.

It is also important for your liver to be working normally when you take metformin or metformin extended-release. Your liver helps remove lactic acid from your blood.

Make sure you tell your doctor before you use metformin or metformin extended-release if you have kidney or liver problems. You should also **stop using metformin or metformin extended-release and call your doctor right away if you have signs of lactic acidosis. Lactic acidosis is a medical emergency that must be treated in a hospital.**

Signs of Lactic Acidosis Are:

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If your medical condition suddenly changes, stop taking metformin or metformin extended-release and call your doctor right away. This may be a sign of lactic acidosis or another serious side effect.

Other Side Effects

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General Advice about Prescription Medicines

If you have questions or problems, talk with your doctor or other healthcare provider. You can ask your doctor or pharmacist for the information about metformin and metformin extended-release that is written for health care professionals. Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use metformin or metformin extended-release for a condition for which it was not prescribed. Do not share your medicine with other people.

Manufactured by
Ivax Pharmaceuticals, Inc.
Miami, FL 33137

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-545** Date of Submission: November 25, 2002
Applicant's Name: Ivax Pharm
Established Name: Metformin Hydrochloride Extended-release Tablets, 500 mg

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Labeling Deficiencies:

1. CONTAINER - 500 mg [100s, 500s, 1000s] bottles

   A. Please revise your storage temperature statement so that it reflects our current standard storage temperature range. Revise to read "Store at 20-25 deg C(68 - 77 deg F).[See USP controlled room temperature].

   B. Revise "Each Tablet contains..." to "Each extended-release tablet contains...".

2. UNIT-DOSE BLISTERS 10s - Satisfactory in draft.

3. UNIT-DOSE BLISTER CARTONS (10 x10s)

   A. We encourage you to relocate "For full prescribing information, see enclosed package insert" to the side panel under a "Usual Dosage" section.

   B. See comments under CONTAINER.

4. PHYSICIAN'S INSERT

   A. GENERAL COMMENT- Where "metformin Hydrochloride tablets" and "metformin hydrochloride extended-release tablets" are joined together by "and/or" in a sentence, please replace the conjoined established names with "metformin". Please retain both established names as they are written in the INDICATIONS and USAGE, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections.

   B. DESCRIPTION - "hydroxypropyl methylcellulose" should be changed to the new title "hypromellose".

   C. CLINICAL PHARMACOLOGY, Clinical Studies, Metformin

   Delete text protected by M-6 that does not expire until April 19, 2004. In the second paragraph delete the ' [redacted] '

   D. INDICATIONS AND USE, revise the section title to "INDICATIONS AND USAGE".

   E. DOSAGE AND ADMINISTRATION, Concomitant Metformin HCl or Metformin HCl extended release and Oral Sulfonylurea Therapy in Adult Patients subsection, 2nd paragraph.

   Delete "[redacted] " This text is covered by the M-6 . exclusivity.

   F. HOW SUPPLIED - See comment regarding our standard temperature statement.

5. PATIENT INFORMATION LEAFLET - See comment "4a" under PHYSICIAN'S INSERT.

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed metformin guidance with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-545
Date of Submission	
Applicant	Ivax Pharm
Drug Name	Metformin hydrochloride extended-release tablets
Strength(s)	500 mg

FPL Approval Summary	
Container Labels	**Submitted**
500 mg	100s & 500s
Unit-Dose Blisters	10s
Unit-Dose Cartons	10 x10
Package Insert Labeling	
Patient Information sheet	

BASIS OF APPROVAL:

No Patent Data for NDA 21-202.

Exclusivity Data For NDA 21-202 and 20-357			
Code/sup	**Expiration**	**Description**	**Labeling impact**
NDF	Oct. 13, 2003	New drug formula (extended- release formulation.)	Same As
M-6	April 19, 2004	Additional information regarding clinical studies done with Glucophage/glyburide combination in the Clinical Pharm. and Dosing and Administration sections.	Carved-out (insert not used) inserted connect with NDA 20-357 combined insert.

Reference Listed Drug

RLD on the 356(h) form	Glucophage® Tablets
NDA Number	21-202
RLD established name	Metformin HCl tablets
Firm	Bristol Myers Squibb
Currently approved PI	S-003
AP Date	January 8, 2002

Note: Firms has a combined insert with their related metformin HCl tablets ANDA 75-975 approved 1/24/02

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	XX		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug is Glucophage XR(Metformin HCl XR tablets, BMS, NDA 20-212; SE/003 Approved 1. 08, 2002, Revised 6/01).
2. The product is manufactured by Ivax Pharmaceutical, Maiami, FL 33137. See Vol. 1.2, page 225.Outside firms are used for testing only. See vol. 1.2, page 241.
2. Container/Closure: HDPE bottles w/white plastic continuos thread, screw caps. Fillers will be used for all bottle configurations. No desiccants are used. See vol. 1.3, page 157-239.
3. Product Line: 500 mg XR, RLD - bottles of 100s, 500s ANDA: bottles of 100s, 500s 1000s and unit-dose of 100s
4. Components/Composition

   Innovator:

   Active: Metformin Hydrochloride 500 mg

   Inactive: sodium caboxymethyl cellulose, magnesium stearate: hydroxypropyl methylcellulose microcrystalline methylcellulose.

   Applicant:

   Active: Metformin 500 mg, 625 mg, 750 mg, 850 mg, 1000 mg

   Inactive: Microcrystalline cellulose, hydroxypropyl methylcellulose, ethylcellulose, microcrystalline Cellulose, [redacted], stearic Acid; Magnesium Stearate. See Vol. 1.1, page 452.
9. Storage/Dispensing

   NDA: Store at 20-25 (68-77 F). See USP CRT. Excursion permitted to 15 - 30C (59 - 86F) Dispense in a light resistant container.

   ANDA: We ask the firm to revised their statement to be in accord with our current storage temperature statement

---

Date of Review: 2/11/03 **Date of Submission: November 25, 2002**

---

cc: ANDA:76-545
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmnz/Ivaxpharm/lets&rev/76545na1.lab Review

2/11/03

2/25/2003

APPEARS THIS WAY
ON ORIGINAL

V 2.1

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-545
Date of Submission	June 10, 2003
Applicant	Ivax Pharm
Drug Name	Metformin hydrochloride extended-release tablets
Strength(s)	500 mg

FPL Approval Summary		
Container Labels 500 mg	100s & 500s	**Submitted FPL Jun 10, 2003 vol. 2.1A**
Unit-Dose Blisters	10s	**Jun 10, 2003 vol. 2.1A**
Unit-Dose Cartons	10 x10	**Jun 10, 2003 vol. 2.1A**
Package Insert Labeling	#0172. 05/03B1	**Jun 10, 2003 vol. 2.1A**
Patient Information sheet	#0172. 05/03B1	**Jun 10, 2003 vol. 2.1A**

BASIS OF APPROVAL:

No Patent Data for NDA 21-202.

Exclusivity Data For NDA 21-202 and 20-357			
Code/sup	**Expiration**	**Description**	**Labeling impact**
NDF	Oct. 13, 2003	New drug formula (extended- release formulation.)	Same As
M-6	April 19, 2004	Additional information regarding clinical studies done with Glucophage/glyburide combination in the Clinical Pharm. and Dosing and Administration sections.	Carved-out (insert not used) inserted connect with NDA 20-357 combined insert.

Reference Listed Drug

RLD on the 356(h) form	Glucophage® Tablets XR
NDA Number	21-202
RLD established name	Metformin HCl tablets
Firm	Bristol Myers Squibb
Currently approved PI	S-003
AP Date	January 8, 2002

Note: Firms has a combined insert with their related metformin HCl tablets ANDA 75-975 approved 1/24/02

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	XX		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug is Glucophage XR(Metformin HCl XR tablets, BMS, NDA 20-212; SE/003 Approved 1. 08, 2002, Revised 6/01).
2. The product is manufactured by Ivax Pharmaceutical, Maiami, FL 33137. See Vol. 1.2, page 225.Outside firms are used for testing only. See vol. 1.2, page 241.
2. Container/Closure: HDPE bottles w/white plastic continuos thread, screw caps. Fillers will be used for all bottle configurations. No desiccants are used. See vol. 1.3, page 157-239.
3. Product Line: 500 mg XR, RLD - bottles of 100s, 500s ANDA: bottles of 100s, 500s 1000s and unit-dose of 100s
4. Components/Composition
   Innovator:
   Active: Metformin Hydrochloride 500 mg
   Inactive: sodium caboxymethyl cellulose, magnesium stearate: hydroxypropyl methylcellulose microcrystalline methylcellulose.
   Applicant:
   Active: Metformin 500 mg, 625 mg, 750 mg, 850 mg, 1000 mg
   Inactive: Microcrystalline cellulose, hydroxypropyl methylcellulose, ethylcellulose, microcrystalline Cellulose, stearic Acid; Magnesium Stearate. See Vol. 1.1, page 452.
9. Storage/Dispensing
   NDA: Store at 20-25 (68-77 F). See USP CRT. Excursion permitted to 15 - 30C (59 - 86F) Dispense in a light resistant container.
   ANDA: We ask the firm to revised their statement to be in accord with our current storage temperature statement

---

Date of Review: 7/2/03 **Date of Submission: June 10, 2003**

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cc: ANDA:76-545
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmnz/Ivaxpharm/lets&rev/76545ap.lab
Review

8/12/03

8/14/2003

patent #6475521 - PIV.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

CHEMISTRY REVIEW(S)

ANDA 76-545

Metformin Hydrochloride Extended-Release Tablets, 500 mg

Ivax Pharmaceuticals, Inc .

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-545

2. REVIEW #: 1

3. REVIEW DATE: March 6-24, 2003 (Revised on March 31, 2003)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed*	Document Date
*Original submission	11-25-02
NC (Tox Information)	1-3-03
NC (Tox Information)	1-13-03

Note: This ANDA is accepted for filing on November 26, 2002 and Acknowledgement letter is issued to the firm on 1-14-03..

7. NAME & ADDRESS OF APPLICANT:

Name:	Ivax Pharmaceuticals, Inc .
Address:	140 Legrand Avenue, Northvale, NJ 07647
Representative:	Patricia Jaworski
Telephone:	201-767-1700, Ext. 323 or 146

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Metformin Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): Glucophage® XR Tablets and it is approved for Bristol-Myers Squibb Co (NDA 021202).

Patent Certification: There are no patents that claim the listed drug, Glucophage® XR Tablets. The certification is based on Approved Drug Products with Therapeutic Equivalence Evaluation, 22nd Edition, Cumulative Supplement 4 .

Based on the information published in Approved Drug Products with Therapeutic Equivalence Evaluation, 22nd Edition, the reference drug is entitled to marketing exclusivity till October 13, 2003.

Ivax intends to market Metformin HCl Extended-Release Tablets, 500 mg upon expiration of October 13, 2003 marketing exclusivity.

Ivax provided Patent Certification that the US Patent # 6,475,521 has been issued which claims Glucophage® XR will expire on March 19, 2018.

Based on 505(j)(2)(A)(vii) Paragraph IV Certification, Ivax certified that US Patent # 6,475,521 is invalid and /or will not be infringed by the manufacture, use or sale of Ivax's Metformin Extended-Release Tablets, 500 mg for which this application is submitted. Ivax will notify the patent holder and the holder of the approved application, BMS.

10. PHARMACOLY CATEGORY:

To control sugar level in patients with Type II Diabetes.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

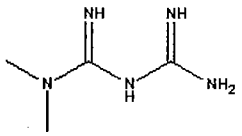
_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Metformin Hydrochloride Extended-Release Tablets

Chemical name: 1,1-Dimethylbiguanide.hydrochloride
Formula: $C_4H_{11}N_5$
Molecular weight: 129.1644
CAS registry number(s): 657-24-9



.HCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	9-27-02	CR # 5 completed by K. Furnkranz
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold	4/7/03	J. D. Ambrogio
Methods Validation	Will be requested later		
Labeling	Deficient	2-11-03	A. Payne
Bioequivalence	Pending		
EA	Adequate	2-24-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-545

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
NA (Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Metformin Hydrochloride Extended-Release Tablets, 500 mg: The Reference Listed Drug is Glucophage® XR (NDA Approved for Bristol-Myers Squibb).

Drug Substance: The active ingredient in this drug product is Metformin Hydrochloride. Metformin Hydrochloride is non-USP material and its acceptance specifications are based on its manufacturer.

B. Description of How the Drug Product is Intended to be Used:
Metformin HCl have been used for many years for treatment of patients with diabetes Type II and historically has been found to be safe and efficacious. It is used orally.

C. Basis for Approvability or Not-Approval Recommendation
Minor issues to be resolved while other discipline reviews are pending.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/3/31/03 4/8/03
HFD-625/MSmela/4/1/03
HFD-617/PChen/ 4/8/03
V:/Firmsam/ivaxpharm/ltrs&rev/76545.R01.doc

C. CC: **ANDA 76-545**
Division File
DUP Jacket
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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-545 APPLICANT: Ivax Pharmaceuticals, Inc

DRUG PRODUCT: Metformin Hydrochloride Extended-Release Tablets, 500 mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your response should also address the labeling deficiencies faxed to you on February 26, 2003.

2. An acceptable compliance evaluation is needed for the approval of your application. We have requested an evaluation from the Office of Compliance.

3. A satisfactory Methods Validation study is needed to support the ANDA. We will schedule the validation with our laboratory when the testing issues are resolved.

4. Please provide any additional stability data that is available.

5. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

Sincerely yours,

Paul J. Seo 4/15/03

Rashmikant M. Patel, Ph.D
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA: 76-545
ANDA DUP
Division File
Field Copy

Endorsements :

HFD-625 /M. Shaikh /3/31/03 4/8/03
HFD-6 25 /M. Smela /4/1/03
HFD-6 17 / PChen /4/4/03 4/8/03
F/t by: ard/4/8/03

M. Smela 4/10/03

V:\FIRMSAM\Ivaxpharm\LTRS&REV\76545.R01.doc

NOT APPROVABLE – MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-545

Metformin Hydrochloride Extended-Release Tablets, 500 mg

Ivax Pharmaceuticals, Inc .

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-545

2. REVIEW #: 2

3. REVIEW DATE: June 30, 2003

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	11-25-02
NC (Tox Information)	1-3-03
NC (Tox Information)	1-13-03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed*	Document Date
Minor Amendment	5-22-03
Amendment (Labeling)	6-10-03
Telephone Amendment	6-27-03

Note: This ANDA is accepted for filing on November 26, 2002 and Acknowledgement letter is issued to the firm on 1-14-03..

7. NAME & ADDRESS OF APPLICANT:

Name:	Ivax Pharmaceuticals, Inc .
Address:	140 Legrand Avenue, Northvale, NJ 07647
Representative:	Patricia Jaworski
Telephone:	201-767-1700, Ext. 323 or 146

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Metformin Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): Glucophage® XR Tablets and it is approved for Bristol-Myers Squibb Co (NDA 021202).

10. PHARMACOLY CATEGORY:

To control sugar level in patients with Type II Diabetes.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

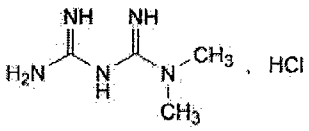
_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Metformin Hydrochloride Extended-Release Tablets

Chemical name: 1,1-Dimethylbiguanide.hydrochloride
Formula: $C_4H_{11}N_5$
Molecular weight: 129.1644



CAS registry number(s): 657-24-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	9-27-02	CR # 5 completed by K. Furnkranz
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold	4-7-03/ 4-21-03	J. D. Ambrogio
Methods Validation	Requested	6-10-03	M. Shaikh
Labeling	Response is pending review.		
Bioequivalence	Pending		
EA	Adequate	2-24-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes __x_ No If no, explain reason(s) below: Minor Amendment

The Chemistry Review for ANDA 76-545

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
Commitment regarding resolution of any Methods Validation (MV) deficiencies identified in MV process is submitted. See section # 31 of this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Metformin Hydrochloride Extended-Release Tablets, 500 mg: The Reference Listed Drug is Glucophage® XR (NDA Approved for Bristol-Myers Squibb).

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B. Description of How the Drug Product is Intended to be Used:
Metformin HCl have been used for many years for treatment of patients with diabetes Type II and historically has been found to be safe and efficacious. It is used orally.

C. Basis for Approvability **or Not-Approval Recommendation**
Approvable pending acceptable EER, FPL and Bio status.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/ mujahid shaikh 6/30/03
HFD-625/MSmela/ M Smela 6/30/03
V:/Firmsam/ivaxpharm/ltrs&rev/76545.R02doc

C. CC: **ANDA 76-545**
Division File
DUP Jacket
Field Copy

APPEARS THIS WAY
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of trade secret and/or

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information from

CHEMISTRY REVIEW #2

[May perform all necessary testing for inactive or active ingredients and /or finished product]

12. 

34. BIOEQUIVALENCE : Pending Review.

Ivax submitted *in-vivo* bio study of Metformin Hydrochloride Extended-Release tablets, 500 mg .

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Categorical Exclusion per 21 CFR 25.24(a) is requested (page 4 552).

Addendum to Chemist Review # 2 for **ANDA 76-545**

Metformin Hydrochloride Extended-Release Tablets, 500 mg
Ivax Pharmaceuticals, Inc.

Amendment (BIO): September 26, 2003
Gratuitous Amendment – Chemistry: October 2, 2003.

This addendum is being written to issue a MINOR amendment action based on the recommendation made in the bio review completed on October 10, 2003 regarding the dissolution method, and the specifications.

Bio Status is found **acceptable** per review conducted by S. Shrivastava and signed off by B. Davit on October 10, 2003. In this review, following recommendations are made regarding the dissolution testing:

The dissolution testing should be conducted in 1000 mL of 0.05 M Phosphate buffer at pH 6.8 using USP Apparatus 2 (Paddle) at 100 rpm. Tentatively, the test product should meet the following specifications:

1 Hr.	— %
2 Hrs.	— %
6 Hrs.	— %
10 Hrs.	Not less than — %

of the labeled amount of the drug in the dosage form is dissolved in the given time.

