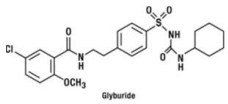
GLYBURIDE AND METFORMIN HYDROCHLORIDE - glyburide and metformin hydrochloride tablet
Zydus Lifesciences Limited

Glyburide and Metformin Hydrochloride Tablets, USP
Rx only

DESCRIPTION

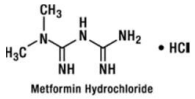
Glyburide and Metformin Hydrochloride Tablets, USP contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes, glyburide, USP and metformin hydrochloride, USP.

Glyburide, USP is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea. Glyburide, USP is a white or almost white, crystalline powder with a molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494. The glyburide used in glyburide and metformin hydrochloride tablets, USP has a particle size at least 20% are less than 2 micron, at least 80% are less than 10 micron and 100% are less than 40 micron. The structural formula is represented below.



Glyburide

Metformin hydrochloride, USP is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide monohydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors. It is a white crystals with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.62. Metformin hydrochloride, USP is freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in acetone and in methylene chloride. The structural formula is as shown:



Metformin Hydrochloride

Each glyburide and metformin hydrochloride tablet, USP intended for oral administration contains 1.25 mg glyburide USP with 250 mg metformin hydrochloride USP, 2.5 mg glyburide USP with 500 mg metformin hydrochloride USP and 5 mg glyburide USP with 500 mg metformin hydrochloride USP. In addition, each tablet contains the following inactive ingredients: calcium carbonate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and povidone.

Additionally, 1.25 mg/250 mg tablets contain opadry II white 33F28398 which contains hypromellose, lactose monohydrate, polyethylene glycol, talc and titanium dioxide.

Additionally, 2.5 mg/500 mg tablets contain opadry II orange 31F530003 which contains FD&C blue #2 aluminum lake, FD&C yellow #5 aluminum lake, FD&C yellow #6 aluminum lake, hypromellose, lactose monohydrate, polyethylene glycol and titanium dioxide.

Additionally, 5 mg/500 mg tablets contain opadry II green 31F510000 which contains iron oxide black, iron oxide red, iron oxide yellow, hypromellose, lactose monohydrate, polyethylene glycol and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Glyburide and metformin hydrochloride tablet combines glyburide and metformin hydrochloride, 2 antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.

Glyburide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in patients with type 2 diabetes, the blood glucose-lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetics

Absorption and Bioavailability

Glyburide and Metformin Hydrochloride

In bioavailability studies of glyburide and metformin hydrochloride 2.5 mg/500 mg and 5 mg/500 mg, the mean area under the plasma concentration versus time curve (AUC) for the glyburide component was 18% and 7%, respectively, greater than that of the Micronase® brand of glyburide coadministered with metformin. The glyburide component of glyburide and metformin hydrochloride, therefore, is not bioequivalent to Micronase®. The metformin component of glyburide and metformin hydrochloride is bioequivalent to metformin coadministered with glyburide.

Following administration of a single glyburide and metformin hydrochloride 5 mg/500 mg tablet with either a 20% glucose solution or a 20% glucose solution with food, there was no effect of food on the C_{max} and a relatively small effect of food on the AUC of the glyburide component. The T_{max} for the glyburide component was shortened from 7.5 hours to 2.75 hours with food compared to the same tablet strength administered fasting with a 20% glucose solution. The clinical significance of an earlier T_{max} for glyburide after food is not known. The effect of food on the pharmacokinetics of the metformin component was indeterminate.

Glyburide

Single-dose studies with Micronase® tablets in normal subjects demonstrate significant absorption of glyburide within 1 hour, peak drug levels at about 4 hours, and low but detectable levels at 24 hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Bioequivalence has not been established between glyburide and metformin hydrochloride and single-ingredient glyburide products.

Metformin Hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets of 500 mg and 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 peak concentration and a 25% lower AUC in plasma and a 35-minute prolongation of time to peak plasma concentration 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.

Distribution

Glyburide

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs, such as phenylbutazone, warfarin, and salicylates, displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding results in fewer

drug-drug interactions with glyburide tablets in clinical use.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. 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 <1 mcg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism and Elimination

Glyburide

The decrease of glyburide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400 and 1/40 as active, respectively, as glyburide) in rabbits. Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Metformin Hydrochloride

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

Multiple-dose studies with glyburide in patients with type 2 diabetes demonstrate drug level concentration-time curves similar to single-dose studies, indicating no buildup of drug in tissue depots.

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.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either glyburide or metformin.

Renal Insufficiency

No information is available on the pharmacokinetics of glyburide in patients with renal insufficiency.

In patients with decreased renal function (based on 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**).

Geriatrics

There is no information on the pharmacokinetics of glyburide in elderly patients.

