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

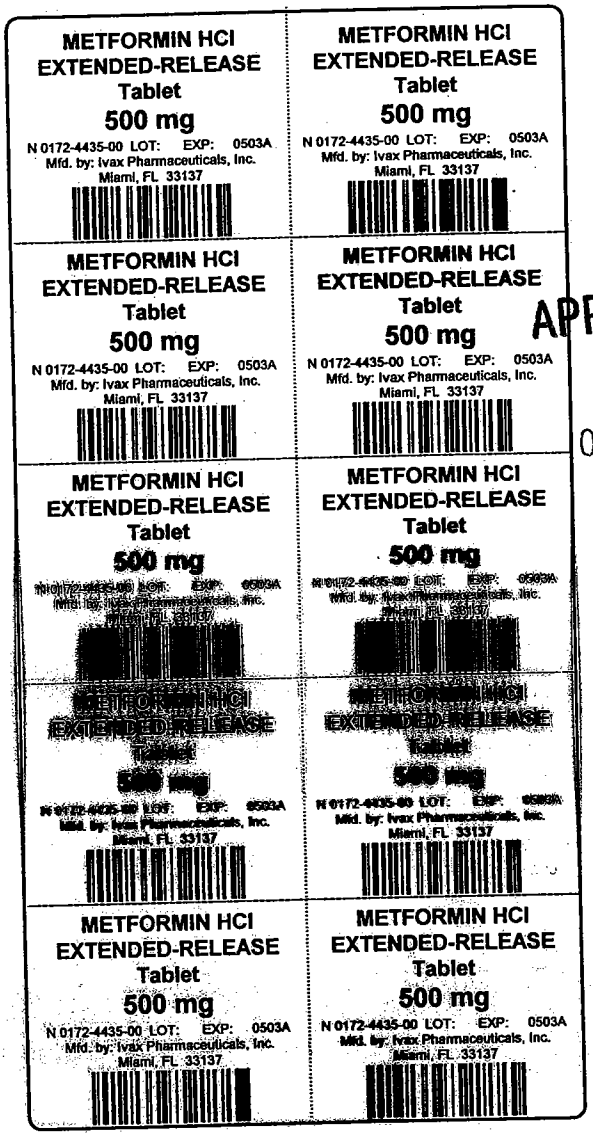
10/27/03

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

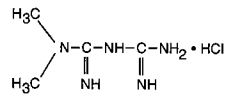
METFORMIN HYDROCHLORIDE TABLETS

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**).