Based on above revisions, Ivax is being asked to test retained samples from accelerated stability for dissolution to demonstrate that the product meet the dissolution specifications recommended by the DBE. Ivax is also being asked to submit revised release and stability specifications. This reviewer likes to clarify that the release and stability specifications submitted in October 2, 2003 amendment do not meet the DBE recommended dissolution specifications.

Current status of other pending items identified in CR # 2 is as follows:

EER: **Acceptable** on August 26, 2003 by J.D. Ambrogio.

FPL: **Acceptable** per A. Payne's review completed on 8-12-03 and signed off on 8-14-03 by John Grace.

MV: Method Validation **request has been withdrawn** under the new guideline of OGD on October 6, 2003 per E-mail sent by Mike Smela to Diane Bargo (DFS).

No new information is submitted for referenced DMF —— since the last review cited in section # 22 of the CR # 2.

Item # 36 is written to request a Minor amendment from the firm.

36. Chemistry Comments to be Provided to the Applicant

ANDA: 76-545 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Metformin Hydrochloride Extended-Release Tablets, 500 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please revise your dissolution method and specification based on the attached recommendation made by the Division of Bioequivalence (DBE) for release and stability of the drug product. Please provide a copy of the revised method.

2. Please test your retained samples from accelerated stability for dissolution to demonstrate that the product meets the dissolution specifications recommended by the DBE. Alternatively, you may test the long term samples and propose the expiration dating period to match the available data.

3. Please provide revised release and stability specifications for the tablets incorporating the revision regarding dissolution.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please submit any additional stability data for the exhibit batch that may be available.

Sincerely yours,

M Smela for 10/15/03

Rashmikant M. Patel, Ph.D
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA: 76-545
ANDA DUP
Division File
Field Copy

Endorsements :

HFD-625/M. Shaikh /10/15/03 Mujahid Shaikh 10/15/03
HFD-6 25/M. Smela /10/15/03 M Smela 10/15/03
HFD-6 17/ PChen /10/15/03 Peter Chen 10/15/03
F/t by:

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NOT APPROVABLE – MINOR

ANDA 76-545

Metformin Hydrochloride Extended-Release Tablets, 500 mg

Ivax Pharmaceuticals, Inc .

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-545

2. REVIEW #: 3

3. REVIEW DATE: October 22, 2003

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	11-25-02
NC (Tox Information)	1-3-03
NC (Tox Information)	1-13-03
Minor Amendment	5-22-03
Amendment (Labeling)	6-10-03
Telephone Amendment	6-27-03
Amendment (Bio)	9-26-03
Amendment (Gratuitous - Chemistry)	10-2-03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed*	Document Date
Minor Amendment (Response to 10-17-03 NA letter)	10-21-03
Telephone Amendment – Patent Information	10-17-03

Note: This ANDA is accepted for filing on November 26, 2002 and Acknowledgement letter is issued to the firm on 1-14-03..

7. NAME & ADDRESS OF APPLICANT:

Name: Ivax Pharmaceuticals, Inc .

Address: 140 Legrand Avenue, Northvale, NJ 07647

Representative: Patricia Jaworski

Telephone: 201-767-1700, Ext. 323 or 146

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Metformin Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): Glucophage® XR Tablets and it is approved for Bristol-Myers Squibb Co (NDA 021202).

10. PHARMACOLY CATEGORY:

To control sugar level in patients with Type II Diabetes.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

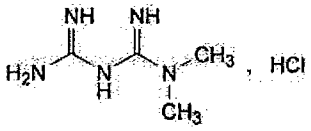
_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Metformin Hydrochloride Extended-Release Tablets

Chemical name: 1,1-Dimethylbiguanide.hydrochloride
Formula: $C_4H_{11}N_5$
Molecular weight: 129.1644
CAS registry number(s): 657-24-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	9-27-02	CR # 5 completed by K. Furnkranz
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8-26-03	J. D. Ambrogio
Methods Validation	Request Withdrawn	10-6-03	Mike Smela's E-mail
Labeling	Acceptable	8-14-03	A.Payne/J.Grace
Bioequivalence	Acceptable	10-10-03	S. Shrivastava/B. Davit
EA	Adequate	2-24-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes __x_ No If no, explain reason(s) below: Minor Amendment

The Chemistry Review for ANDA 76-545

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Metformin Hydrochloride Extended-Release Tablets, 500 mg: The Reference Listed Drug is Glucophage® XR (NDA Approved for Bristol-Myers Squibb).

Drug Substance: The active ingredient in this drug product is Metformin Hydrochloride. Metformin Hydrochloride is non-USP material and its acceptance specifications are based on its manufacturer.

B. Description of How the Drug Product is Intended to be Used:

Metformin HCl have been used for many years for treatment of patients with diabetes Type II and historically has been found to be safe and efficacious. It is used orally.

C. Basis for Approvability **or Not-Approval Recommendation**

Approved based on acceptable EER, FPL, DMF, release and stability specifications and Bio status.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/10/22/03 mupaida Shaikh 10/22/03
HFD-625/MSmela/10/22/03 M Smela 10/27/03
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C. CC: **ANDA 76-545**
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CHEMISTRY REVIEW #3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-545
Drug Product Name	Metformin Hydrochloride ER Tablets
Strength	500 mg
Applicant Name	Ivax
Address	Northvale, NJ
Submission Date(s)	November 25, 2002
Amendment Date(s)	None
Reviewer	**S. P. Shrivastava**
First Generic	**No**
File Location	**V:\firmsam\ ivax\ltrs&rev\76545n1102**

I. Executive Summary

This application references Glucophage® XR tablets, 500 mg (metformin hydrochloride) and includes one fasting study in India, and two fed BE studies, one in India (Fed-1) and another in Canada (Fed-2). The purpose of conducting two fed studies is to demonstrate that BE studies conducted in India and Canada are comparable, and in future such studies could be conducted in India. The fasting study is a single-dose two-way crossover study using 64 male normal healthy volunteers, each dosed with 500 mg ER tablets. The results (point estimate and 90% CI) for the fasting BE study are: LAUCt of 107, 100.91-113.36%; LAUCi of 107, 101.10-113.01%; and LCmax of 105, 99.17-111.46%. The Fed-1 BE study is a single-dose two-way crossover study using 18 male normal healthy volunteers each dosed with 500 mg ER tablets. The results of the Fed-1 BE study are LAUCt of 100, 92.25-108.49%; LAUCi of 100, 93.68-106.85%; and LCmax of 100, 92.63-107.19%. These two studies are incomplete due to analytical method deficiencies. The Fed-2 BE study is a single-dose two-way crossover study using 18 male and female normal healthy volunteers each dosed with 500 mg ER tablets. The results of the Fed-2 BE study are LAUCt of 90, 83.25-96.52%; LAUCi of 90, 83.67-96.27%; and LCmax of 103, 98.16-107.52. Fed-2 study is acceptable. The dissolution in 900 mL phosphate buffer at pH 6.8, using Apparatus 2 (Paddle) at 75 rpm, is incomplete because i) the firm did not use the FDA dissolution testing method and ii) the firm did not provide the multimedia dissolution testing for characterizing its formulation. The firm is requested to respond to the deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Metformin Hydrochloride ER Tablets
Reference Product	Glucophage® -XR Tablets 500 mg
RLD Manufacturer	Bristol-Myers Squibb
NDA No.	21-202
RLD Approval Date	10/13/2000
Indication	To improve glycemic control in patients with Type 2 diabetes

B. PK/PD Information

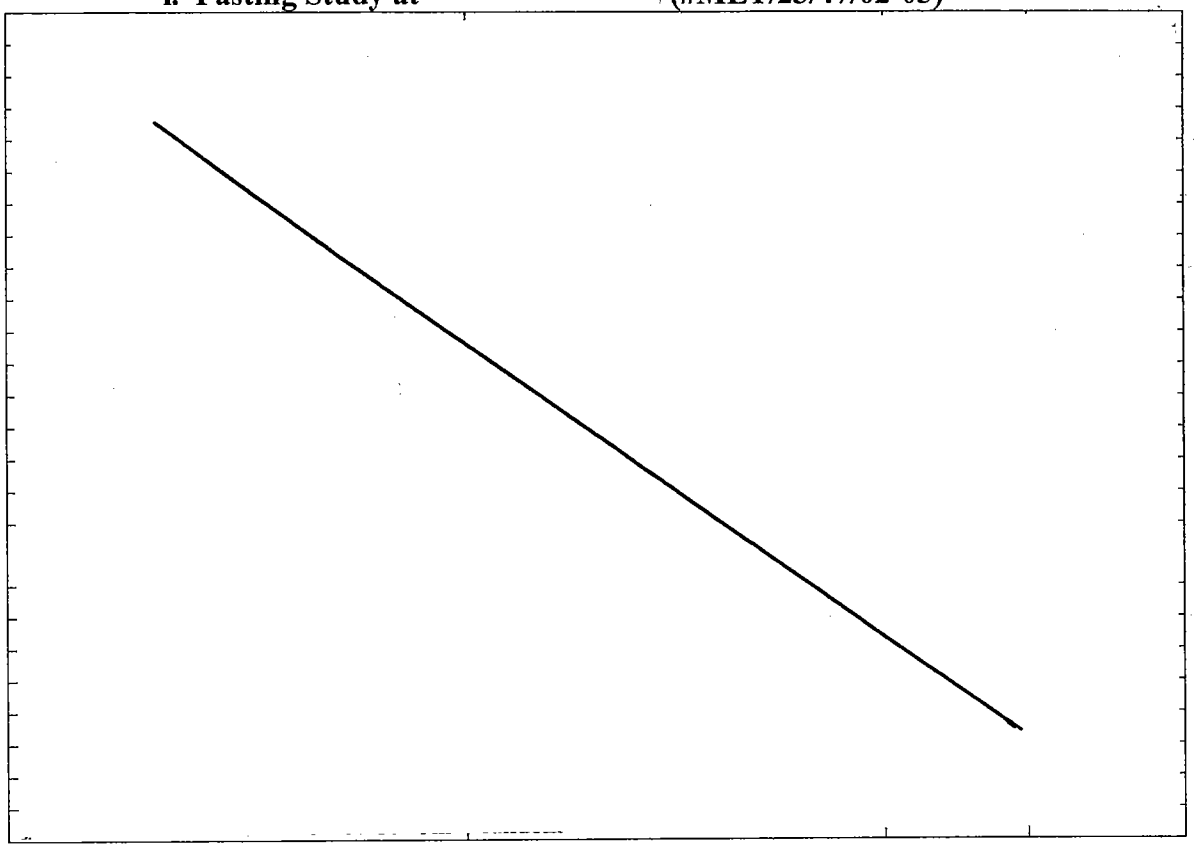
Bioavailability	50-60%
Food Effect	40% lower Cmax, 25% lower AUC and 35 min. longer Tmax compared to fasting study.
Tmax	7 hrs. (4-8 hrs.)
Metabolism	No hepatic metabolism have been identified
Excretion	90% eliminated, unchanged, via kidney in 24 hrs.
Half-life	Plasma - 6.2 hrs.; blood – 17.6 hrs.
Relevant OGD or DBE History	**CD #00-460, 01-188, 01-511:** Single-dose fasting and non-fasting BE studies were recommended using a replicate design. **CD 02-057:** Dissolution in water, SGF without enzyme at pH 1.2, buffer at pH 4.5, SIF without enzyme at pH 6.8, and in phosphate buffer at pH 6.8 (innovator's method) were recommended. Basket and Paddle at various speeds and 1000 mL media volume were recommended. **ANDAs: 76-172, 76-223, 76-249, 76-269.** In all cases single-dose fasting and non-fasting studies with replicate design were submitted. The recommended dissolution media was phosphate buffer at pH 6.8; volume varied between 900 and 1000 mL; Apparatus II (Paddle) at 75 or 100 rpm; Sampling time varied between 1 - 10 and 1-12 hrs. and specifications also varied among the ANDAs. **ANDA 76-450:** In this case single-dose fasting and non-fasting studies in a 2-way crossover design, were conducted and accepted by the DBE.
Agency Guidance	None
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Y	1
Single-dose fed	Y	2
Steady-state	N	
In vitro dissolution	Y	1
Waiver requests	N	
BCS Waivers	N	
Vasoconstrictor Studies	N	
Clinical Endpoints	N	
Failed Studies	N	
Amendments	N	

Pre-Study Bioanalytical Method Validation

i. Fasting Study at [redacted] (#MET/23/47/02-03)



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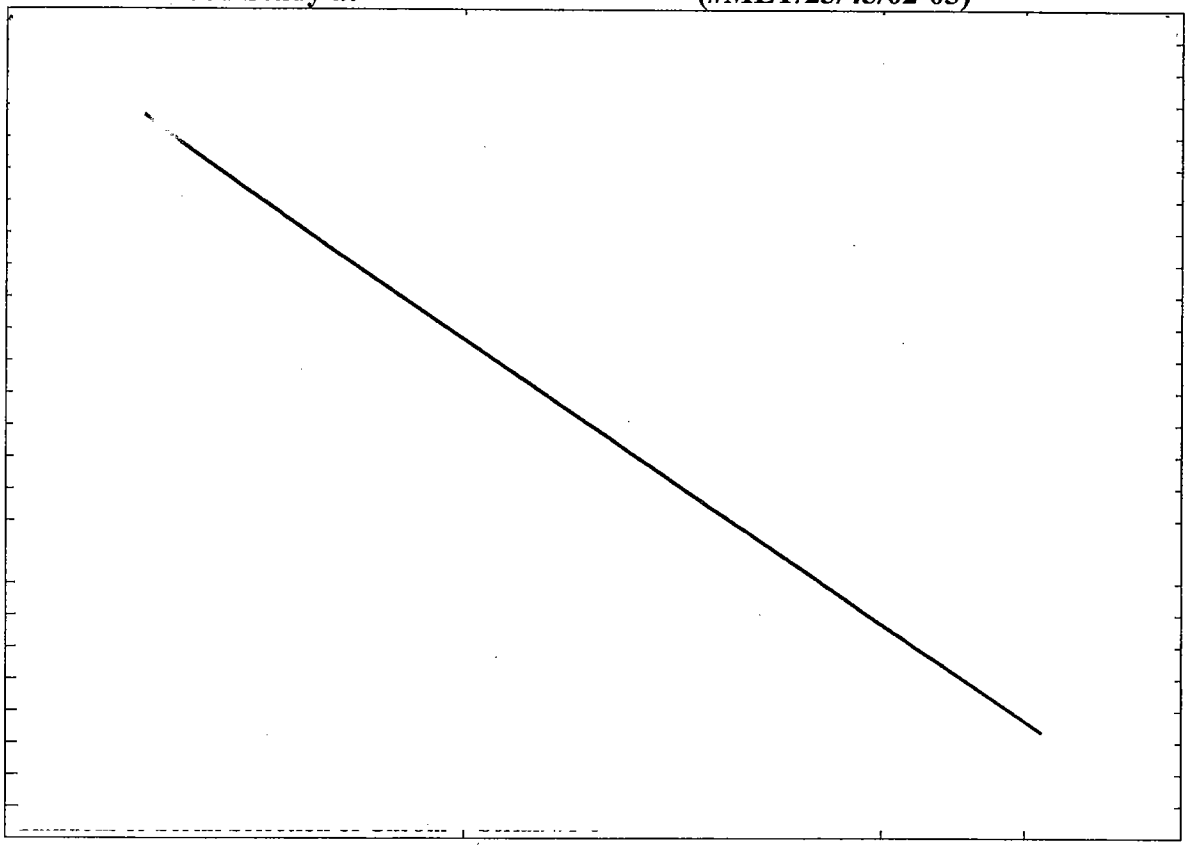
ii. **Food Study at [redacted] (#MET/23/45/02-03)**



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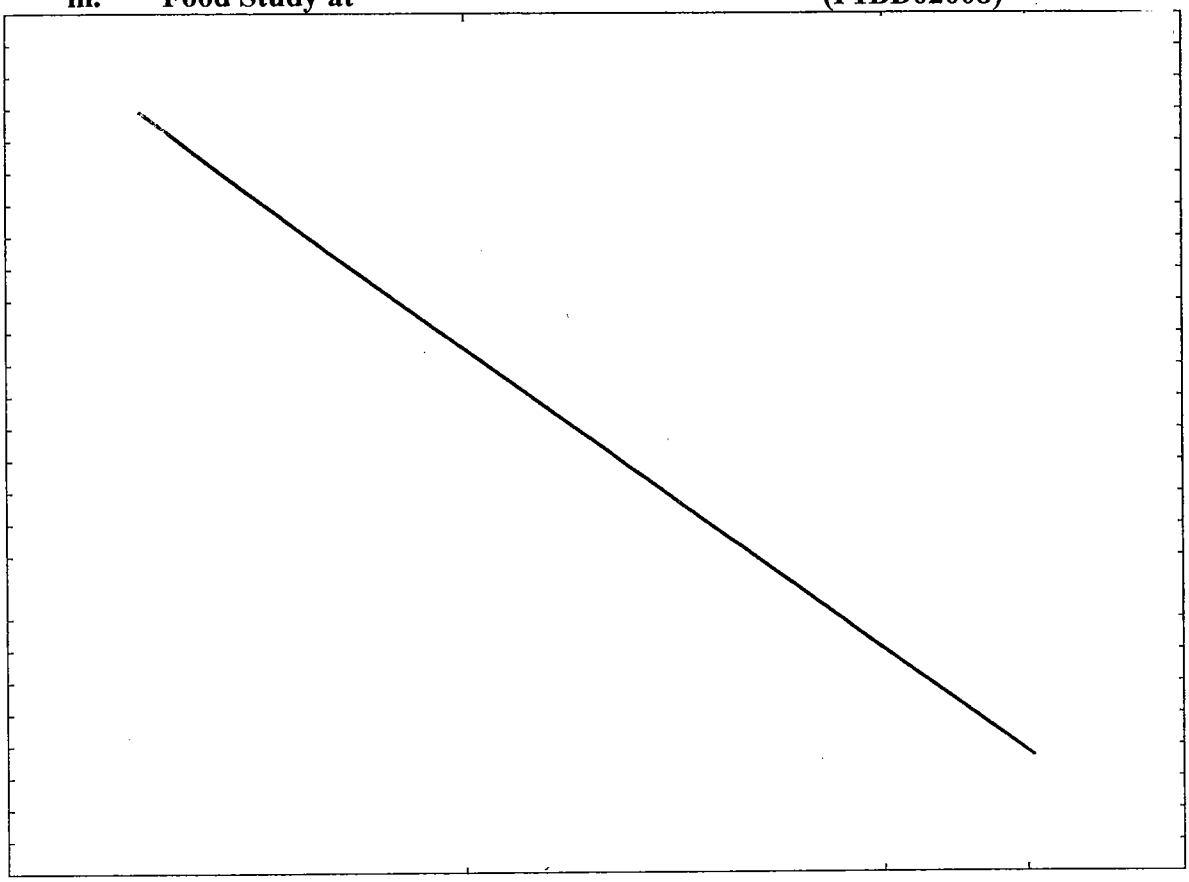
iii. **Food Study at** ——————————— **(P1BD02008)**



D. In Vivo Studies

1. **Single-dose Fasting Bioequivalence Study**

Study Summary	
Study No.	MET/23/47/02-03
Study Design	Randomized, 2-Way cross-over
No. of subjects enrolled	70
No. of subjects completing	68
No. of subjects analyzed	64 as per protocol
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 70 Female: 0
Test product	Metformin HCl ER tablets
Reference product	Glucophage®-XR tablets Bristol Myers-Squibb
Strength tested	500 mg
Dose	1 x 500 mg

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	1.07	100.91-113.36
AUC∞	1.07	101.10-113.01
Cmax	1.05	99.17-111.46

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Inconsistent with pharmacokinetic data	**3**	**0**	**0.1**	**0.0**	**0**	**0**	**0.0**	**0.0**
Total	**3**	**0**	**0.1**	**0.0**	**0**	**0**	**0.0**	**0.0**

Did use of recalculated plasma concentration data change study outcome? --- No

Conclusion: The fasting BE study is incomplete because of the analytical method validation is incomplete.