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, when 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 treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Table 1: Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin

Subject Groups: Metformin Dose* (number of subjects)	C_{max}† (mcg/mL)	T_{max}‡ (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg SD§ (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg SD (74)¶	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg t.i.d. for 19 doses# (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg SD (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg t.i.d. for 19 doses# (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
ElderlyÞ**, healthy nondiabetic adults:**			
850 mg SD (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults: 850 mg SD			
Mild (CL_{cr}ß 61 to 90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31 to 60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10 to 30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

* All doses given fasting except the first 18 doses of the multiple-dose studies
† Peak plasma concentration
‡ Time to peak plasma concentration
§ SD=single dose
¶ Combined results (average means) of 5 studies: mean age 32 years (range 23 to 59 years)
# Kinetic study done following dose 19, given fasting
Þ Elderly subjects, mean age 71 years (range 65 to 81 years)
ß CL_{cr}=creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

After administration of a single oral GLUCOPHAGE® (metformin hydrochloride) 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed <5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

After administration of a single oral glyburide and metformin hydrochloride tablet with food, dose-normalized geometric mean glyburide C_{max} and AUC in pediatric patients with type 2 diabetes (11 to 16 years of age, n=28, mean body weight of 97 kg) differed <6% from historical values in healthy adults.

Gender

There is no information on the effect of gender on the pharmacokinetics of glyburide.

Metformin pharmacokinetic parameters did not differ significantly in subjects with or without 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 was comparable in males and females.

Race

No information is available on race differences in the pharmacokinetics of glyburide.

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

Patients with Inadequate Glycemic Control on Diet and Exercise Alone

In a 20-week, double-blind, multicenter U.S. clinical trial, a total of 806 drug-naive patients with type 2 diabetes, whose hyperglycemia was not adequately controlled with diet and exercise alone (baseline fasting plasma glucose [FPG] <240 mg/dL, baseline hemoglobin A_{1c} [HbA_{1c}] between 7% and 11%), were randomized to receive initial therapy with placebo, 2.5 mg glyburide, 500 mg metformin, glyburide and metformin hydrochloride 1.25 mg/250 mg, or glyburide and metformin hydrochloride 2.5 mg/500 mg. After 4 weeks, the dose was progressively increased (up to the 8-week visit) to a maximum of 4 tablets daily as needed to reach a target FPG of 126 mg/dL. Trial data at 20 weeks are summarized in **Table 2**.

Table 2: Placebo- and Active-Controlled Trial of Glyburide and Metformin Hydrochloride in Patients with Inadequate Glycemic Control on Diet and Exercise Alone: Summary of Trial Data at 20 Weeks

	Placebo	Glyburide 2.5 mg tablets	Metformin 500 mg tablets	Glyburide and Metformin Hydrochloride 1.25 mg/250 mg tablets	Glyburide and Metformin Hydrochloride 2.5 mg/500 mg tablets
Mean Final Dose	0 mg	5.3 mg	1317 mg	2.78 mg/557 mg	4.1 mg/824 mg
Hemoglobin A_{1c}	N=147	N=142	N=141	N=149	N=152
Baseline Mean (%)	8.14	8.14	8.23	8.22	8.20

Mean Change from Baseline	−0.21	−1.24	−1.03	−1.48	−1.53
Difference from Placebo		−1.02	−0.82	−1.26*	−1.31*
Difference from Glyburide				−0.24†	−0.29†
Difference from Metformin				−0.44†	−0.49†
Fasting Plasma Glucose	N=159	N=158	N=156	N=153	N=154
Baseline Mean FPG (mg/dL)	177.2	178.9	175.1	178	176.6
Mean Change from Baseline	4.6	−35.7	−21.2	−41.5	−40.1
Difference from Placebo		−40.3	−25.8	−46.1*	−44.7*
Difference from Glyburide				−5.8‡	−4.5‡
Difference from Metformin				−20.3‡	−18.9‡
Body Weight Mean Change from Baseline	−0.7 kg	+1.7 kg	−0.6 kg	+1.4 kg	+1.9 kg
Final HbA_{1c} Distribution (%)	N=147	N=142	N=141	N=149	N=152
<7%	19.7%	59.9%	50.4%	66.4%	71.7%
≥7% and <8%	37.4%	26.1%	29.8%	25.5%	19.1%
≥8%	42.9%	14.1%	19.9%	8.1%	9.2%

* p<0.001
† p<0.05
‡ p=NS

Treatment with glyburide and metformin hydrochloride resulted in significantly greater reduction in HbA_{1c} and postprandial plasma glucose (PPG) compared to glyburide, metformin, or placebo. Also, glyburide and metformin hydrochloride therapy resulted in greater reduction in FPG compared to glyburide, metformin, or placebo, but the differences from glyburide and metformin did not reach statistical significance.

Changes in the lipid profile associated with glyburide and metformin hydrochloride treatment were similar to those seen with glyburide, metformin, and placebo.