2. Single-dose Fed Bioequivalence Study:

a) Study Conducted at ——————————

Study No.	MET/23/45/02-03
Study Design	Randomized 2-way cross-over
No. of subjects enrolled	24
No. of subjects completing	24
No. of subjects analyzed	18 as per protocol
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male -18 Female - 0
Test product	Metformin HCl ER tablets
Reference product	Glucophage®-XR tablets Bristol Myers-Squibb
Strength tested	500 mg
Dose	1 x 500 mg

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	1.00	92.25-108.49
AUC∞	1.00	93.68-106.85
Cmax	1.00	92.63-107.19

Repeat Analysis:

The firm performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but has not provided i) the identification of the subject samples that were assayed again, ii) reasons for the repeat assay, iii) identification of the value (original or repeated) that was used in PK analysis along with the objective criteria of acceptance, and iv) a table containing the information mentioned in the item i to iii .

Conclusion: The Indian, single-dose fed bioequivalence study is deficient due to the following reason: Inadequate methods validation information available for evaluation (see above, Comments on Within-Study Validation).

b) Study Conducted at _____

Study No.	P1BD02008
Study Design	Randomized 2-way cross-over
No. of subjects enrolled	24
No. of subjects completing	22
No. of subjects analyzed	19 as per protocol
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male 16 Female 8
Test product	Metformin HCl ER tablets
Reference product	Glucophage®-XR tablets Bristol Myers-Squibb
Strength tested	500 mg
Dose	1 x 500 mg

Summary of Statistical Analysis		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.90	83.25-96.52
AUC_{∞}	0.90	83.67-96.27
C_{max}	1.03	98.16-107.52

- Repeat Analysis: Run #4 (Subject #8 and 10) failed because the two QC samples were out of range. The run was repeated as Run #11.

Conclusion: The single-dose fed bioequivalence study is acceptable.

B. Formulation

Location in appendix	Section IV.B, Page 36
Inactive ingredients within IIG Limits (yes or no)	**no**
If no, list ingredients outside of limits	**Hydroxypropyl cellulose. Re: consult by J. E. Hage, 3/7/03**
If a tablet, is the product scored? (yes or no)	**Tablet, not scored**
If yes, which strengths are scored?	---
Is scoring of RLD the same as test? (yes or no)	**N/A**
Formulation is acceptable (yes or no)	**Yes, because of the consult**
If not acceptable, why?	---

C. In Vitro Dissolution

Source of Method (Firm)	
Medium	0.05 M Potassium phosphate buffer at pH 6.8
Volume (mL)	900 mL at 37 ^{0}C
USP Apparatus type	2 (Paddle)
Rotation (rpm)	75
Firm's proposed specifications	1 Hr. – —— %; 4 Hrs. – —— %; 10 Hrs. - NLT —%
	Note: Method differs from the FDA method in medium volume and Paddle speed.
FDA-recommended specifications	NDA Method: Medium: 1000 mL 0.05 M phosphate buffer, pH 6.8 at 37 ^{0}C Apparatus 2 (Paddle) at 100 rpm This method and following specifications were suggested for ANDA 76-269: 1 Hr. —— % 2 Hrs. —— % 6 Hrs. —— % 10 Hrs. NLT —%
F2 metric calculated (yes or no)	Yes
If no, reason why F2 not calculated	----
Method is acceptable (yes or no)	No

F2 metric, lower strengths compared to highest strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
NONE			
add rows as needed			

F2 metric, test compared to reference	
Strength	F2 metric
n=6 (1-10 hrs)	47.01
n=7 (1-12 hrs)	47.83
add rows as needed	

D. Waiver Request(s) --- N/A

Strengths for which waivers requested
Regulation cited
Proportional to strength tested in vivo (yes or no)
Dissolution is acceptable (yes or no)
Waiver granted (yes or no)

E. Deficiency/Comments

1. In the single-dose fasting study, #MET/23/47/02-03:

   a. The firm has not provided signed and dated letter from Independent Ethics Committee (IRB) pertaining to the approval of the protocol and applicable deviations.

   b. The firm has not provided SOPs for repeat assays, and acceptance criteria for accepting/rejecting repeated values.

2. In the single-dose fed (Indian) study:

   a. The firm performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but has not provided i) the identification of the subject samples that were assayed again, ii) reasons for the repeat assay, iii) identification of the value (original or repeated) was used in PK analysis along with the objective criteria of acceptance, and iv) a table containing the information mentioned in the item i to iii .

   b. The firm has not provided SOPs for repeat assays, and acceptance criteria for repeat values.

3. Since there is no USP method, the FDA recommends the following dissolution method developed for the RLD - Medium – 0.05 M phosphate buffer at pH 6.8, Volume 1000 mL at 37 °C, and Apparatus 2 (Paddle) at 100 rpm. The firm has conducted dissolution testing using a slightly different method - 900 mL of the medium and Paddle speed of 75 rpm. The study should be repeated using the FDA method.

4. Additionally, for controlled release drug products, the DBE requests dissolution testing in multiple media. The firm is requested to provide comparative dissolution data in the 1000 ml of multiple media (e.g. in water and in buffered media at pH 1.2, 4.5 and 6.8) using apparatus 2 (paddle) at 100 rpm and at 1, 2, 6 and 10 hours sampling time points or until at least 85% of the labeled amount is dissolved.

F. Recommendations

1. The bioequivalence study conducted under fasting conditions on metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage®-XR, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb is incomplete due to deficiency #1 cited above.

2. The bioequivalence study conducted at ———— under non-fasting conditions on its metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to

Glucophage®-XR, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb is incomplete due to deficiencies #2 cited above.

3. The bioequivalence study conducted at ——————— under non-fasting conditions on its metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage®-XR, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb is acceptable.

4. The dissolution testing conducted by the firm on its metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage-XR®, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb is incomplete due to deficiencies #3-4 cited above.

From bioequivalence point of view, the firm has not met the requirements of *in vivo* and *in vitro* bioequivalence studies, and the application is incomplete.

The firm should be informed of the deficiencies and recommendations.

Surendra P. Shrivastava, Ph.D.

9/5/2003

Shriniwas Nerurkar, Ph.D.

9/5/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

SPS/sps/8-1-03/76545n1102

cc: ANDA #76-545 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	MET/23/47/02-03
Clinical Site	[redacted]
Principal Investigator	[redacted] M.D.
Study/Dosing Dates	July 23, 2002 and July 30, 2002
Analytical Site	[redacted]
Analytical Director	[redacted] Ph.D.
Analysis Dates	8/23/2002-9/18/2002
Storage Period (no. of days from first sample to final analysis)	57 Days

Treatment ID	A	B
Test or Reference	Ref	Test
Product Name	Glucophage®-XR	Metformin HCl ER
Manufacturer	Bristol-Myers Squibb	Ivax
Batch/Lot No.	MAM21	105915-ND
Manufacture Date	N/A	3/4/02
Expiration Date	1/03	3/03 (Tentative)
Strength	500 mg	500 mg
Dosage Form	Tablets	Tablets
Batch Size	----	[redacted] Tablets
Production Batch Size	----	[redacted] Tablets
Potency	97.3%	98.7%
Content Uniformity	93.4-98.8%	96.9-100.2%
Formulation	----	See Appendix Section B
Dose Administered	1 x 500 mg	1 x 500 mg
Route of Administration	Oral	
Co-administration	240 mL 20% glucose water followed by additional 60 mL glucose water every hr. for 9 hrs. post-dosing.	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization Scheme	AB: 2, 5, 6, 7, 9, 10, 12, 14, 16, 18, 19, 20, 24, 25, 26, 27, 28, 33, 34, 36, 40, 42, 44, 45, 48, 49, 51, 54, 55, 57, 58, 61, 63, 65, 68, 69 BA: 1, 3, 4, 8, 11, 13, 14, 15, 17, 21, 22, 23, 29, 30, 31, 32, 35, 37, 38, 39, 41, 43, 46, 47, 50, 52, 53, 56, 59, 60, 62, 64, 66, 67, 70
Blood Sampling Times (Hr)	0, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20, 24, 30, and 36
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Plasma stored at –20 ^{0}C until analysis
IRB Approval	Not submitted
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hrs. pre-dose and 4 hrs. post-dose
Length of Confinement	Dosing time minus 12 Hrs to +36 hrs
Safety Monitoring	Vitals at 0, 4, 12, 24 and 36 hrs post-dosing

Table 1. Demographics of Study Subjects

Age		Weight, Kg		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	
Mean	25.2	Mean	57.73	18-40	100.0	Male	100.0	Afr. Amer.	
SD	4.6	SD	6.23	41-64	0.0	Female	0.0	Hispanic	
Range	19-39	Range	51-74	65-75	0.0			Asian	100.0
				>75	0.0			Others	

Study Results

Table 2 Dropout Information

Subject No	53	56
Reason	Discontinued after Per 1	Discontinued after Per 1
Period	2	2
Replacement	Y, substituted Sub #66 with same SEQ	Y, substituted Sub #67 with same SEQ

Table 3 Study Adverse Events: None related to the drug administered.

Adverse Event Description	# in Test Group	# in Reference Group
None		
Total:		

Table 4 Protocol Deviations: None significant

Type	Subject #s (Test)	Subject #s (Reference)
None		

Comments: (indicate whether adverse events, protocol deviations compromised the integrity of study) --- N/A

Table 5 Assay Validation – Within Study (Vol. 1.3, pages13-17)

	Parent	Metabolite
QC Conc. (ng/mL)		
Inter day Precision (%CV)		
Inter day Accuracy (%)		
Cal. Standards Conc. (ng/mL)		
Inter day Precision (%CV)		
Inter day Accuracy (%)		
Linearity Range (range of R^2 values)		

Chromatograms: Any interfering peaks? -- None

Table 6. SOP's dealing with analyses of study samples

SOP No.	Date of SOP	SOP Title
BA-08-01 BA-08-02	3/23/02 9/13/02	Preparation of calibration Curve and QC samples, and defining analytical batch acceptance criteria
BA-11-02	3/23/02	Analytical Methods Validation
MS-59-01 MS-59-02	9/16/02 9/30/02	Assay of metformin in human plasma by [redacted]

Comments on repeat assays. *ALWAYS include your comments on the topics listed below. Other comments may be listed if appropriate. You do not have to include the exact text listed below.*

- Did recalculation of plasma concentrations change the study outcome? -- No
- Does the reviewer agree with the outcome of the repeat assays? -- Yes
- Pharmacokinetic Repeats:
  There were 3 pharmacokinetic repeats out of 2816 samples analyzed. They were for Subject #66, Per 1, B (Test) at 24, 30 and 36 hrs. post-dose, because of inconsistent PK values. The original values were accepted.

Comments on Within-Study Validation:

1. The firm has not provided signed and dated letter from Independent Ethics Committee (IRB) pertaining to approval of the protocol and applicable deviations.

2. The firm has not provided SOPs for repeat assays, and acceptance criteria for acceptance/rejection of repeat values.

Conclusion: The study is incomplete because of the analytical method validation is incomplete.

Table 7 Additional Study Information

Root mean square error, AUCt	0.1972
Root mean square error, Cmax	0.1979
mean ratio AUC0-t/AUC∞	Test – 0.96; Ref – 0.96
Range of values, ratio AUC0-t/AUC∞	Test – 0.91-0.98; Ref – 0.88-0.98

Comments: (on pharmacokinetic analysis, data in Tables 8-10, Fig. 1)

ALWAYS include your comments on the topics listed below. Other comments may be listed if appropriate. You do not have to include the exact text listed below.

- Ke and AUCi were determined for **all** subjects. If there are cases in which Ke cannot be calculated, indicate if you agree or disagree with firm's decision. --- N/A
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr, --- None
  b. first scheduled post-dose sampling time as Tmax, and ---None
  c. first measurable drug concentration as Cmax. --- None
  (If none fall into these categories, indicate "none" for each item.)
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? ---Yes
- Were there statistically significant sequence or period effects? If so, did these affect the integrity of the study? Significant PER and TRT effect on AUCt and AUCi were observed. However, it does not appear to affect the integrity of the study.

- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. --- yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect --- N/A

Conclusion: The single-dose fasting bioequivalence study is incomplete due to inadequate information on methods validation (see above, Comments on Within-Study Validation).

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

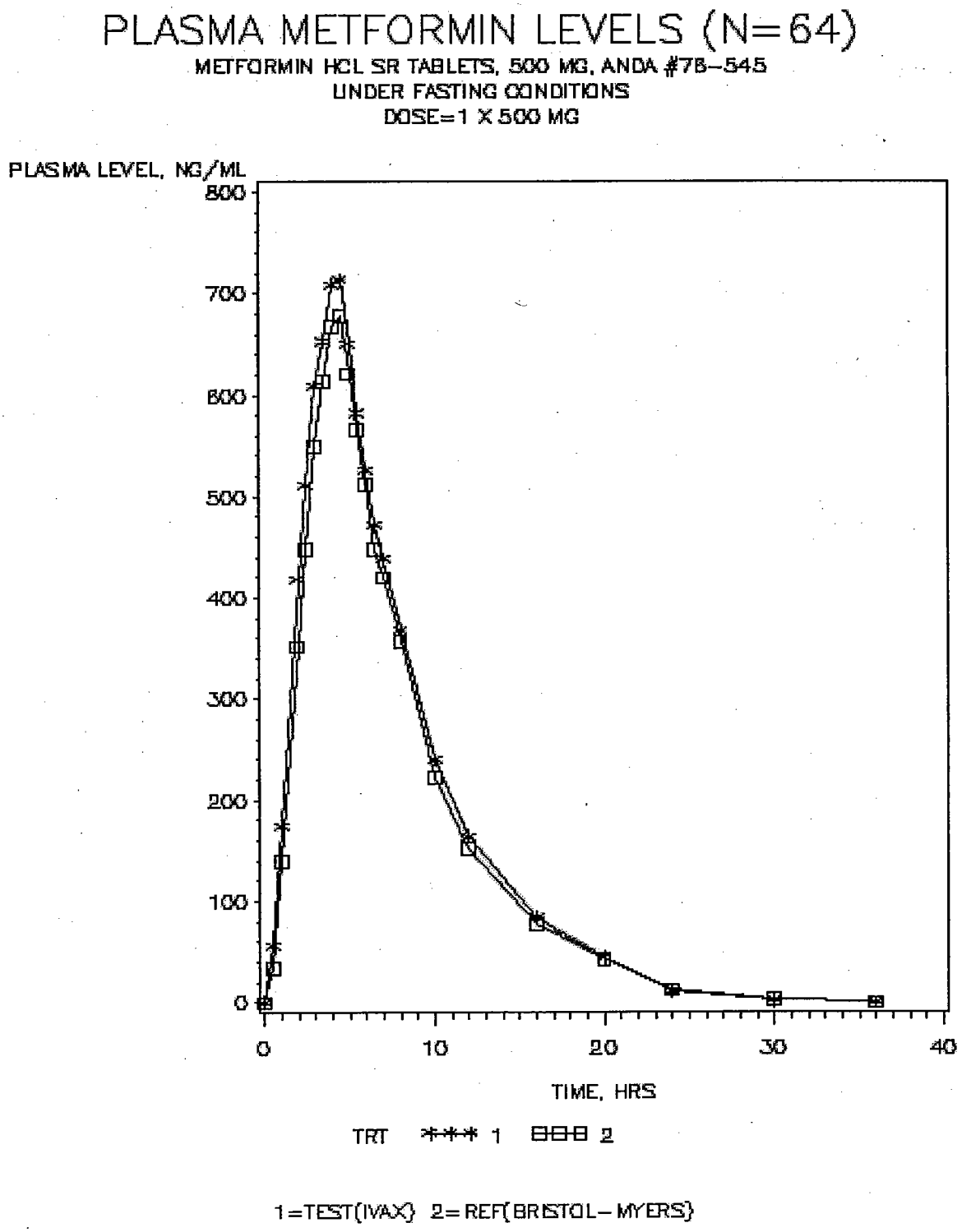


TABLE 8. METFORMIN LEVELS FOR TEST AND REFERENCE PRODUCTS UNDER FASTING CONDITIONS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	56.25	41.42	34.10	31.96	1.65
1	174.20	70.69	140.20	62.13	1.24
2	417.43	131.39	352.15	108.23	1.19
2.5	512.17	146.24	447.65	122.07	1.14
3	608.39	174.49	550.37	153.03	1.11
3.5	653.39	176.86	613.31	168.38	1.07
4	708.47	208.81	667.54	184.20	1.06
4.5	713.93	192.60	677.82	173.93	1.05
5	649.92	172.16	621.08	154.18	1.05
5.5	582.79	154.01	566.01	139.86	1.03
6	525.75	142.42	512.04	135.42	1.03
6.5	471.73	131.82	448.38	120.96	1.05
7	438.43	127.95	420.39	117.72	1.04
8	368.36	118.82	357.85	111.36	1.03
10	240.22	94.70	222.76	84.95	1.08
12	164.27	85.13	151.31	70.51	1.09
16	83.62	58.29	77.02	57.14	1.09
20	44.37	42.02	42.05	44.42	1.06
24	10.83	23.90	12.20	30.33	0.89
30	1.60	7.33	2.38	9.49	0.67
36	0.00	0.00	0.00	0.00	.

Mean1=TEST; MEAN2=REFERENCE; UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 9. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
LAUCI	5521.95	0.29	5165.97	0.27	1.07
LAUCT	5301.96	0.30	4957.24	0.29	1.07
LCMAX	723.67	0.29	688.32	0.28	1.05
Kel	0.18	0.04	0.18	0.04	1.00
Thalf	3.91	0.83	4.00	0.93	0.98
Tmax	4.16	0.64	4.37	0.67	0.95

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 10. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	5521.95	5165.97	1.07	101.10	113.01
LAUCT	5301.96	4957.24	1.07	100.91	113.36
LCMAX	723.67	688.32	1.05	99.17	111.46

2. Single-dose Fed Bioequivalence Study

a. Food Study Conducted in India at Vimta Labs. (#MET/23/45/02-03)

Study Information	
Study Number	MET/23/45/02-03
Clinical Site	[redacted]
Principal Investigator	[redacted], M.D.
Study/Dosing Dates	8/2/02 – 8/10/02
Analytical Site	[redacted]
Analytical Director	[redacted], M.Sc.
Analysis Dates	9/12/02 – 9/29/02
Storage Period (no. of days from first sample to final analysis)	58 Days

Treatment ID	A	B
Test or Reference	Reference	Test
Product Name	Glucophage®-XR	Metformin HCl ER
Manufacturer	Bristol-Myers Squibb	Ivax
Batch/Lot No.	MAM21	105915-ND
Manufacture Date	N/A	3/4/02
Expiration Date	1/03	3/03 (Tentative)
Strength	500 mg	500 mg
Dosage Form	Tablets	Tablets
Batch Size	----	[redacted] Tablets
Production Batch Size	----	[redacted] Tablets
Potency	97.3%	98.7%
Content Uniformity	93.4-98.8%	96.9-100.2%
Formulation	----	See Appendix Section B
Dose Administered	1 x 500 mg	1 x 500 mg
Route of Administration	Oral	
Co-administration	240 mL water	

Subjects consumed Indian high fat breakfast which compared with reference American high fat breakfast used in another food study (see below, Study #P1BD02008). It consisted of the following:

<u>Indian Breakfast (used in the study)</u>

Upma (a semolina and lentil based steamed spiced dish)	160 g
Puri (2, deep fried wheat based pancake)	50 g
Potato Curry (vegetable)	110 g
Coconut Chutney (spicy sauce)	55 g
Egg, Boiled (2)	100 g
Milk (Whole, 5.8% fat)	100 mL

Reference American Breakfast

Buttered English Muffin	1
Fried Egg	1
Sliced American Cheese	1
Sliced Canadian Bacon	1
Hash Brown Potatoes	2.45 oz
Orange Juice	180 mL
Whole Milk	240 mL

Comparison of Indian and American breakfasts. The composition of Indian high fat breakfast used in the study may be considered comparable to the American high fat breakfast, even though it is 5% higher in fat and 4% lower in protein contents (see table below).

	Indian Breakfast Used		**Reference American Breakfast**	
Nutrient	**Percent**	**Calories**	**Percent**	**Calories**
Carbohydrate	30	288	35	315
Fats	54	511	45	405
Proteins	16	146	20	280
Total		**945**		**1000**

No. of Sequences	~~2~~
No. of Periods	~~2~~
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization Scheme	AB: 2, 5, 6, 7, 9, 10, 12, 16, 18, 19, 20, 24 BA: 1, 3, 4, 8, 11, 13, 14, 15, 17, 21, 22, 23
Blood Sampling Times (Hr)	0, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20, 24, 30, and 36
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Plasma stored at –20 ^{0}C until analysis
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 8
Length of Fasting	10 hrs. pre-dose and 4 hrs. post-dose
Length of Confinement	Dosing time minus 12 Hrs to +36 hrs post-dose
Safety Monitoring	Vitals at 0, 4, 12, 24 and 36 hrs post-dose

Table 8 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	0.0
Mean	26.2	Mean	59.7	18-40	100.0	Male	100.0	Afr. Amer.	0.0
SD	4.9	SD	5.9	41-64	0.0	Female	0.0	Hispanic	0.0
Range	20-37	Range	50-72	65-75	0.0			Asian	100.0
				>75	0.0			Others	0.0

Study Results

Table 9. Dropout Information --- None (Recruited 24 but planned to analyze only 18. Additional subjects were recruited to fill in for any dropouts)

Subject No
Reason Provide brief description
Period
Replacement Y/N; explain if appropriate

Table 10 Study Adverse Events: None observed

Adverse Event Description	# in Test Group	# in Reference Group
None		
Total:		

Table 11 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Reference)
None		
Blood sampling times	see Vol 16, Page 508	see Vol 16, Page 508
Clinical lab results outside the normal range	see Vol 16, Page 509-512	see Vol 16, Page 509-512

Comments: (indicate whether adverse events, protocol deviations compromised the integrity of study) --- There were no significant deviations or adverse events observed during the study.

Table 12 Assay Validation – Within Study

	Parent	Metabolite
QC Conc. (ng/mL)		
Inter day Precision (%CV)		
Inter day Accuracy (% Accuracy)		
Cal. Standards Conc. (ng/mL)		
Inter day Precision (%CV)		
Inter day Accuracy (% Accuracy)		
Linearity Range (range of R^2 values)		

Chromatograms: Any interfering peaks? --- No

Table 13 SOP's dealing with analytical methods

SOP No.	Date of SOP	SOP Title
SOP 23/MV/69/1	**9/12/02**	**Analytical method for the estimation of metformin in human plasma**
		Note: Analysis also started on 9/12/02. The inspectors should look into any discrepancies in dates and signatures on SOPs, Protocols and studies during the pre-approval inspection.

Comments on repeat assays. *ALWAYS include your comments on the topics listed below. Other comments may be listed if appropriate. You do not have to include the exact text listed below.*

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. --- N/A
- Did recalculation of plasma concentrations change the study outcome? --- N/A
- Does the reviewer agree with the outcome of the repeat assays? ---N/A

Provide any other comments about repeat assays. --- The firm performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but has not provided i) the identification of the subject samples that were assayed again, ii) reasons for the repeat assay, iii) identification of the value (original or repeated) was used in PK analysis along with the objective criteria of acceptance, and iv) a table containing the information mentioned in the item i to iii.

Comments on Within-Study Validation:

Conclusion: Analytical method is not acceptable. If not acceptable, give reason.

1. The firm performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but did not submit i) the original values and values obtained by repeating the assay, ii) reason for repeating the assay and iii) information whether the original or the repeated value was use for PK and statistical analysis.

2. SOPs for repeat assay and acceptance criteria are not available for evaluation.

3. Plasma samples were stored for 58 days at -60 ^{0}C, and the long-term stability studies were conducted for 31 days. However, the firm has conducted two other stability studies on the drug stored in plasma at -20 ^{0}C for 90 and 155 days (Re: fasting study above and food study below). Therefore, another stability study is not recommended. These samples were stored at lower temperature (-60 ^{0}C), which should increases the stability even further.

Table 14 Arithmetic Mean and Ratios

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
LAUCI	8552.62	0.20	8548.44	0.22	1.00
LAUCT	7692.90	0.24	7689.46	0.25	1.00
LCMAX	929.80	0.19	933.13	0.21	1.00
Tmax	6.75	0.67	6.83	0.42	0.99
Thalf	3.77	0.84	3.72	0.69	1.01
Kel	0.19	0.04	0.19	0.04	1.00

Mean plasma concentrations are presented in Table 17 and Fig. 2.

Table 15 Geometric Means and 90% Confidence Intervals

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	8552.62	8548.44	1.00	93.68	106.85
LAUCT	7692.90	7689.46	1.00	92.25	108.49
LCMAX	929.80	933.13	1.00	92.63	107.19

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 16 Additional Study Information

Root mean square error, AUC	0.1393
Root mean square error, Cmax	0.1254
mean ratio AUC0-t/AUC∞	Test-0.90, Ref-0.90
Range of values, ratio AUC0-t/AUC∞	Test – 0.7-0.94; Ref – 0.76-0.96

Comments: (on pharmacokinetic analysis, see Tables 14-17, Fig. 2)

ALWAYS include your comments on the topics listed below. Other comments may be listed if appropriate. You do not have to include the exact text listed below.

- Ke and AUCi were determined for 18 subjects. The reviewer agrees with firm's decision.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr, --- None
  b. first scheduled post-dose sampling time as Tmax, and --- None
  c. first measurable drug concentration as Cmax. --- None
  (If none fall into these categories, indicate "none" for each item.)
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Agree
- There were statistically significant period effects. It did not affect the integrity of the study.
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. ---Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect--- N/A

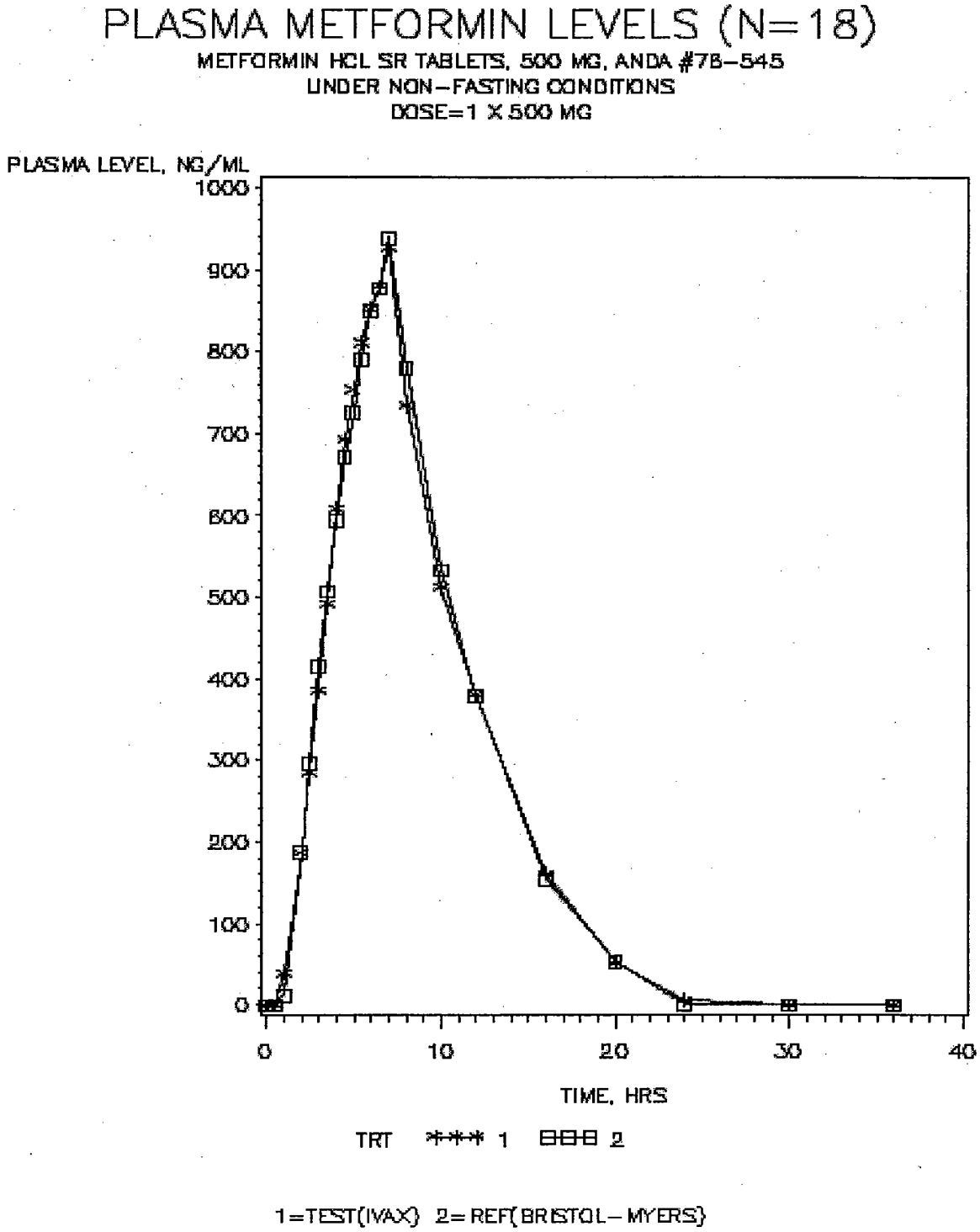
Conclusion: The Indian, single-dose fed bioequivalence study is deficient due to the following reasons: Inadequate methods validation information available for evaluation (see above, Comments on Within-Study Validation).

Table 17. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	0.00	0.00	0.00	0.00	.
1	39.42	69.83	12.38	36.04	3.18
2	187.31	144.27	187.44	133.16	1.00
2.5	284.82	166.99	296.81	190.37	0.96
3	386.50	185.25	415.43	186.35	0.93
3.5	491.44	180.03	507.10	181.51	0.97
4	607.51	159.37	594.51	157.07	1.02
4.5	693.92	155.17	671.55	159.72	1.03
5	754.43	156.34	726.05	149.92	1.04
5.5	811.33	141.54	791.53	156.10	1.03
6	852.05	148.51	850.01	168.79	1.00
6.5	879.09	164.12	877.29	175.67	1.00
7	927.31	194.18	939.28	199.56	0.99
8	734.76	161.24	780.29	204.86	0.94
10	511.72	138.07	533.18	164.35	0.96
12	380.17	126.81	379.83	124.54	1.00
16	160.93	84.04	154.48	89.59	1.04
20	52.67	71.48	51.88	69.66	1.02
24	5.74	24.36	0.00	0.00	.
30	0.00	0.00	0.00	0.00	.
36	0.00	0.00	0.00	0.00	.

MEAN1=TEST MEAN2=REF UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



b. Food Study Conducted in Canada (#P1BD02008)

Study Information	
Study Number	MET/23/45/02-03
Clinical Site	[redacted] Canada
Principal Investigator	[redacted], M.D., FRCP
Study/Dosing Dates	7/31/02 -8/16/02
Analytical Site	[redacted]
Chief Scientific Officer	[redacted] M.S.
Analysis Dates	8/24/02 – 9/6/02
Storage Period (no. of days from first sample to final analysis)	37

Treatment ID	B	A
Test or Reference	Reference	Test
Product Name	Glucophage®-XR	Metformin HCl ER
Manufacturer	Bristol-Myers Squibb	Ivax
Batch/Lot No.	MAM21	105915-ND
Manufacture Date	N/A	3/4/02
Expiration Date	1/03	3/03 (Tentative)
Strength	500 mg	500 mg
Dosage Form	Tablets	Tablets
Batch Size	----	[redacted] Tablets
Production Batch Size	----	[redacted] Tablets
Potency	97.3%	98.7%
Content Uniformity	93.4-98.8%	96.9-100.2%
Formulation	----	See Appendix Section B
Dose Administered	1 x 500 mg	1 x 500 mg
Route of Administration	Oral	
Co-administration	240 mL water	

Subjects consumed reference American high fat breakfast. It consisted of the following:

Reference American Breakfast

Buttered English Muffin	1
Fried Egg	1
Sliced American Cheese	1
Sliced Canadian Bacon	1
Hash Brown Potatoes	2.45 oz
Orange Juice	180 mL
Whole Milk	240 mL

No. of Sequences	~~2~~
No. of Periods	~~2~~
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization Scheme	AB: 1, 4, 5, 6, 8, 11, 12, 15, 18, 21, 22, 24 BA: 2, 3, 7, 9, 10, 13, 14, 16, 17, 19, 20, 23
Blood Sampling Times (Hr)	0, 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 24 and 36
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Plasma stored at –20 ^{0}C until analysis
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 21
Length of Fasting	10 hrs. pre-dose and 4 hrs. post-dose
Length of Confinement	Dosing time minus 10 Hrs to +24 hrs post-dose
Safety Monitoring	Vitals at pre-dose and at 24 hrs post-dose

Table 21 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	58.3
Mean	34	Mean	71.8	18-40	70.8	Male	66.7	Afr. Amer.	16.7
SD	7.71	SD	11.56	41-64	29.2	Female	33.3	Hispanic	12.5
Range	21-48	Range	50.5-95.0	65-75	0.0			Asian	12.5
				>75	0.0			Others	0.0

Study Results

Table 22. Dropout Information

Subject No	#7	#9	#14
Reason	Personal	Personal	Breakfast delayed
Period	Period 2	Period 2	Samples collected, analyzed and included or excluded in ANOVA
Replacement	Y with #19, appropriate	Y with #20, appropriate	Yes with #23. It is appropriate

Table 18 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Loose Bowel	2	1
Unusual Taste	2	0
Dizziness	1	0
Numbness in Tongue	1	0
Tiredness	1	0
Upset Stomach	0	0
Headache	0	3
Nausea	0	2
Heartburn	0	1
Lack of Coordination	0	1
Total:	**7**	**8**

Table 24 Protocol Deviations: None significant

Type	Subject #s (Test)	Subject #s (Reference)

Comments: (indicate whether adverse events, protocol deviations compromised the integrity of study) --- There were no deviations or adverse events that compromised the study.