The double-blind, placebo-controlled trial described above restricted enrollment to patients with HbA_{1c} <11% or FPG <240 mg/dL. Screened patients ineligible for the first trial because of HbA_{1c} and/or FPG exceeding these limits were treated directly with glyburide and metformin hydrochloride 2.5 mg/500 mg in an open-label, uncontrolled protocol. In this study, 3 out of 173 patients (1.7%) discontinued because of inadequate therapeutic response.

Across the group of 144 patients who completed 26 weeks of treatment, mean HbA_{1c} was reduced from a baseline of 10.6% to 7.1%. The mean baseline FPG was 283 mg/dL and reduced to 164 and 161 mg/dL after 2 and 26 weeks, respectively. The mean final titrated dose of glyburide and metformin hydrochloride was 7.85 mg/1569 mg (equivalent to approximately 3 glyburide and metformin hydrochloride 2.5 mg/500 mg tablets per day).

Patients with Inadequate Glycemic Control on Sulfonylurea Alone

In a 16-week, double-blind, active-controlled U.S. clinical trial, a total of 639 patients with type 2 diabetes not adequately controlled (mean baseline HbA_{1c} 9.5%, mean baseline FPG 213 mg/dL) while being treated with at least one-half the maximum dose of a sulfonylurea (eg, glyburide 10 mg, glipizide 20 mg) were randomized to receive glyburide (fixed dose, 20 mg), metformin (500 mg), glyburide and metformin hydrochloride 2.5 mg/500 mg, or glyburide and metformin hydrochloride 5 mg/500 mg. The doses of metformin and glyburide and metformin hydrochloride were titrated to a maximum of 4 tablets daily as needed to achieve FPG <140 mg/dL. Trial data at 16 weeks are summarized in **Table 3**.

Table 3: Glyburide and Metformin Hydrochloride in Patients with Inadequate Glycemic Control on Sulfonylurea Alone: Summary of Trial Data at 16 Weeks

	Glyburide 5 mg tablets	Metformin 500 mg tablets	Glyburide and Metformin Hydrochloride 2.5 mg/500 mg tablets	Glyburide and Metformin Hydrochloride 5 mg/500 mg tablets
Mean Final Dose	20 mg	1840 mg	8.8 mg/1760 mg	17 mg/1740 mg
Hemoglobin A_{1c}	N=158	N=142	N=154	N=159
Baseline Mean (%)	9.63	9.51	9.43	9.44
Final Mean	9.61	9.82	7.92	7.91
Difference from Glyburide			−1.69*	−1.70*
Difference from Metformin			−1.90*	−1.91*
Fasting Plasma Glucose	N=163	N=152	N=160	N=160
Baseline Mean (mg/dL)	218.4	213.4	212.2	210.2
Final Mean	221	233.8	169.6	161.1
Difference from Glyburide			−51.3*	−59.9*
Difference from Metformin			−64.2*	−72.7*
Body Weight Mean Change from Baseline	+0.43 kg	−2.76 kg	+0.75 kg	+0.47 kg
Final HbA_{1c} Distribution (%)	N=158	N=142	N=154	N=159
<7%	2.5%	2.8%	24.7%	22.6%
≥7% and <8%	9.5%	11.3%	33.1%	37.1%
≥8%	88%	85.9%	42.2%	40.3%

* p<0.001

After 16 weeks, there was no significant change in the mean HbA_{1c} in patients randomized to glyburide or metformin therapy. Treatment with glyburide and metformin hydrochloride at doses up to 20 mg/2000 mg per day resulted in significant lowering of HbA_{1c}, FPG, and PPG from baseline compared to glyburide or metformin alone.

Addition of Thiazolidinediones to Glyburide and Metformin Hydrochloride Therapy

In a 24-week, double-blind, multicenter U.S. clinical trial, patients with type 2 diabetes not adequately controlled on current oral antihyperglycemic therapy (either monotherapy or combination therapy) were first switched to open label glyburide and metformin hydrochloride 2.5 mg/500 mg tablets and titrated to a maximum daily dose of 10 mg/2000 mg. A total of 365 patients inadequately controlled (HbA_{1c} >7% and ≤10%) after 10 to 12 weeks of a daily glyburide and metformin hydrochloride dose of at least 7.5 mg/1500 mg were randomized to receive add-on therapy with rosiglitazone 4 mg or placebo once daily. After 8 weeks, the rosiglitazone dose was increased to a maximum of 8 mg daily as needed to reach a target mean daily glucose of 126 mg/dL or HbA_{1c} <7%. Trial data at 24 weeks or the last prior visit are summarized in **Table 4**.

Table 4: Effects of Adding Rosiglitazone or Placebo in Patients Treated with Glyburide and Metformin Hydrochloride in a 24-Week Trial

	Placebo + Glyburide and Metformin Hydrochloride	Rosiglitazone + Glyburide and Metformin Hydrochloride
Mean Final Dose		
Glyburide and Metformin Hydrochloride	10 mg/1992 mg	9.6 mg/1914 mg
Rosiglitazone	0 mg	7.4 mg
Hemoglobin A_{1c}	N=178	N=177
Baseline Mean (%)	8.09	8.14
Final Mean	8.21	7.23
Difference from Placebo*		−1.02†
Fasting Plasma Glucose	N=181	N=176
Baseline Mean (mg/dL)	173.1	178.4
Final Mean	181.4	136.3
Difference from Placebo*		−48.5†
Body Weight Mean Change from Baseline	+0.03 kg	+3.03 kg
Final HbA_{1c} Distribution (%)	N=178	N=177
<7%	13.5%	42.4%
≥7% and <8%	32%	38.4%
≥8%	54.5%	19.2%

* Adjusted for the baseline mean difference
† p<0.001

For patients who did not achieve adequate glycemic control on glyburide and metformin hydrochloride, the addition of rosiglitazone, compared to placebo, resulted in significant lowering of HbA_{1c} and FPG.

INDICATIONS AND USAGE

Glyburide and Metformin Hydrochloride Tablets, USP are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

Glyburide and metformin hydrochloride tablets are contraindicated in patients with:
1. Renal disease or renal dysfunction (eg, 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. Known hypersensitivity to metformin hydrochloride or glyburide.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
4. Concomitant administration of bosentan.

Glyburide and metformin hydrochloride tablets 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

Metformin Hydrochloride

Lactic acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glyburide and metformin hydrochloride tablets; 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 mcg/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). In more than 20,000 patientyears exposure to metformin in clinical trials, there were no reports of lactic acidosis. 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 and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glyburide and metformin hydrochloride 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, glyburide and metformin hydrochloride 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, glyburide and metformin hydrochloride 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 glyburide and metformin hydrochloride, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, glyburide and metformin hydrochloride 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). Glyburide and metformin hydrochloride 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 glyburide and metformin hydrochloride, gastrointestinal symptoms, which are common during initiation of therapy with metformin, 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 glyburide and metformin hydrochloride 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 glyburide and metformin hydrochloride, 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.)

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to 1 of 4 treatment groups (*Diabetes* 19 (Suppl. 2):747 to 830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone.

A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of glyburide and of alternative modes of therapy.

Although only 1 drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

General

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glyburide and metformin hydrochloride or any other antidiabetic drug.

Glyburide and Metformin Hydrochloride

Hypoglycemia

Glyburide and metformin hydrochloride is capable of producing hypoglycemia or hypoglycemic symptoms, therefore, proper patient selection, dosing, and instructions are important to avoid potential hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, when strenuous exercise is not compensated

by caloric supplementation, or during concomitant use with other glucose-lowering agents or ethanol. Renal or hepatic insufficiency may cause elevated drug levels of both glyburide and metformin hydrochloride, and the hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of hypoglycemic reactions. 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 people who are taking beta-adrenergic blocking drugs.

Glyburide

Hemolytic anemia

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because glyburide and metformin hydrochloride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

Metformin Hydrochloride

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 glyburide and metformin hydrochloride. In patients with advanced age, glyburide and metformin hydrochloride 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, glyburide and metformin hydrochloride should not be titrated to the maximum dose (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**). Before initiation of glyburide and metformin hydrochloride 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 glyburide and metformin hydrochloride 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, glyburide and metformin hydrochloride 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 reevaluated 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 glyburide and metformin hydrochloride therapy, the drug should be promptly discontinued.

Surgical procedures

Glyburide and metformin hydrochloride 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 glyburide and metformin hydrochloride. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Impaired hepatic function

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

Vitamin B_{12} levels

In controlled clinical trials with metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12}, 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 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 2- to 3-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 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, glyburide and metformin hydrochloride must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Addition of Thiazolidinediones to Glyburide and Metformin Hydrochloride Therapy

Hypoglycemia

Patients receiving glyburide and metformin hydrochloride in combination with a thiazolidinedione may be at risk for hypoglycemia.

Weight gain

Weight gain was seen with the addition of rosiglitazone to glyburide and metformin hydrochloride, similar to that reported for thiazolidinedione therapy alone.

Hepatic effects

When a thiazolidinedione is used in combination with glyburide and metformin hydrochloride, periodic monitoring of liver function tests should be performed in compliance with the labeled recommendations for the thiazolidinedione.

Information for Patients

Glyburide and Metformin Hydrochloride

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

The risks of lactic acidosis associated with metformin therapy, 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 glyburide and metformin hydrochloride immediately and 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 glyburide and metformin hydrochloride, 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.

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 counseled against excessive alcohol intake, either acute or chronic, while receiving glyburide and metformin hydrochloride. (See **Patient Information** printed below.)

Laboratory Tests

Periodic fasting blood glucose (FBG) and HbA_{1c} measurements should be performed to monitor therapeutic response.

Initial and periodic monitoring of hematologic parameters (eg, 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

Glyburide and Metformin Hydrochloride

Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control.