Table 25 Assay Validation – Within Study

	Parent	Metabolite
QC Conc. (ng/mL)		
Inter day Precision (%CV)		
Inter day Accuracy (% Accuracy)		
Cal. Standards Conc. (ng/mL)		
Inter day Precision (%CV)		
Inter day Accuracy (% accuracy)		
Linearity Range (range of R values)		

Chromatograms: Any interfering peaks? --- No

Table 26 SOP's dealing with analytical methods

SOP No.	Date of SOP	SOP Title
SOP L200.107	6/20/02	Sample Analysis (Chromatographic)

Comments on repeat assays. *ALWAYS include your comments on the topics listed below. Other comments may be listed if appropriate. You do not have to include the exact text listed below.*

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. --- Run #4 (Subject #8 and 10) failed because the two QC samples were out of range. The run was repeated as Run #11.
- Did recalculation of plasma concentrations change the study outcome? --- N/A
- Does the reviewer agree with the outcome of the repeat assays? ---yes
- Provide any other comments about repeat assays. --- none

Comments on Within-Study Validation:

Conclusion: Analytical method is acceptable. If not acceptable, give reason. --- N/A

Table 27 Arithmetic Mean and Ratios

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	6964.67	1663.80	7616.22	1173.19	0.91
AUCT	6803.11	1660.76	7442.67	1172.50	0.91
LAUCI	6761.40	0.26	7533.47	0.15	0.90
LAUCT	6595.54	0.26	7357.78	0.16	0.90
LCMAX	603.85	0.16	587.78	0.16	1.03
Tmax	4.97	1.29	5.50	0.14	0.90
Thalf	5.09	0.83	5.40	0.85	0.94
Kel	0.14	0.02	0.13	0.02	1.08

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Mean plasma concentrations are presented in Table 30 and Fig. 3.

Table 28 Geometric Means and 90% Confidence Intervals

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	6964.67	7616.22	0.91	85.93	96.96
AUCT	6803.11	7442.67	0.91	85.60	97.21
LAUCI	6761.40	7533.47	0.90	83.67	96.27
LAUCT	6595.54	7357.78	0.90	83.25	96.52
LCMAX	603.85	587.78	1.03	98.16	107.52

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 29 Additional Study Information

Root mean square error, AUC	0.1271
Root mean square error, Cmax	0.0782
mean ratio AUC0-t/AUC∞	Test – 0.98, Ref – 0.98
Range of values, ratio AUC0-t/AUC∞	Test – 0.96-0.98, ref – 0.92-0.99

Comments: (on pharmacokinetic analysis, see Tables 27-30, Fig. 3)

ALWAYS include your comments on the topics listed below. Other comments may be listed if appropriate. You do not have to include the exact text listed below.

- Ke and AUCi were determined for 18 subjects. The reviewer agrees with firm's decision.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr, --- None
  b. first scheduled post-dose sampling time as Tmax, and --- None
  c. first measurable drug concentration as Cmax. --- None
  (If none fall into these categories, indicate "none" for each item.)
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Agree
- There were statistically significant treatment effects. It did not affect the integrity of the study.
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. ---Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect--- N/A

Conclusion: The single-dose fed bioequivalence study is acceptable.

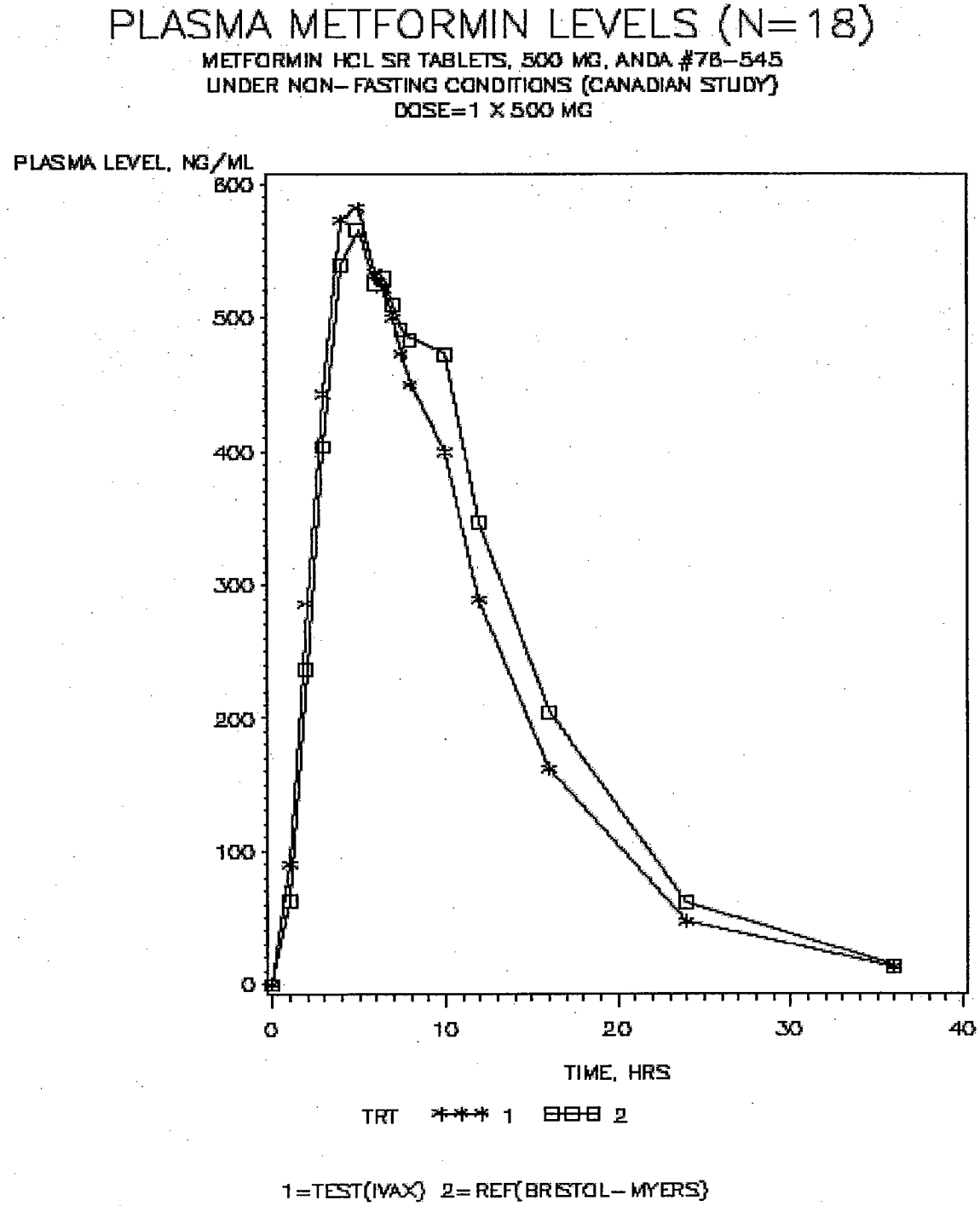
Table 30. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

MEAN PLASMA METFORMIN LEVELS FOR TEST AND REFERENCE PRODUCTS UNDER NON-FASTING CONDITIONS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	89.87	48.33	63.01	44.28	1.43
2	285.97	83.12	236.28	63.23	1.21
3	443.44	90.26	403.89	85.02	1.10
4	573.06	106.88	539.72	77.34	1.06
5	582.06	90.94	566.11	80.38	1.03
6	533.67	100.25	525.22	75.62	1.02
6.5	521.61	112.22	530.67	106.76	0.98
7	500.72	120.29	510.00	97.45	0.98
7.5	473.11	124.09	491.78	92.78	0.96
8	450.39	129.51	484.28	90.38	0.93
10	400.00	126.51	473.44	73.75	0.84
12	288.41	113.96	346.78	77.40	0.83
16	161.98	75.14	204.72	45.59	0.79
24	47.05	22.34	61.22	27.24	0.77
36	12.29	9.22	13.49	8.08	0.91

MEAN1=TEST MEAN2=REF UNIT:PLASMA LEVEL=NG/ML TIME=HRS

Figure 3 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Ingredients	Amount per tablet	%w/w
Metformin hydrochloride	500.0	51.02
Hydroxypropy methylcellulose USP ——		
Hydroxypropyl cellulose NF		
Ethylcellulose NF——		
Microcrystalline cellulose NF		
Hydroxypropyl methylcellulose USP ——		
—————— *		
Stearic Acid NF		
Magnesium Stearate NF		
Total Theoretical Wt.	980.00	100.0

*Removed during processing

Provide data for all strengths of test and also reference (if necessary).

Comments: According to the electronic inactive ingredient guide (IIG), the highest amount of hydroxypropyl cellulose (HPC) in sustained release oral tablet is 187.6 mg/tablet. By using —— mg of HPC, the firm has exceeded the limit. Therefore, the firm was requested to provide safety and toxicity data. The data provided by the firm was sent to Pharm-Tox for consult. As per March 7, 2003 review of Dr. Jeri El-Hage, supervisor pharmacologist, the maximum daily dose, of five (5) 500 mg tablets per day would administer 5 x ——mg = —— mg of HPC per day. This daily dose of HPC (hydroxypropyl cellulose) is safe based on Fao/who Expert Committees determination. The Expert Committee has determined that 1500 mg/day of HPC is permissible daily exposure (PDI) and acceptable daily intake (ADI). Therefore, the formulation is acceptable. [Note: Even though the OGD consulted Dr. Jeri El-Hage for HPC, Dr. El-Hage inadvertently wrote hydroxylpropyl methylcellulose (HPMC) instead of hydroxypropyl cellulose HPC) in the review. The scanned review of Dr. El-Hage is attached].

Dissolution Data (Table 31)

Apparatus - 2 (Paddle) at 75 rpm
Medium - 0.05 M Potassium Phosphate Buffer, pH 6.8 at 37 °C
Volume – 900 mL
Specifications – 1 Hr - ——%; 4 Hrs. – ——%; 10 Hrs – NLT —%

Table 31. Summary of Dissolution Data

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. MAM21		
	Mean	%CV	Range	Mean	%CV	Range
1	35	6.8		26	3.0	
2	49	6.5		38	2.4	
4	68	6.0		55	4.2	
6	81	4.9		68	2.6	

8	90	4.0		78	1.6	
10	95	3.4		85	1.4	
12	99	2.5		91	1.3	
F2, n=6	**1-10 Hrs.**	**47.01**				
F2, n=7	**1-12 Hrs.**	**47.83**				

Dissolution Comments

1. Since there is no USP method, the FDA recommends the following dissolution method developed for the RLD - Medium – 0.05 M phosphate buffer at pH 6.8, Volume 1000 mL at 37 0C, and Apparatus 2 (Paddle) at 100 rpm. The firm has conducted dissolution testing using a slightly different method - 900 mL of the medium and Paddle speed of 75 rpm. Study should be repeated using the FDA method.

2. Additionally, for control release drug products, the DBE requests dissolution testing in the multiple media. The firm is requested to provide comparative the dissolution data in 900 and 1000 mL of the multiple media (e.g. in water and in buffered media at pH 1.2, 4.5 and 6.8) using Apparatus 2 (Paddle) at 75 and 100 rpm at 1, 2, 6 and 10 hours sampling time points or until at least 85% of the labeled amount is dissolved.

C. Consult Reviews

CONSULT-1 (Two Scanned Pages)

Greenberg, Harvey A

From: El Hage, Jeri D
Sent: Friday, March 07, 2003 3:22 PM
To: Allen, Stanley (OND/ODEII); Greenberg, Harvey A; Marshall, Susan; Ripper, Leah W
Subject: ANDA 76-545 pharm/tox consult.

All,

Attached is an electronic copy of this consult. The background materials and hard copy will follow.

Jeri

ANDA76545.co
nsult.doc

Jeri El-Hage, Ph.D.
Pharmacology Supervisor
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research, FDA
Phone: 301-827-6369
Fax: 301-443-9282

ANDA 76-545 **Review Completed: March 7, 2003**
Sponsor: Ivax

Date Consult Received by Reviewer: January 23,2003

PHARMACOLOGY COMMENTS ON CONSULT REQUEST

DRUG: Metformin HCl Extended ReleaseTablets, 500 mg

Reference Drug: Glucophage XR, NDA 21-202, Bristol Myers Squibb

CONSULT REQUEST: OGD requested a safety evaluation by DMEDP (HFD-510) of the concentration of hydroxypropyl methyl cellulose in a new generic metformin formulation.

APPLICANT RESPONSE: The Applicant provided a Facsimile on January 3, 2003 which provided references for preclinical toxicity studies with hydroxypropyl cellulose and safety evaluations based on permissible daily exposure(PDE) and acceptable daily intake(ADI) calculations. Unfortunately, the sponsor's calculations are incorrect because they calculate safety margins based on — mg/day doses of hydroxypropyl methyl cellulose (HPMC). However, the HPMC is present at concentrations of — mg/ tablet, not — mg/day. Since each tablet contains 500 mg of metformin and the approved maximum daily dose of metformin is 2500 mg/day, patients may receive up to —— mg HPMC /day (—— mg/tablet X 5 tablets).

The applicant calculated the PDE of HPMC as —— mg/day with a safety margin of — times the proposed dose (see pg 07 of fax). However, the accurate PDE calculation is ——mg/day ÷ ——— mg/day = —times the proposed dose.

The applicant states the FAO/WHO Expert Committee on Food Additives has established the acceptable daily intake (ADI) of HPMC as 25 mg/kg/day (pg. 08 of fax). Using 60 kg as an average adult body weight, the ADI equals 25 mg/kg/day x 60 kg = 1500 mg/day. This ADI is approximately equal to the proposed maximum daily HPMC dose of ——mg/day.

Conclusion: The conclusion that can be drawn from the sponsors submission is that although their calculations were not based on accurate maximum daily doses of — mg HPMC , the recalculated PDE and ADI support the safety of the daily HPMC doses achieved with this generic product.

Jeri El-Hage, Ph.D.
Pharmacology Supervisor

cc: ANDA 76-545
HFD510/Consult file
HFD510/ElHage/Johnsonk/MarshallS
HFD-102/L. Ripper

D. SAS Outputs

E. Additional Attachments

To include memos, additional tables of data. For example, recalculations of plasma concentrations and statistics can be included here. Each attachment should be numbered.

BIOEQUIVALENCY DEFICIENCIES

ANDA:76-538 APPLICANT: Ivax

DRUG PRODUCT: Metformin Hydrochloride, ER Tablets, 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. In the single-dose fasting study, #MET/23/47/02-03:

   a. Please provide signed and dated letter from the Independent Ethics Committee (IRB) pertaining to the approval of the protocol and applicable deviations.

   b. Please provide the information regarding reassay and SOPs that is highlighted below in the item 2.

2. In the single-dose fed (Indian) study:

   You performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but have not provided the necessary details. **Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.**

3. Since there is no USP method, the FDA recommends the following dissolution method developed for the RLD - Medium - 0.05 M phosphate buffer at pH 6.8, Volume 1000 mL at 37 0C, and Apparatus 2 (Paddle) at 100 rpm. You have conducted dissolution testing using a slightly

different method - 900 mL of the medium and Paddle speed of 75 rpm. Please provide the comparative dissolution data using the FDA method.

4. Additionally, for control release drug products, the DBE requests dissolution testing in the multiple media. You are requested to provide comparative dissolution data in the 900 and 1000 mL of multiple media (e.g. in water and in buffered media at pH 1.2, 4.5 and 6.8) using Apparatus 2 (Paddle) at 75 and 100 rpm and at 1, 2, 6 and 10 hours sampling time points or until at least 85% of the labeled amount is dissolved.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ SShrivastava

v:\FIRMSam\ivax\ltrs&rev\76545n1102
Printed in final on 7/5/03

9/5/03

Endorsements: (Final ~~with~~ Dates)
HFD-655/ SShrivastava 9/5/03
HFD-655/ SNerurkar
HFD-650/ D. Conner 9/5/03

BIOEQUIVALENCY - DEFICIENCIES submission date:11/25/02

1. **FASTING STUDY** (STF) Strengths:500 mg ER Tablets
Clinical: ——— **Outcome: IC**
Analytical: ———

2. **FOOD STUDY** (STP-1) Strengths:500 mg ER Tablets
Clinical: ——— **Outcome: IC**
Analytical: ———

3. **FOOD STUDY** (STP-2) Strengths: 500 mg, ER Tablets
Clinical: ——— **Outcome: AC**
Analytical: ———

4. ~~**DISSOLUTION DATA** (DIS)~~ ~~Strengths: 500 mg ER Tablets~~
Outcome: **IC**

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-545
Drug Product Name	Metformin Hydrochloride ER Tablets
Strength	500 mg
Applicant Name	Ivax
Address	Northvale, NJ
Submission Date(s)	----
Amendment Date(s)	September 26, 2003
Reviewer	**S. P. Shrivastava**
First Generic	**No**
File Location	**V:\firmsam\ ivax\ltrs&rev\76545a0903**

I. Executive Summary

This Amendment references Glucophage® XR tablets, 500 mg (metformin hydrochloride) and includes one fasting study in India, and two fed BE studies, one in India (Fed-1) and another in Canada (Fed-2). The purpose of conducting two fed studies was to demonstrate that BE studies conducted in India and Canada are comparable, and in future such studies could be conducted in India. The fasting, Fed-1 and dissolution studies were deficient. In this amendment the firm has responded to the deficiencies. The response to the deficiencies is acceptable. The fasting, non-fasting and dissolution studies are acceptable. From the bioequivalence point of view the ANDA is acceptable.

II. Review of the Amendment

DEFICIENCY 1: ***In the single-dose fasting study, #MET/23/47/02-03***

a. Please provide signed and dated letter from Independent Ethics Committee (IRB) pertaining to the approval of the protocol and applicable deviations.

Response

The firm has provided the signed and dated documents pertaining to the approval of protocols and deviations from the Independent Ethics Committee. Study Started on July 23, 2002 and the protocol and deviation (for recruiting additional subject from 52 to 70) were signed by the IEC on July 16, 2002 and July 17, 2002, respectively.

Conclusion: The response is acceptable.

b. Please provide the information regarding reassay and SOPs that is highlighted below in the Item 2.

Response: The firm has provided the SOPs for repeat assays, and acceptance criteria for accepting/rejecting repeat values. There were three PK repeat samples (see review, SShrivastava 9/5/03) and in all cases original values were accepted.

Conclusion: The response is acceptable.

DEFICIENCY 2: ***In the single-dose fed (Indian) study:***

You performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but have not provided the necessary details. ***Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.***

Response: The firm has provided the table of samples that were reassayed. It includes sample ID, reasons for reassay, and original, repeat and accepted values. There were no PK repeats. The firm has also included the SOP No. 23/13 and criteria for repeat assays. The SOP dated 6/15/02 was written prior to the study (8/2/02). Repeat assays were conducted according to the SOP.

Conclusion: The response is acceptable.

DEFICIENCY 3. *Since there is no USP method, the FDA recommends the following dissolution method developed for the RLD - Medium – 0.05 M phosphate buffer at pH 6.8, Volume 1000 mL at 37 0C, and Apparatus 2 (Paddle) at 100 rpm. You have conducted dissolution testing using a slightly different method - 900 mL of the medium and Paddle speed of 75 rpm. Please provide the comparative dissolution data using the FDA method.*

Response: The firm has conducted dissolution testing as requested, and has submitted results as follows (Table 1): Note : The reference biolot expired on 1/2003. The firm has used different unexpired lot of the reference drug product. The test product used in these testing is from the biolot .

Table 1. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 100 rpm
Medium - 0.05 M Potassium Phosphate Buffer, pH 6.8 at 37 °C
Volume – 1000 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	37	2.1		31	1.3	
2	51	1.3		45	2.5	

6	83	1.2		79	4.3	
10	97	1.9		95	1.2	
F2	**65.49**					

Comment: The F2 value is acceptable. This is an NDA/DBE method. The test also meets the following specifications suggested by DBE (ANDA 76-269):

1 Hr. —— **%**
2 Hrs. —— **%**
6 Hrs. —— **%**
10 Hrs. **NLT —%**

Conclusion: The response is acceptable. In this amendment Ivax did not propose any dissolution specifications for its product. The DBE therefore, can suggest the same specifications that were given to Teva (ANDA 76-269). However, based on the dissolution testing data in this amendment, the following specification would be appropriate.

1 Hr. —— **%**
2 Hrs. —— **%**
6 Hrs. —— **%**
10 Hrs. **NLT —%**

DEFICIENCY 4. *Additionally, for control release drug products, the DBE requests dissolution testing in the multiple media. You are requested to provide comparative dissolution data in the 900 and 1000 mL of multiple media (e.g. in water and in buffered media at pH 1.2, 4.5 and 6.8) using Apparatus 2 (Paddle) at 75 and 100 rpm and at 1, 2, 6 and 10 hours sampling time points or until at least 85% of the labeled amount is dissolved.*

Response: The firm has conducted dissolution testing as requested, and has submitted results as follows (Tables 2-8):

Table 2. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 75 rpm
Medium - Phosphate Buffer, pH 6.8 at 37 °C
Volume – 900 mL

Sampling Time, Hr.	**Test Product, Strength, 500 mg Lot No.105915-ND**			**Reference Product, Strength, 500 mg Lot No. 304606**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
1	35	2.3		26	6.7	
2	49	2.5		37	10.4	
6	80	2.1		68	5.1	
10	97	2.6		85	4.3	
F2	**47.21**					

Comment: F2 value is <50.

Table 3. Summary of Dissolution Data

Apparatus - 2 (Paddle) at 75 rpm
Medium - Acetate Buffer, pH 4.5 at 37 °C
Volume – 900 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	35	3.2		27	4.0	
2	50	3.4		38	5.3	
6	83	3.8		70	1.7	
10	98	2.3		87	1.0	
F2	**47.53**					

Comment: F2 value is <50.

Table 4. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 100 rpm
Medium - 0.05 M Sodium Acetate Buffer, pH 4.5 at 37 °C
Volume – 1000 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	37	1.4		32	6.8	
2	51	1.2		45	5.0	
6	84	1.3		78	4.4	
10	98	1.5		94	3.6	
F2	**63.35**					

Comment: The F2 value is >50.

Table 5. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 75 rpm
Medium - Water at 37 °C
Volume – 900 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	36	5.6		27	3.2	
2	51	5.4		39	3.5	
6	83	5.3		71	1.7	
10	98	3.6		85	4.1	
F2	**46.70**					

Comment: The F2 value is <50.

Table 6. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 100 rpm
Medium - Deaerated Water at 37 °C
Volume – 1000 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	36	1.4		31	3.6	
2	51	0.6		46	3.5	
6	84	1.3		78	2.9	
10	98	2.0		90	2.9	
F2	**57.00**					

Comment: The F2 value is >50.

Table 7. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 75 rpm
Medium - 0.01 N HCl at 37 °C
Volume – 900 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	37	11.9		24	12.7	
2	52	12.4		35	12.7	
6	83	11.9		63	12.9	
10	100	12.1		80	12.7	
F2	**48.63**					

Comment: The F2 value is <50.

Table 8. Summary of Dissolution Data
Apparatus - 2 (Paddle) at 100 rpm
Medium - 0.01 N HCl at 37 °C
Volume – 1000 mL

Sampling Time, Hr.	Test Product, Strength, 500 mg Lot No.105915-ND			Reference Product, Strength, 500 mg Lot No. 304606		
	Mean	%CV	Range	Mean	%CV	Range
1	38	6.7		32	7.3	
2	53	7.2		45	11.8	
6	88	7.7		78	10.9	
10	103	6.7		92	8.4	
F2	**66.69**					

Comment: The F2 value is >50.

conclusion: The response is acceptable

A. Recommendations

1. The bioequivalence study conducted under fasting conditions on metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage®-XR, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb is acceptable.

2. The bioequivalence study conducted at ————————. under non-fasting conditions on its metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage®-XR, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb is acceptable.

3. The firm has carried out another acceptable bioequivalence study conducted at ———— ———————— under non-fasting conditions on its metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage®-XR, 500 mg tablets, Lot MAM21, manufactured by Bristol-Myers Squibb.

4. The dissolution testing conducted by the firm on its metformin hydrochloride, 500 mg ER tablets, Lot #105915-ND comparing it to Glucophage-XR®, 500 mg tablets, Lot #304606, manufactured by Bristol-Myers Squibb is acceptable.

From bioequivalence point of view, the firm has met the requirements of *in vivo* and *in vitro* bioequivalence studies, and the application is complete.

The firm should be informed of the recommendations.

for 10/10/2003
Surendra P. Shrivastava, Ph.D.

10/10/2003
Shriniwas Nerurkar, Ph.D.

for Barbara M. Davit 10/10/03
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

SPS/sps/10-10-03/76545n0903
cc: ANDA #76-545 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-545 APPLICANT: Ivax

DRUG PRODUCT: Metformin Hydrochloride ER Tablets, 500 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer at pH 6.8 at 37 ^{0}C using USP Apparatus 2 (Paddle)at 100 rpm. Tentatively the test product should meet the following specifications:

Q1	1 Hr.	—— %
Q2	2 Hrs.	—— %
Q3	6 Hrs.	—— %
Q4	10 Hrs.	Not less than —%

of the labeled amount of the drug in the dosage form is dissolved in the given time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ SShrivastava

v:\FIRMSam\ivax\ltrs&rev\76545a0903
Printed in final on 10/10/03

10/10/03

Endorsements: (Final with Dates)
HFD-655/ SShrivastava
HFD-655/ SNerurkar
HFD-650/ D. Conner 10/16/03

BIOEQUIVALENCY -ACCEPTABLE submission date:9/26/03

1. ~~FASTING STUDY (STF)~~ ~~Strengths:500 mg ER Tablets~~
Clinical: [ ] X **Outcome: AC**
Analytical: [ ] India

~~FOOD STUDY (STP 1)~~ ~~Strengths:500 mg ER Tablets~~
Clinical: [ ] X **Outcome: AC**
Analytical [ ] India

~~FOOD STUDY (STP 2)~~ X Strengths: ~~500 mg~~, ER Tablets
Clinical: [ ] Canada **Outcome: AC**
Analytical: [ ]

~~DISSOLUTION DATA (DIS)~~ Strengths: 500 mg ER Tablets
Study Amendment STA Outcome: **AC**

APPEARS THIS WAY ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : ~~75-546~~ 76-545 SPONSOR : IVAX

DRUG AND DOSAGE FORM : Metformin Hydrochloride, Extended-Release Tablets

STRENGTH(S) : **500 mg**

TYPES OF STUDIES : Single-dose fasting, single-dose fed and dissolution data

CLINICAL STUDY SITE(S) Clinical: _____ India
_____ **Canada**

ANALYTICAL SITE(S) : _____, India

STUDY SUMMARY : One fasting and two non-fasting studies are acceptable

DISSOLUTION : The dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: ~~Yes~~ NO for Lambda Ther. Res. and Vimta Pharm., India	Inspection status: Cancelled	Inspection results:
First Generic __No__ New facility __Yes_ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

for INITIAL : _____ DATE : 10/10/2003

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH :

INITIAL : _____ DATE : 10/10/2003

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 10/10/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

PHARMACOLOGY REVIEW

ANDA 76-545 **Review Completed: March 7, 2003**
Sponsor: Ivax

Date Consult Received by Reviewer: January 23,2003

PHARMACOLOGY COMMENTS ON CONSULT REQUEST

DRUG: Metformin HCl Extended ReleaseTablets, 500 mg

Reference Drug: Glucophage XR, NDA 21-202, Bristol Myers Squibb

CONSULT REQUEST: OGD requested a safety evaluation by DMEDP (HFD-510) of the concentration of hydroxypropyl methyl cellulose in a new generic metformin formulation.

APPLICANT RESPONSE: The Applicant provided a Facsimile on January 3, 2003 which provided references for preclinical toxicity studies with hydroxypropyl cellulose and safety evaluations based on permissible daily exposure(PDE) and acceptable daily intake(ADI) calculations. Unfortunately, the sponsor's calculations are incorrect because they calculate safety margins based on — mg/day doses of hydroxypropyl methyl cellulose (HPMC). However, the HPMC is present at concentrations of — mg/ tablet, not — mg/day. Since each tablet contains 500 mg of metformin and the approved maximum daily dose of metformin is 2500 mg/day, patients may receive up to —— mg HPMC /day (—— mg/tablet X 5 tablets).

The applicant calculated the PDE of HPMC as—— mg/day with a safety margin of — times the proposed dose (see pg 07 of fax). However, the accurate PDE calculation is —— mg/day ÷ —— mg/day = — times the proposed dose.

The applicant states the FAO/WHO Expert Committee on Food Additives has established the acceptable daily intake (ADI) of HPMC as 25 mg/kg/day (pg. 08 of fax). Using 60 kg as an average adult body weight, the ADI equals 25 mg/kg/day x 60 kg = 1500 mg/day. This ADI is approximately equal to the proposed maximum daily HPMC dose of —— mg/day.

Conclusion: The conclusion that can be drawn from the sponsors submission is that although their calculations were not based on the accurate daily dose of —— mg HPMC , the recalculated PDE and ADI support the safety of the daily HPMC doses achieved with this generic product.

Jeri El-Hage 3/7/03

Jeri El-Hage, Ph.D.
Pharmacology Supervisor

cc: ANDA 76-545
HFD510/Consult file
HFD510/ElHage/Johnsonk/MarshallS
HFD-102/L. Ripper L Ripper 3/10/03

ANDA 76-545 **Review Completed: March 7, 2003**
Sponsor: Ivax

Date Consult Received by Reviewer: January 23,2003

PHARMACOLOGY COMMENTS ON CONSULT REQUEST

DRUG: Metformin HCl Extended ReleaseTablets, 500 mg

Reference Drug: Glucophage XR, NDA 21-202, Bristol Myers Squibb

CONSULT REQUEST: OGD requested a safety evaluation by DMEDP (HFD-510) of the concentration of hydroxypropyl cellulose (HPC) in a new generic metformin formulation.

APPLICANT RESPONSE: The Applicant provided a Facsimile on January 3, 2003 which provided references for preclinical toxicity studies with hydroxypropyl cellulose and safety evaluations based on permissible daily exposure(PDE) and acceptable daily intake(ADI) calculations. Unfortunately, the sponsor's calculations are incorrect because they calculate safety margins based on — mg/day doses of hydroxypropyl cellulose (HPC). However, the HPC is present at concentrations of— mg/ tablet, not — mg/day. Since each tablet contains 500 mg of metformin and the approved maximum daily dose of metformin is 2500 mg/day, patients may receive up to —— mg HPC /day (— mg/tablet X 5 tablets).

The applicant calculated the PDE of HPC as —— mg/day with a safety margin of — times the proposed dose (see pg 07 of fax). However, the accurate PDE calculation is —— mg/day ÷ —— mg/day = — times the proposed dose.

The applicant states the FAO/WHO Expert Committee on Food Additives has established the acceptable daily intake (ADI) of HPC as 25 mg/kg/day (pg. 08 of fax). Using 60 kg as an average adult body weight, the ADI equals 25 mg/kg/day x 60 kg = 1500 mg/day. This ADI is approximately equal to the proposed maximum daily HPC dose of —— mg/day.

Conclusion: The conclusion that can be drawn from the sponsors submission is that although their calculations were not based on the accurate daily dose of ——mg HPC , the recalculated PDE and ADI support the safety of the daily hydroxypropyl cellulose (HPC) doses achieved with this generic product.

Jeri El-Hage 4/10/03
Jeri El-Hage, Ph.D.
Pharmacology Supervisor

cc: ANDA 76-545
HFD510/Consult file
HFD510/ElHage/Johnsonk/MarshallS
HFD-102/L. Ripper

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

DATE: 6-17-03

PRODUCT NAME: Metformin Hydrochloride Extended-Release Tablets, 500 mg

ANDA NUMBER: 76-545

FIRM NAME: Ivax Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Stacy Bates

PARTICIPANT(S) TELEPHONE: 201-767-1700 Ext. 323

MINUTES OF CONVERSATION:

Telecon:

Mike Smela and M. Shaikh called the firm to discuss their response in May 22, 2003 amendment regarding the 2nd non-specific test to the release specification of the drug product. In their response, Ivax proposed ——— test for Metformin Hydrochloride as an identification test. Mike told Stacy that ——— test, as an identification test is not acceptable. Instead, Ivax needs to include second ID test for the organic portion of the molecule (e.g., UV, TLC, etc). After making this revision, Ivax needs to submit revised release specifications. Mike told her to submit this information as a telephone amendment.

Mike gave her the fax number so that he can fax the telephone amendment to M. Shaikh's attention.

NAME OF OGD REPRESENTATIVE: Mike Smela/M. Shaikh mujahid shaikh 6/17/03

V:\firmsam\ivaxpharm\telecons\76545.TC1

M Smela 6/17/03

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 28, 2003 C Parise 10/28/03

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Gary J. Buehler 10/28/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECTS: 180-Day Exclusivity for Metformin Extended-Release Tablets, 500 mg
Pediatric Exclusivity for Metformin Extended-Release Tablets, 500 mg

TO: The ANDA files for:
ANDA 76-450, Purepac
ANDA 76-545, Ivax

I. 180-DAY EXCLUSIVITY

The question of which application was the first filed with a PIV certification for Metformin Extended-Release Tablets, 500 mg, was posed and analyzed for determining eligibility for 180-day exclusivity by the Office of Generic Drugs with input from the Office of the Chief Counsel.

Background:

Bristol Myers Squibb submitted a U.S. patent # 6475521 (the '521 patent) to NDA 21-202 Glucophage-XR (Metformin) Extended-Release Tablets for listing with the Agency on 11/20/02.

21202 Glucophage XR (Metformin HCl)
6475521 exp 3/19/18 formulation
per 11/19/02 ltr recd 11/20/02
issued 11/5/02 per internet

ANDA 76-450 for Purepac was previously filed when the patent was listed. Purepac submitted daily PIV certifications from the date of issuance of the patent. Purepac submitted a patent amendment on 11/20/02 (the date the patent was received by the FDA) and Purepac sent the required notice to Bristol on 11/27/02.

The statute states that in the case of a patent amendment containing a paragraph IV certification the notice of the paragraph IV certification shall be given "when the amended application is submitted." Section 505(j)(2)(b)(iii)of the Federal Food, Drug, and Cosmetic Act ("Act"). The regulations state that if an ANDA is amended to include a paragraph IV certification, notice of the paragraph IV certification must be given "at the same time that the amendment . . . is submitted to FDA." 21 CFR 314.95(d). FDA has interpreted this language to require both a paragraph IV certification and notice for an amendment containing a paragraph IV certification to be complete. Therefore, Purepac's amendment containing a PIV certification is considered complete as of 11/27/02, the date on which the patent certification and notice obligations had both been satisfied.