These drugs include 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 glyburide and metformin hydrochloride, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving glyburide and metformin hydrochloride, the patient should be observed closely for hypoglycemia. 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 sulfonylureas, which are extensively bound to serum proteins.

Glyburide

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving glyburide and metformin hydrochloride, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glyburide and metformin hydrochloride, the patient should be observed closely for loss of blood glucose control.

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore concomitant administration of glyburide and metformin hydrochloride and bosentan is contraindicated.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Colesevelam: Concomitant administration of colesevelam and glyburide resulted in reductions in glyburide AUC and C_{max} of 32% and 47%, respectively. The reductions in glyburide AUC and C_{max} were 20% and 15%, respectively, when administered 1 hour before, and not significantly changed (−7% and 4%, respectively) when administered 4 hours before colesevelam.

Metformin Hydrochloride

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 (eg, 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 glyburide and metformin hydrochloride 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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with the combined products in glyburide and metformin hydrochloride. The following data are based on findings in studies performed with the individual products.

Glyburide

Studies in rats with glyburide alone at doses up to 300 mg/kg/day (approximately 145 times the maximum recommended human daily [MRHD] dose of 20 mg for the glyburide component of glyburide and metformin hydrochloride based on body surface area comparisons) for 18 months revealed no carcinogenic effects. In a 2-year oncogenicity study of glyburide in mice, there was no evidence of treatment-related tumors.

There was no evidence of mutagenic potential of glyburide alone in the following *in vitro* tests: *Salmonella* microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Metformin Hydrochloride

Long-term carcinogenicity studies were performed with metformin alone 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 4 times the MRHD dose of 2000 mg of the metformin component of glyburide and metformin hydrochloride based on body surface area comparisons. No evidence of carcinogenicity with metformin alone was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin alone in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day of metformin alone.

There was no evidence of a mutagenic potential of metformin alone 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 alone when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the MRHD dose of the metformin component of glyburide and metformin hydrochloride 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 as close to normal as possible. Because animal reproduction studies are not always predictive of human response, glyburide and metformin hydrochloride should not be used during pregnancy unless clearly needed. (See below.)

There are no adequate and well-controlled studies in pregnant women with glyburide and metformin hydrochloride or its individual components. No animal studies have been conducted with the combined products in glyburide and metformin hydrochloride. The

following data are based on findings in studies performed with the individual products.

Glyburide

Reproduction studies were performed in rats and rabbits at doses up to 500 times the MRHD dose of 20 mg of the glyburide component of glyburide and metformin hydrochloride based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to glyburide.

Metformin Hydrochloride

Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the MRHD dose of 2000 mg of the metformin component of glyburide and metformin hydrochloride based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nonteratogenic Effects

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that glyburide and metformin hydrochloride be used during pregnancy. However, if it is used, glyburide and metformin hydrochloride should be discontinued at least 2 weeks before the expected delivery date. (See **Pregnancy: Teratogenic Effects: Pregnancy Category B.**)

Nursing Mothers

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. 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 glyburide and metformin hydrochloride, taking into account the importance of the drug to the mother. If glyburide and metformin hydrochloride is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and efficacy of glyburide and metformin hydrochloride were evaluated in an active-controlled, double-blind, 26-week randomized trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. Glyburide and metformin hydrochloride was not shown statistically to be superior to either metformin or glyburide with respect to reducing HbA_{1c} from baseline (see **Table 5**). No unexpected safety findings were associated with glyburide and metformin hydrochloride in this trial.

Table 5: HbA_{1c} (Percent) Change From Baseline at 26 Weeks: Pediatric Study

	Glyburide 2.5 mg tablets	Metformin 500 mg tablets	Glyburide and Metformin Hydrochloride 1.25 mg/250 mg tablets
Mean Final Dose	6.5 mg	1500 mg	3.1 mg/623 mg
Hemoglobin A_{1c}	N=49	N=54	N=57
Baseline Mean (%)	7.70	7.99	7.85
Mean Change from Baseline	−0.96	−0.48	−0.80
Difference from Metformin			−0.32
Difference from Glyburide			+0.16

Geriatric Use

Of the 642 patients who received glyburide and metformin hydrochloride in double-blind clinical studies, 23.8% were 65 and older while 2.8% were 75 and older. Of the 1302 patients who received glyburide and metformin hydrochloride in open-label clinical studies, 20.7% were 65 and older while 2.5% were 75 and older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride 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, glyburide and metformin hydrochloride 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, glyburide and metformin hydrochloride 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 glyburide and metformin hydrochloride (see also **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Glyburide and Metformin Hydrochloride

In double-blind clinical trials involving glyburide and metformin hydrochloride as initial therapy or as second-line therapy, a total of 642 patients received glyburide and metformin hydrochloride, 312 received metformin therapy, 324 received glyburide therapy, and 161 received placebo. The percent of patients reporting events and types of adverse events reported in clinical trials of glyburide and metformin hydrochloride (all strengths) as initial therapy and second-line therapy are listed in **Table 6**.