Ivax submitted an original application, ANDA 76-545, which was received by the FDA on 11/26/02. The FDA issued the acknowledgement letter for ANDA 76-545, Metformin Hydrochloride Extended-release Tablets, 500 mg, on January 14, 2003. Subsequently Ivax sent notice of the PIV filing on February 3, 2003. IVAX was not sued.

The statute is silent on the timing of notice of a paragraph IV certification received in an original application; it merely states the parties who are to receive the requisite notice. See Section 505(j)(2)(b)(i) of the Act. The regulations indicate that the applicant shall send the notice when it receives from FDA an acknowledgement letter stating that its abbreviated new drug application is sufficiently complete to permit a substantive review. 21 CFR 314.95(b). If, after a review for completeness, an ackowledgment letter indicating substantial completeness is issued, the application is considered to have been complete for filing on the date it was received by the FDA. If notice is given after the acknowledgement is received (as required by the regulations), the paragraph IV certification is considered to have been complete as of the date the application was originally received. Therefore, the FDA considers the date IVAX's ANDA was received as substantially complete, 11/26/02, as the controlling date of receipt of its paragraph IV certification to the '521 patent.

This means that FDA considers IVAX to be the first to file for 180-day exclusivity eligibility purposes with respect to the '521 patent.

II. PEDIATRIC EXCLUSIVITY

The issue of whether the second grant of pediatric exclusivity would attach to the Glucophage-XR patent was also considered by the Office of Generic Drugs with input from the Office of the Chief Counsel.

Rationale for Determining to which applications pediatric exclusivity attaches:

Metformin received a first grant of pediatric exclusivity on 3/15/00. This exclusivity attached to all patents and exclusivities for the metformin moiety listed at the time the pediatric exclusivity was granted and to protections listed for any later approved applications for which the pediatric studies that gained the grant of exclusivity were essential to approval. See 505A(c) of the Act; See also Guidance for Industry, Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act (Revised September 1999) ("Pediatric Exclusivity Guidance") at 13-14, 15.

Pediatric exclusivity was granted to NDA 21178 for Glucovance (a glyburide/metformin combination product) on 10/8/03. This exclusivity, based on a pediatric supplement to the combination product, Glucovance, that contains metformin and glyburide, was the first grant of exclusivity for glyburide and the second for metformin. Accordingly it attached to extend all protections listed for glyburide at the time of approval (which are limited to protections on the combination product because BMS does not market glyburide alone) and, if the pediatric supplement receives 3 years of H-W exclusivity, will attach to that 3 year exclusivity upon approval of the supplement. Because metformin has previously received pediatric exclusivity, it will not attach to other metformin products. See the Act, section 505(A)(h); see also Pediatric Exclusivity Guidance at 14.

Accordingly, the second grant of exclusivity will involve the following changes to the OB database:

1. NDA 20357 - Metformin - no action needed at this time.

2. 21278 Glucovance (glyburide/metformin) NDA

   currently lists one patent, 6303146, and two exclusivities NC, and I-368

---all will be extended with 6 months pediatric exclusivity as the written request went out relative to this NDA and encompassed both ingredients

---if H-W exclusivity is granted for the pediatric supplement, this will also be extended by 6 months

3. 21202 Glucophage XR (Metformin HCL) extended release

   currently lists one patent, 6475521, and one exclusivity, NDF

-----neither of these was extended for pediatric exclusivity for the first grant of pediatric exclusivity for the following reasons:

Pediatric exclusivity was first granted for metformin on 3/15/00; the NDA for Glucophage XR was approved 10/13/00, subsequent to that exclusivity grant. Because the Glucophage XR approval followed the original grant of pediatric exclusivity and the studies done to earn the

pediatric exclusivity for metformin were not essential for this approval, the pediatric exclusivity did not extend the patents and exclusivities for Glucophage XR.

---neither patent or exclusivity for Glucophage XR will be extended by the pediatric exclusivity earned for studies of the metformin/glyburide combination for the following reason:

The second period of exclusivity that will be awarded to metformin based on studies of the metformin/glyburide combination will not apply to either the exclusivity or patent listed on the Glucophage XR because second periods of pediatric exclusivity are limited by Section 505(A)(h) of the Act to extend H-W exclusivity on a supplement that is approved as a result of the second grant of pediatric exclusivity. No supplement to the Glucophage XR has been submitted based on the studies that earned pediatric exclusivity for the metformin/glyburide combination so no pediatric exclusivity will attach.

q:\issues\metformin\memos\180daypedsmemo.doc

Drafted by: C. Parise 10/23/03
Edited by: K. Dettelbach 10/27/03

cc: G. Buehler
R. West
C. Parise
P. Rickman
G. Davis
D. Hare
M. Shimer
M. Holovac
K. Dettelbach

OGD APPROVAL ROUTING SUMMARY

ANDA #76-545 **Applicant** IVAX Pharmaceuticals, Inc.
Drug Metformin HCl Extended-release Tablets **Strength** 500 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:
1. Project Manager, Peter Chen
Review Support Br Team 2

DRAFT Package Date 10/22/03 Initials PC
FINAL Package Date 10/23/03 Initials PC

Application Summary:
Original Rec'd date 11/26/02
Date Acceptable for Filing 11/26/03 J
Patent Certification (type) IV
Date Patent/Exclus.expires 3/19/18; 10/13/03
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 8/26/03
Date of Office Bio Review 10/10/03
Date of Labeling Approv. Sum 8/14/03
Date of Sterility Assur. App. N.A.
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

Gregg Davis **PPIII and PPIV ANDAs Only**
Supv., Reg. Support Branch

Date 27-OCT 2003 Initials ☒
Date 27OCT2003 Initials ☒

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: N/A Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Comments: PIV received 11/26/02
no suit w/in 45 days

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked N/A-see memo.
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
RLD=Glucophage XR-Extended-Bristol-Myers Squibb Co. release tablets, 500mg NDA 21-202

* need Cec memo in final to complete the admin. hx

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:

Date 10/27
Initials

CMC OK

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
N/A. Multiple ANDAs have been tentatively approved for this drug product.
Date _____
Initials _____

5. Peter Rickman
Director, DLPS
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable CES dated 8/26/03 (Verified 9/27/03) No OAI-Alert noted, Pharm/tox consult on level of inactive ingredient, HPMC, found acceptable 9/7/03, 9/16/03 Bioequivalence studies (fasting, non-fasting) found acceptable 10/1/03. Interim dissolution data also found acceptable. Bio studies conducted by _____ India (fasting and non-fasting) and _____ Canada (non-fasting). Analytical studies conducted by _____ both _____ and _____ India and _____ have acceptable GMP/GLP inspectional histories & Office-Wellbio endorsed 10/16/03. FPL found acceptable for approval 8/14/03. CFC found acceptable 10/22/03. Methods validation cancelled due to recent office policy.
Date 10/27/03 for
Initials JM

5. Robert L. West
Deputy Director, OGD
Date 10/27/2003
Initials Robert West

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: IVAX made a paragraph IV Certification to the '521 patent at the time of submission of the ANDA. IVAX was not sued by the NDA/patent holder within 45-days of notification. The agency has determined that the NDF exclusivity expiring on 10/13/03 was not extended upon the agency's granting of pediatric exclusivity to BMS's combination product Glucovance (glyburide/metformin). See memo dated 10/7/03 G. Buehler and e-Mail dated 10/22/03 from K. Bethel. IVAX is also eligible for 180-day generic drug exclusivity for this drug product. This ANDA is recommended for approval.

6. Gary Buehler
Director, OGD
Comments:
Date 10/28/03
Initials GB

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Peter Chen
Review Support Branch Team 2
Date 10/28/03
Initials PC

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9:54A Time notified of approval by phone 9:56 Time approval letter faxed

FDA Notification:
10/28/03 Date e-mail message sent to "CDER-OGDAPPROVALS☐ distribution list.
10/28/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-545

CORRESPONDENCE

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Federal Express

NOV 25 2002

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(j)(2)(A) OK
14-JAN-2003
Gregory D. Davis
fax submitted pharm/tox
to justify HPC

ABBREVIATED NEW DRUG APPLICATION

Re: Metformin Hydrochloride Extended-Release Tablets, 500 mg
Original ANDA Submission

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and in compliance with 21 CFR §314.94, IVAX Pharmaceuticals, Inc., herewith submits an Abbreviated New Drug Application (ANDA) for Metformin Hydrochloride Extended-Release Tablets, 500 mg.

IVAX has organized its ANDA in accordance with the OGD guidance of February 1999, entitled, *Organization of an ANDA*. In support of this application, the information outlined below is provided:

- Table of Contents
- Form FDA 356h
- Basis for Submission
- Patent Certification and Exclusivity Statement
- Comparison between the proposed drug and the reference listed drug (Glucophage® XR Tablets, manufactured by Bristol-Myers Squibb Company)
- Draft Labeling (Four copies each in the archival [blue] binder, chemistry review [red] binder and the pharmacokinetic and bioavailability review [orange] binder.)
- Certification of Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454)
- *In-Vivo* Bioequivalence Studies (one fasting and two fed):

  Protocol No. MET/23/47/02-03: Single Dose Crossover Comparative Bioavailability Study of Metformin Hydrochloride 500 mg Extended-Release Tablets in Healthy Male Volunteers under Fasting Conditions

  Protocol No. MET/23/45/02-03: Single Dose Crossover Comparative Bioavailability Study of Metformin Hydrochloride 500 mg Extended-Release Tablets in Healthy Male Volunteers under Fed Conditions

  Protocol No. P1BD02008: Single Dose Crossover Comparative Bioavailability Study of Metformin Hydrochloride 500 mg Extended-Release Tablets in Healthy Male Volunteers under Fed Conditions

Study numbers MET/23/47/02-03 (fasting) and MET/23/45/02-03 (fed) were both conducted by [redacted], India. Study number P1BD02008 (fed) was conducted by [redacted], Canada. The two fed studies (one in India, one in Canada) were performed to demonstrate that fed studies performed in India yield equivalent results to those performed in the US or Canada. Based on the results, IVAX Pharmaceuticals, Inc., intends to perform future fed bioequivalence studies in India.

Data diskettes are included in the front covers of the pharmacokinetic and bioavailability review (orange) binders: Volumes 2 of 21, 15 of 21 and 19 of 21, respectively.

- Chemistry, Manufacturing and Controls Information
- Debarment, Conviction and Field Copy Certifications
- Methods Validation Package: Three (3) separately bound and identified copies are provided. IVAX Pharmaceuticals, Inc., commits to satisfactorily resolve any issues which might be identified during review of the methods validation, whether this occurs before or after ANDA approval.

The archival copy of this application consists of 24 volumes. The chemistry review copy consists of 4 volumes. The pharmacokinetic and bioavailability review copy consists of 21 volumes.

The exhibit batch for this application was manufactured and packaged at IVAX Pharmaceuticals Caribe Inc., Cidra, Puerto Rico, a wholly-owned subsidiary of IVAX Corporation, Miami, Florida.

IVAX Pharmaceuticals, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We have made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

cc: District Office

76-545

NEW CORRESP

IVAX Pharmaceuticals, Inc.
140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

VIA FACSIMILE

NC

JAN 0 3 2003

Ms Emily Thomas, Project Manager
Regulatory Review Branch
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GENERAL CORRESPONDENCE

Re: IVAX ANDA for Metformin Extended Release Tablets, 500 mg
Submission dated November 25, 2002

Dear Ms. Thomas,

Reference is made to our telephone conversation of December 12, 2002 in which you asked IVAX to provide additional safety and toxicity data for an inactive ingredient (hydroxypropyl cellulose) used in the above subject ANDA's formulation. You advised that the daily dosage limit for this ingredient published in the FDA's 1996 Inactive Ingredients Guide (IIG) of 0.58 g is in error, and that IVAX Pharmaceutical's formulation uses a maximum daily dosage of — mg, which exceeds the yet unpublished IIG limit.

Given the above information, IVAX has assembled safety and toxicity data to justify the — mg maximum daily dosage of hydroxypropyl cellulose in our formulation. Attached for your review please find our Safety Evaluation along with a tabular Summary of Oral Toxicity Studies with HPC as well as a tabular Calculation of Acceptable Levels and published references.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this submission contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

Enclosures

PJ/GO

RECEIVED
JAN 17 2003
OGD / CDER

Post-it® Fax Note 7671	Date 1/3/03	# of pages ▶ 13
To Emily Thomas	From P. Jaworski	
Co./Dept. FDA/CDER/OGD	Co. IVAX	
Phone #	Phone # 201-767-1700	
Fax # 301-594-1174	Fax #	EXT 32

ANDA 76-545

IVAX Pharmaceuticals, Inc.
Attention: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

JAN 14 2003

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversations dated December 12, 2002 and January 6, 2003 and your correspondences dated January 3, 2003, January 13, 2003 and January 14, 2003.

NAME OF DRUG: Metformin Hydrochloride Extended-release Tablets, 500 mg

DATE OF APPLICATION: November 25, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 26, 2002

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice.

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement, or a settlement agreement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Gregory K. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-545
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB 14-JAN-2003 date
HFD-615/EThomas, CSO 1/14/03 date
Word File V:\Firmsam\ivaxpharm\ltrs&review\76545.ack
FT/EST 01/14/03
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

ANDA 76-545

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APR 16 2003

APPLICANT: IVAX Pharmaceuticals, Inc.

TEL: 201-767-1700

ATTN: Patricia Jaworski

FAX: 201-767-3804

FROM: Peter Chen

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 25, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metformin Hydrochloride Extended-release Tablets, 500 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry comments included.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-545 APPLICANT: Ivax Pharmaceuticals, Inc

DRUG PRODUCT: Metformin Hydrochloride Extended-Release Tablets, 500 mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your response should also address the labeling deficiencies faxed to you on February 26, 2003.

2. An acceptable compliance evaluation is needed for the approval of your application. We have requested an evaluation from the Office of Compliance.

3. A satisfactory Methods Validation study is needed to support the ANDA. We will schedule the validation with our laboratory when the testing issues are resolved.

4. Please provide any additional stability data that is available.

5. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

Sincerely yours,

Rashmikant M. Patel, Ph.D
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

MAY 2 2 2003

VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/Afm

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT - CHEMISTRY

Re: ANDA 76-545 for Metformin Hydrochloride Extended Release Tablets, 500 mg

Dear Mr. Buehler,

Reference is made to IVAX's pending ANDA 76-545 for Metformin Hydrochloride Extended Release Tablets, 500 mg. Further reference is made to the Agency's correspondences dated February 26, 2003 and April 16, 2003. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc. is amending the application by responding to the comments cited in the Agency's letter. As instructed in the Agency's correspondence, this response is considered a MINOR AMENDMENT.

In response to the Agency's comments, we submit the following:

A. Deficiencies:

1. [redacted]

Response:

[redacted]

2. [redacted]

Response:

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Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

5/22/2003 IVAX LETTER

Response:

IVAX Pharmaceuticals, Inc. notes and acknowledges that an acceptable compliance evaluation is needed for the approval of our application.

3. *A satisfactory Methods Validation study is needed to support the ANDA. We will schedule the validation with our laboratory when the testing issues are resolved.*

Response:

IVAX Pharmaceuticals, Inc. acknowledges that a satisfactory Methods Validation study is required, and IVAX commits to work expeditiously to respond to all inquiries for the Methods Validation study, when scheduled.

4. *Please provide any additional stability data that is available.*

Response:

As requested by the Agency, IVAX Pharmaceuticals, Inc. herewith submits updated Stability Summary Reports. Please refer to **Exhibit 3** for 9 Months Controlled Room Temperature stability data.

5. *Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.*

Response:

IVAX Pharmaceuticals, Inc. acknowledges that the bioequivalence information is pending review. If any deficiencies are cited by the Agency, IVAX commits to resolve them expeditiously.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this submission contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/mn

Archival

JUN 10 2003

IVAX Pharmaceuticals, Inc.
140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Federal Express

ORIG AMENDMENT
N/AF
FPL

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

Re: ANDA 76-545 – Metformin Hydrochloride Extended-release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-release Tablets, 50 mg, filed November 25, 2002, and to the Agency's facsimile correspondence dated February 26, 2003. In response to the Agency's comments and pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc. is amending its application by responding to the deficiencies cited:

Labeling Deficiencies:

1. *CONTAINER – 500 mg [100's, 500's, 1000s] bottles*

   A. *Please revise your storage temperature statement so that it reflects our current standard storage temperature range. Revise to read "Store at 20–25 deg C (68-77 deg F). [See USP controlled room temperature]".*

   B. *Revise "Each Tablet contains..." to "Each extended-release tablet contains...".*

2. *UNIT-DOSE BLISTERS 10s – Satisfactory in draft.*

3. *UNIT-DOSE BLISTER CARTONS (10 X 10s)*

   A. *We encourage you to relocate "For full prescribing information, see enclosed package insert" to the side panel under a "Usual Dosage" section.*

   B. *See comments under CONTAINER.*

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4. PHYSICIAN'S INSERT

A. GENERAL COMMENT – Where "metformin Hydrochloride tablets" and "metformin hydrochloride extended-release tablets" are joined together by "and/or" in a sentence, please replace the conjoined established names with "metformin". Please retain both established names as they are written in the INDICATIONS and USAGE, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections.

B. DESCRIPTION – "hydroxypropyl methylcellulose" should be changed to the new title "hypromellose".

C. CLINICAL PHARMACOLOGY, Clinical Studies, Metformin

Delete text protected by M-6 that does not expire until April 19, 2004. In the second paragraph delete the " [redacted] *."*

D. INDICATIONS AND USE, revise the section title to "INDICATIONS AND USAGE".

E. DOSAGE AND ADMINISTRATION, Concomitant Metformin HCl or Metformin HCl extended release and Oral Sulfonylurea Therapy in Adult Patients subsection, 2nd paragraph.