Table 6: Most Common Clinical Adverse Events (>5%) in Double-Blind Clinical Studies of Glyburide and Metformin Hydrochloride Used as Initial or Second-Line Therapy

Adverse Event	Number (%) of Patients			
	Placebo N=161	Glyburide N=324	Metformin N=312	Glyburide and Metformin Hydrochloride N=642
Upper respiratory infection	22 (13.7)	57 (17.6)	51 (16.3)	111 (17.3)
Diarrhea	9 (5.6)	20 (6.2)	64 (20.5)	109 (17)
Headache	17 (10.6)	37 (11.4)	29 (9.3)	57 (8.9)
Nausea/vomiting	10 (6.2)	17 (5.2)	38 (12.2)	49 (7.6)
Abdominal pain	6 (3.7)	10 (3.1)	25 (8)	44 (6.9)
Dizziness	7 (4.3)	18 (5.6)	12 (3.8)	35 (5.5)

In a controlled clinical trial of rosiglitazone versus placebo in patients treated with glyburide and metformin hydrochloride (n=365), 181 patients received glyburide and metformin hydrochloride with rosiglitazone and 184 received glyburide and metformin hydrochloride with placebo.

Edema was reported in 7.7% (14/181) of patients treated with rosiglitazone compared to 2.2% (4/184) of patients treated with placebo. A mean weight gain of 3 kg was observed in rosiglitazone-treated patients.

Disulfiram-like reactions have very rarely been reported in patients treated with glyburide tablets.

Hypoglycemia

In controlled clinical trials of glyburide and metformin hydrochloride there were no hypoglycemic episodes requiring medical intervention and/or pharmacologic therapy; all events were managed by the patients. The incidence of reported symptoms of hypoglycemia (such as dizziness, shakiness, sweating, and hunger), in the initial therapy trial of glyburide and metformin hydrochloride are summarized in **Table 7**.

The frequency of hypoglycemic symptoms in patients treated with glyburide and metformin hydrochloride 1.25 mg/250 mg was highest in patients with a baseline HbA_{1c} <7%, lower in those with a baseline HbA_{1c} of between 7% and 8%, and was comparable to placebo and metformin in those with a baseline HbA_{1c} >8%. For patients with a baseline HbA_{1c} between 8% and 11% treated with glyburide and metformin hydrochloride 2.5 mg/500 mg as initial therapy, the frequency of hypoglycemic symptoms was 30% to 35%. As second-line therapy in patients inadequately controlled on sulfonylurea alone, approximately 6.8% of all patients treated with glyburide and metformin hydrochloride experienced hypoglycemic symptoms. When rosiglitazone was added to glyburide and metformin hydrochloride therapy, 22% of patients reported 1 or more fingerstick glucose measurements ≤50 mg/dL compared to 3.3% of placebo-treated patients. All hypoglycemic events were managed by the patients and only 1 patient discontinued for hypoglycemia. (See **PRECAUTIONS: General: Addition of Thiazolidinediones to Glyburide and Metformin Hydrochloride Therapy.**)

Gastrointestinal Reactions

The incidence of gastrointestinal (GI) side effects (diarrhea, nausea/vomiting, and

abdominal pain) in the initial therapy trial are summarized in **Table 7**. Across all glyburide and metformin hydrochloride trials, GI symptoms were the most common adverse events with glyburide and metformin hydrochloride and were more frequent at higher dose levels. In controlled trials, <2% of patients discontinued glyburide and metformin hydrochloride therapy due to GI adverse events.

Table 7: Treatment Emergent Symptoms of Hypoglycemia or Gastrointestinal Adverse Events in a Placebo- and Active-Controlled Trial of Glyburide and Metformin Hydrochloride as Initial Therapy

Variable	Placebo N=161	Glyburide Tablets N=160	Metformin Tablets N=159	Glyburide and Metformin Hydrochloride 1.25 mg/250 mg Tablets N=158	Glyburide and Metformin Hydrochloride 2.5 mg/500 mg Tablets N=162
Mean Final Dose	0 mg	5.3 mg	1317 mg	2.78 mg/557 mg	4.1 mg/824 mg
Number (%) of patients with symptoms of hypoglycemia	5 (3.1)	34 (21.3)	5 (3.1)	18 (11.4)	61 (37.7)
Number (%) of patients with gastrointestinal adverse events	39 (24.2)	38 (23.8)	69 (43.3)	50 (31.6)	62 (38.3)

In postmarketing reports cholestatic jaundice and hepatitis may occur rarely which may progress to liver failure; glyburide and metformin hydrochloride should be discontinued if this occurs.

OVERDOSAGE

Glyburide

Overdosage of sulfonylureas, including glyburide tablets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

Metformin Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50 g. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (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

General Considerations

Dosage of glyburide and metformin hydrochloride tablets must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glyburide/2000 mg metformin.
Glyburide and metformin hydrochloride tablets should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glyburide), reduce GI side effects (largely due to metformin), and permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to glyburide and metformin hydrochloride tablets and to identify the minimum effective dose for the patient. Thereafter, HbA_{1c} should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA_{1c} to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using HbA_{1c} (glycosylated hemoglobin), which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to glyburide and metformin hydrochloride tablets therapy in patients taking concomitant glyburide (or other sulfonylurea) plus metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring.

Glyburide and Metformin Hydrochloride Tablets in Patients with Inadequate Glycemic Control on Diet and Exercise

Recommended starting dose: 1.25 mg/250 mg once or twice daily with meals.

For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of glyburide and metformin hydrochloride tablet is 1.25 mg/250 mg once a day with a meal. As initial therapy in patients with baseline HbA_{1c} >9% or an FPG >200 mg/dL, a starting dose of glyburide and metformin hydrochloride tablet 1.25 mg/250 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 1.25 mg/250 mg per day every 2 weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose. In clinical trials of glyburide and metformin hydrochloride tablets as initial therapy, there was no experience with total daily doses >10 mg/2000 mg per day.
Glyburide and metformin hydrochloride tablets 5 mg/500 mg should not be used as initial therapy due to an increased risk of hypoglycemia.

Glyburide and Metformin Hydrochloride Tablets Use in Patients with Inadequate Glycemic Control on a Sulfonylurea and/or Metformin

Recommended starting dose: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals.

For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone, the recommended starting dose of glyburide and metformin hydrochloride tablet is 2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of glyburide and metformin hydrochloride tablets should not exceed the daily doses of glyburide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.

For patients previously treated with combination therapy of glyburide (or another sulfonylurea) plus metformin, if switched to glyburide and metformin hydrochloride tablets, the starting dose should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of glyburide and metformin hydrochloride tablets should be titrated as described above to achieve adequate control of blood glucose.

Addition of Thiazolidinediones to Glyburide and Metformin Hydrochloride Tablets Therapy

For patients not adequately controlled on glyburide and metformin hydrochloride tablets, a thiazolidinedione can be added to glyburide and metformin hydrochloride tablets therapy. When a thiazolidinedione is added to glyburide and metformin hydrochloride tablets therapy, the current dose of glyburide and metformin hydrochloride tablets can be continued and the thiazolidinedione initiated at its recommended starting dose. For patients needing additional glycemic control, the dose of the thiazolidinedione can be increased based on its recommended titration schedule. The increased glycemic control attainable with glyburide and metformin hydrochloride tablets plus a thiazolidinedione may increase the potential for hypoglycemia at any time of day. In patients who develop hypoglycemia when receiving glyburide and metformin hydrochloride tablets and a thiazolidinedione, consideration should be given to reducing the dose of the glyburide component of glyburide and metformin hydrochloride tablets. As clinically warranted, adjustment of the dosages of the other components of the antidiabetic regimen should also be considered.

Patients Receiving Colesevelam

When colesevelam is coadministered with glyburide, maximum plasma concentration and total exposure to glyburide is reduced. Therefore, glyburide and metformin hydrochloride tablets should be administered at least 4 hours prior to colesevelam.

Specific Patient Populations

Glyburide and metformin hydrochloride tablets are not recommended for use during pregnancy. The initial and maintenance dosing of glyburide and metformin hydrochloride tablets should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful

assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of glyburide and metformin hydrochloride tablets to avoid the risk of hypoglycemia. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly. (See **WARNINGS.**)

HOW SUPPLIED

Glyburide and Metformin Hydrochloride Tablets USP, 1.25 mg/250 mg are white to off white colored, capsule shaped, biconvex coated tablets, debossed with "653" on one side and plain on the other side and are supplied as follows:

NDC 65841-824-06 in bottles of 30 tablets

NDC 65841-824-16 in bottles of 90 tablets

NDC 65841-824-01 in bottles of 100 tablets

NDC 65841-824-05 in bottles of 500 tablets

NDC 65841-824-10 in bottles of 1000 tablets

NDC 65841-824-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

Glyburide and Metformin Hydrochloride Tablets USP, 2.5 mg/500 mg are tan to scarlet yellow colored, capsule shaped, biconvex coated tablets debossed with "654" on one side and plain on the other side and are supplied as follows:

NDC 65841-825-06 in bottles of 30 tablets

NDC 65841-825-16 in bottles of 90 tablets

NDC 65841-825-01 in bottles of 100 tablets

NDC 65841-825-05 in bottles of 500 tablets

NDC 65841-825-10 in bottles of 1000 tablets

NDC 65841-825-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

Glyburide and Metformin Hydrochloride Tablets USP, 5 mg/500 mg are pale yellow colored, capsule shaped, biconvex coated tablets, debossed with "655" on one side and plain on the other side and are supplied as follows:

NDC 65841-826-06 in bottles of 30 tablets

NDC 65841-826-16 in bottles of 90 tablets

NDC 65841-826-01 in bottles of 100 tablets

NDC 65841-826-05 in bottles of 500 tablets

NDC 65841-826-10 in bottles of 1000 tablets

NDC 65841-826-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

STORAGE

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

Dispense in a tight container (USP).