Delete " [redacted] *." This text is covered by the M-6 exclusivity.*

F. HOW SUPPLIED – See comment regarding our standard temperature statement.

5. PATIENT INFORMATION LEAFLET – See comment "4a" under PHYSICIAN'S INSERT

Response:

As requested by the Agency, revised final printed container labels are provided as **Exhibit 1**. To facilitate review, and in accordance with 21 CFR 314.94(a)(8)(iv), we have provided a side-by-side comparison of the labeling proposed in the amendment versus the last submitted labeling, with all differences annotated and explained.

Please note with specific reference to comment 3.A., on Unit dose blister cartons, IVAX' standard practice is to provide "For full prescribing information, see enclosed package insert" directions on the front panel. Historically this has been found acceptable by the Agency.

In addition, IVAX Pharmaceuticals, Inc. has provided revised final printed package insert labeling in **Exhibit 2**. To facilitate review, and in accordance with 21 CFR 314.94(a)(8)(iv), we have provided a side-by-side comparison of the labeling proposed in the amendment versus the last submitted labeling, with all differences annotated and explained.

In addition, IVAX Pharmaceuticals, Inc. has provided revised final printed patient leaflet labeling in **Exhibit 3**. To facilitate review, and in accordance with 21 CFR 314.94(a)(8)(iv), we have provided a side-by-side comparison of the labeling proposed in the amendment versus the last submitted labeling, with all differences annotated and explained.

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this amendment contains all of the information requested by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/GO

APPEARS THIS WAY
ON ORIGINAL

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Telefax

Mr. Mike Smela, DCI, OGD, (301) 594-0180

ORIG AMENDMENT

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

JUN 27 2003

TELEPHONE AMENDMENT- Chemistry

Re: ANDA 76-545 for Metformin Hydrochloride Extended-Release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to IVAX's pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-Release Tablets, 500 mg, and to our Minor Amendment dated May 22, 2003. Further reference is made to the Agency's telephone communication on June 17, 2003. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc., is amending the application by responding to OGD's comments. As instructed, this response should be considered a TELEPHONE AMENDMENT.

In response to the Agency's comments, we submit the following:

1. *The OGD acknowledges IVAX's response #A.1. from the firm's Minor Amendment dated May 22, 2003. However, the Agency believes that a second identification test for finished product release is necessary. The reason for this is that the retention time in the existing ——— test is non-specific. Please revise your finished product specifications and methods to include a second identification test which is specific to the organic portion of the molecule. A UV, TLC or another unique HPLC test are all examples of analyses which would be acceptable for this purpose.*

   Response:
   As requested, IVAX has revised the finished product release specifications for Metformin Hydrochloride Extended-Release Tablets, 500 mg, to include an additional identification test specific to the molecule's organic portion. The test will be conducted using ——————— Please refer to Exhibit 1, in which copies of the updated specification and analytical method can be found.

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JUN 30 2003
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IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this response is complete, and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/sb

cc: District Office

APPEARS THIS WAY
ON ORIGINAL

AUG 12 2003

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Federal Express

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AUG 13 2003
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NEW CORRESP
NC

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CORRESPONDENCE

Re: ANDA 76-545 for Metformin Hydrochloride Extended-Release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to IVAX's pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-Release Tablets, 500 mg, and to our subsequent amendments. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc., is amending our application.

IVAX Pharmaceuticals, Inc. kindly requests that ———————————, and its provision as an Outside Contract Laboratory/Alternate Testing Facility be withdrawn from our ANDA 76-545 for Metformin Hydrochloride Extended-Release Tablets, 500 mg.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this response is complete, and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director of Regulatory Affairs

PJ/mn

BIOEQUIVALENCY AMENDMENT

ANDA 76-545

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

SEP 12 2003

APPLICANT: Ivax Pharmaceuticals, Inc. TEL: 201-767-1700

ATTN: Patricia Jaworski FAX: 201-767-3804

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 25, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metformin Hydrochloride Extended Release Tablets, 500 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY DEFICIENCIES

SEP 12 2003

ANDA:76-538 APPLICANT: Ivax

DRUG PRODUCT: Metformin Hydrochloride, ER Tablets, 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. In the single-dose fasting study, #MET/23/47/02-03:

   a. Please provide signed and dated letter from the Independent Ethics Committee (IRB) pertaining to the approval of the protocol and applicable deviations.

   b. Please provide the information regarding reassay and SOPs that is highlighted below in the item 2.

2. In the single-dose fed (Indian) study:

   You performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but have not provided the necessary details. **Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.**

3. Since there is no USP method, the FDA recommends the following dissolution method developed for the RLD - Medium - 0.05 M phosphate buffer at pH 6.8, Volume 1000 mL at 37 0C, and Apparatus 2 (Paddle) at 100 rpm. You have conducted dissolution testing using a slightly

different method - 900 mL of the medium and Paddle speed of 75 rpm. Please provide the comparative dissolution data using the FDA method.

4. Additionally, for control release drug products, the DBE requests dissolution testing in the multiple media. You are requested to provide comparative dissolution data in the 900 and 1000 mL of multiple media (e.g. in water and in buffered media at pH 1.2, 4.5 and 6.8) using Apparatus 2 (Paddle) at 75 and 100 rpm and at 1, 2, 6 and 10 hours sampling time points or until at least 85% of the labeled amount is dissolved.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

ORIG AMENDMENT

N|AB

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

SEP 26 2003

BIOEQUIVALENCE AMENDMENT

Re: ANDA 76-545 for Metformin Hydrochloride Extended-Release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to IVAX's pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-Release Tablets, 500 mg, and to the Agency's correspondence dated September 12, 2003. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc., is amending the application by responding to DBE's comments. As instructed, this response should be considered a BIOEQUIVALENCE AMENDMENT.

In response to the Division of Bioequivalence's comments, we submit the following:

1. *In the single-dose fasting study, #MET/23/47/02-03:*

   a. *Please provide signed and dated letter from the Independent Ethics Committee (IRB) pertaining to the approval of the protocol and applicable deviations.*

   Response:
   As requested, IVAX is providing a signed and dated letter from the Independent Ethics Committee pertaining to the approval of the fasting study protocol #MET/23/47/02-03 and applicable deviations. Please refer to Exhibit 1.

   b. *Please provide the information regarding reassay and SOPs that is highlighted below in the Item 2.*

   Response:
   Please refer to Exhibit 1, in which we have provided a written report from ——— and three (3) CD's (CD's provided in REVIEW COPY ONLY) which contain the following information:

   - IRB approval for the study
   - PK parameters using all re-assayed values only
   - PK parameters using original values only
   - Rationale and values for the repeat analysis for the study
   - ——— SOP BA-28-01 for repeat analyses
   - Summary statistics using all reassayed values
   - Summary statistics using original values only

   We trust that this data will be satisfactory.

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SEP 29 2003
OGD/CDER

2. *In the single-dose fed (Indian) study (#MET/23/45/02-03):*

You performed repeat analyses on a number of samples on 9/15/02, 9/18/02 and 9/28/02, but have not provided the necessary details. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

Response:
Please refer to Exhibit 1, in which we have provided a written report from ———, and three (3) CD's (CD's provided in REVIEW COPY ONLY) which contain the following information:

- PK parameters using all re-assayed values only
- PK parameters using original values only
- Rationale and values for the repeat analysis for the study
- —— SOP 23/13 for repeat analyses
- Summary statistics using all reassayed values
- Summary statistics using original values only
- Comments by Principal Investigator concerning missing values

We trust that this data will be satisfactory.

3. *Since there is no USP method, the FDA recommends the following dissolution method developed for the RLD:*

Medium 0.05M phosphate buffer at pH 6.8, Volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm.

You have conducted dissolution testing using a slightly different method: 900 mL of the medium and paddle speed of 75 rpm. Please provide the comparative dissolution data using the FDA method.

Response:
As instructed, IVAX has conducted dissolution testing using the FDA recommended method which was developed for the RLD. The conditions are as follows:

- 0.05M phosphate buffer at pH 6.8, Volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm

Comparative dissolution data and profiles are provided in Exhibit 2.

4. Additionally, for control release drug products, the DBE requests dissolution testing in the multiple media. You are requested to provide comparative dissolution data in the 900 and 1000 mL of multiple media (e.g. in water and in buffered media at pH 1.2, 4.5 and 6.8) using Apparatus 2 (paddle) at 75 and 100 rpm and at 1, 2, 6 and 10 hours sampling time points or until at least 85% of the labeled amount is dissolved.

   Response:
   As requested, IVAX has conducted dissolution testing in 900 and 1000 mL of multiple media using Apparatus 2 (paddle) at 75 and 100 rpm, at 1, 2, 6 and 10 hours sampling time points. The conditions are as follows:

   - phosphate buffer at pH 6.8, volume 900 mL at 37°C, and USP Apparatus 2 (paddle) at 75 rpm
   - phosphate buffer at pH 6.8, volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm
   - acetate buffer at pH 4.5, volume 900 mL at 37°C, and USP Apparatus 2 (paddle) at 75 rpm
   - acetate buffer at pH 4.5, volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm
   - deaerated water, volume 900 mL at 37°C, and USP Apparatus 2 (paddle) at 75 rpm
   - deaerated water, volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm
   - 0.01N HCl, volume 900 mL at 37°C, and USP Apparatus 2 (paddle) at 75 rpm
   - 0.01N HCl, volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm

   Comparative dissolution data and profiles are provided in Exhibit 3.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this response is complete, and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Stacy Bate / for

Patricia Jaworski
Director, Regulatory Affairs

PJ/sb

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

Via Telefax

Mr. Peter Chen, DCI, OGD, (301) 594-0180

ORIG AMENDMENT

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

OCT - 2 2003

GRATUITOUS AMENDMENT- Chemistry

Re: ANDA 76-545 for Metformin Hydrochloride Extended-Release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to IVAX's pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-Release Tablets, 500 mg, and to our Bioequivalence Amendment dated September 26, 2003 (copy provided in Reference). Further reference is made to our telephone discussion with the Agency on October 2, 2003. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc., is amending the application to provide for the change in the dissolution method as requested by the Division of Bioequivalence (DBE). IVAX believes that the request made by DBE will necessitate the analytical method, finished product release specifications and stability protocol/specifications to be revised to satisfy the Division of Chemistry. In an effort to expedite this process, IVAX Pharmaceuticals, Inc., is submitting this GRATUITOUS AMENDMENT.

In response to the Agency's bioequivalence comment which would affect chemistry, we submit the following:

1. *"Since there is no USP method, the FDA recommends the following dissolution method developed for the Reference Listed Drug:*

   Medium 0.05M phosphate buffer at pH 6.8, Volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm.

   You have conducted dissolution testing using a slightly different method: 900 mL of the medium and paddle speed of 75 rpm. Please provide the comparative dissolution data using the FDA method."

   Response:
   IVAX has revised the dissolution method, finished product release specifications and stability protocol/specifications for Metformin Hydrochloride Extended-Release Tablets, 500 mg, to provide for DBE's recommended dissolution method using 0.05M phosphate buffer at pH 6.8, Volume 1000 mL at 37°C, and USP Apparatus 2 (paddle) at 100 rpm. Please refer to Exhibit 1.

OCT 0 3 2003

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this response is complete, and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs
New Product Submissions

PJ/sb

cc: District Office

APPEARS THIS WAY
ON ORIGINAL

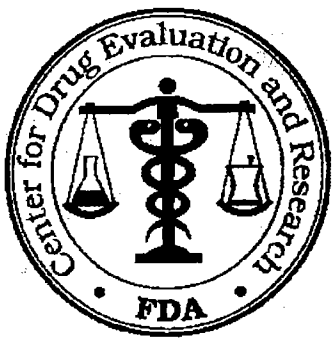
2.1

MINOR AMENDMENT

ANDA 76-545

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 17 2003



APPLICANT: IVAX Pharmaceuticals, Inc. TEL: 201-767-1700 x323

ATTN: Pat Jaworski FAX: 201-767-3804

FROM: Peter Chen PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 25, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metformin Hydrochloride Extended-release Tablets, 500 mg.

Reference is also made to your amendment(s) dated: May 22 and June 27, 2003. Additional reference is made to your gratuitous amendment dated October 2, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry and Bioequivalence comments included.

PC 10/17/03

36. Chemistry Comments to be Provided to the Applicant OCT 17 2003

ANDA: 76-545 APPLICANT: IVAX Pharmaceuticals, Inc.

DRUG PRODUCT: Metformin Hydrochloride Extended-Release Tablets, 500 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please revise your dissolution method and specification based on the attached recommendation made by the Division of Bioequivalence (DBE) for release and stability of the drug product. Please provide a copy of the revised method.

2. Please test your retained samples from accelerated stability for dissolution to demonstrate that the product meets the dissolution specifications recommended by the DBE. Alternatively, you may test the long term samples and propose the expiration dating period to match the available data.

3. Please provide revised release and stability specifications for the tablets incorporating the revision regarding dissolution.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please submit any additional stability data for the exhibit batch that may be available.

Sincerely yours,

M Smela for

Rashmikant M. Patel, Ph.D
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Archival

NAI
10/27/03
NEW CORRESP
NC

IVAX
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Facsimile Transmission to Dr. Martin Shimer, OGD
301-594-1174

Hard Copy Via Federal Express to:

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

OCT 17 2003

Telephone Amendment – Patent Information

Re: ANDA 76-545 for Metformin Hydrochloride Extended Release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to IVAX's pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-Release Tablets, 500 mg submitted on November 25, 2002, and to the Agency's telephone communication today.

In response to the Agency's request for patent notification we provide the following confirmation:

On February 3, 2003, the patent holder, Bristol-Meyers Squibb Company, was notified in writing via Certified Mail (Article Number 7099 3400 0006 6489 8920) that IVAX Pharmaceuticals Inc., filed an Abbreviated New Drug Application in order to obtain approval to engage in the commercial manufacture, use and sale of metformin hydrochloride before the expiration of U.S. Patent Nos. 6,475,521 (the '521 patent). The patent holder signed and received the letter on February 5, 2003. IVAX Pharmaceuticals, Inc., confirms that no lawsuit has been filed as a result of said notification.

Provided for your review are photocopies of the following:

- U.S. Postal Service Certified Mail Receipt for Article 7099 3400 0006 6489 8920 sent to Donald Barrack, Esq, Vice President and Patent Counsel for Bristol Meyers Squibb, and
- Domestic Return Receipt, U.S. Postal Service PS Form 3811, signed by a representative of BMS and dated by the U.S. Postal Service for delivery on February 5, 2003.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this correspondence contains all of the information requested by the Agency. We now look forward to the approval of ANDA 76-545. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Andrea Wigfall /for

Patricia Jaworski
Director, Regulatory Affairs

/sh

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Archival

IVAX
Pharmaceuticals, Inc.

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Fascimile Copies to:
Mr. Robert West
Mr. Peter Chen
Mr. Steve Mazella

Via Federal Express

ORIG AMENDMENT
N/Am

OCT 2 1 2003

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT –
Chemistry & Bioequivalence

Re: ANDA 76-545 for Metformin Hydrochloride Extended-Release Tablets, 500 mg

Dear Mr. Buehler:

Reference is made to IVAX's pending Abbreviated New Drug Application for Metformin Hydrochloride Extended-Release Tablets, 500 mg, and to our amendments dated September 26, 2003 and October 2, 2003. Further reference is made to the Agency's correspondence dated October 17, 2003. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc., is amending the application by responding to the Agency's comments. As instructed, this response should be considered a MINOR AMENDMENT.

In response to the Agency's Chemistry comments, we submit the following:

A. Deficiencies:

1. *Please revise your dissolution method and specification based on the attached recommendation made by the Division of Bioequivalence (DBE) for release and stability of the drug product. Please provide a copy of the revised method.*

Response:
As requested, the dissolution method, MTF-ER-UV-DREL-1, has been revised based on the recommendation made by the Division of Bioequivalence for release and stability of the drug product. A copy of the revised method is provided at **Exhibit #1.**

2. *Please test your retained samples from accelerated stability for dissolution to demonstrate that the product meets the dissolution specifications recommended by the DBE. Alternatively, you may test the long term samples and propose the expiration dating period to match the available data.*

Response:
Retained samples from accelerated stability have been tested, as well as long term samples to demonstrate the product meets the recommendation by DBE. This data can be found at **Exhibit #2.**

Given this information, Ivax proposes a 24 month expiry.

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3. *Please provide revised release and stability specifications for the tablets incorporating the revision regarding dissolution.*

Response:
As requested, finished product release and stability specifications, as well as the stability protocol for the tablets have been revised incorporating the revision regarding dissolution. The referenced documents are provided at **Exhibit #3.**

B. *In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:*

Please submit any additional stability data for the exhibit batch that may be available.

Response:
Ivax Pharmaceuticals Inc. acknowledges the comment regarding additional stability data for the exhibit batch. Updated Controlled Room Temperature stability data is provided at **Exhibit #4.**

In response to the Division of Bioequivalence's comments, we submit:

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer at pH 6.8 at 37°C using Apparatus 2 (Paddle) at 100 rpm. Tentatively, the test product should meet the following specifications:

Q1	*1 Hr.*	*— %*
Q2	*2 Hrs.*	*— %*
Q3	*6 Hrs.*	*— %*
Q4	*10 Hrs*	*Not less than — %*

Of the labeled amount of the drug in the dosage form is dissolved in the given time.

Response:
Exhibits 1 through 3 confirm that the recommendation made by the DBE have been incorporated into the stability and quality control programs.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this response is complete, and that the information contained herein is satisfactory. We expect all comments regarding this application have now been addressed and that this amendment will be expeditiously reviewed, as we anxiously await your reply that the application is approved.

Should the Office of Generic Drugs have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Director, Regulatory Affairs

PJ/sh