GLUCOPHAGE® is a registered trademark of Merck SantÉ S.A.S., an associate of Merck KGaA of Darmstadt, Germany. Licensed to Bristol-Myers Squibb Company.

Micronase® is a registered trademark of Pharmacia & Upjohn Company.

Manufactured by:

Cadila Healthcare Ltd.

Baddi, India

Rev.: 03/16

Revision Date: 11/03/16

PATIENT INFORMATION

Glyburide and Metformin Hydrochloride Tablets, USP

WARNING: A small number of people who have taken metformin hydrochloride have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take glyburide and metformin hydrochloride tablets. (See Question Nos. 9 to 13.)

Q1. Why do I need to take glyburide and metformin hydrochloride tablets?

Your doctor has prescribed glyburide and metformin hydrochloride tablets to treat your type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus.

Q2. What is type 2 diabetes?

People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does 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.

Q3. Why is it important to control type 2 diabetes?

The main goal of treating diabetes is to lower your blood sugar to a normal level. Studies have shown that good control of blood sugar may prevent or delay complications, such as heart disease, kidney disease, or blindness.

Q4. How is type 2 diabetes usually controlled?

High blood sugar can be lowered by diet and exercise, a number of oral medications, and insulin injections. Before taking glyburide and metformin hydrochloride tablets you should first try to control your diabetes by exercise and weight loss. Even if you are taking glyburide and metformin hydrochloride tablets, you should still exercise and follow the diet recommended for your diabetes.

Q5. Does glyburide and metformin hydrochloride tablets work differently from other glucose-control medications?

Yes, it does. Glyburide and metformin hydrochloride tablet combines 2 glucose-lowering drugs, glyburide and metformin.

These 2 drugs work together to improve the different metabolic defects found in type 2 diabetes. Glyburide lowers blood sugar primarily by causing more of the body's own insulin to be released, and metformin lowers blood sugar, in part, by helping your body use your own insulin more effectively. Together, they are efficient in helping you to achieve better glucose control.

Q6. What happens if my blood sugar is still too high?

When blood sugar cannot be lowered enough by glyburide and metformin hydrochloride tablets your doctor may prescribe injectable insulin or take other measures to control your diabetes.

Q7. Can glyburide and metformin hydrochloride tablets cause side effects?

Glyburide and metformin hydrochloride tablets, like all blood sugar-lowering medications, can cause side effects in some patients. Most of these side effects are minor. However, there are also serious, but rare, side effects related to glyburide and metformin hydrochloride tablets (see **Q9 to Q13**).

Q8. What are the most common side effects of glyburide and metformin hydrochloride tablets?

The most common side effects of glyburide and metformin hydrochloride tablets are normally minor ones such as diarrhea, nausea, and upset stomach. If these side effects occur, they usually occur during the first few weeks of therapy. Taking your glyburide and metformin hydrochloride tablets with meals can help reduce these side effects.

Less frequently, symptoms of hypoglycemia (low blood sugar), such as lightheadedness, dizziness, shakiness, or hunger may occur. The risk of hypoglycemic symptoms increases when meals are skipped, too much alcohol is consumed, or heavy exercise occurs without enough food. Following the advice of your doctor can help you to avoid these symptoms.

Q9. Are there any serious side effects that glyburide and metformin hydrochloride tablets can cause?

People who have a condition known as glucose-6-phosphate dehydrogenase (G6PD) deficiency and who take glyburide and metformin hydrochloride tablets may develop hemolytic anemia (fast breakdown of red blood cells). G6PD deficiency usually runs in families. Tell your doctor if you or any members of your family have been diagnosed with G6PD deficiency before you start taking glyburide and metformin hydrochloride tablets.

Glyburide and metformin hydrochloride tablet rarely causes serious side effects. The most serious side effect that glyburide and metformin hydrochloride tablets can cause is called lactic acidosis.

Q10. What is lactic acidosis and can it happen to me?

Lactic acidosis is caused by a buildup of lactic acid in the blood. Lactic acidosis associated with metformin is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about 1 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 cases.

It's also important for your liver to be working normally when you take glyburide and metformin hydrochloride tablets. Your liver helps remove lactic acid from your bloodstream.

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 glyburide and metformin hydrochloride tablets causes harm to the kidneys or liver.

Q11. Are there other risk factors for lactic acidosis?

Your risk of developing lactic acidosis from taking glyburide and metformin hydrochloride tablets is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should discuss your risk with your doctor.

You should not take glyburide and metformin hydrochloride tablets if:

- You have chronic kidney or liver problems
- You have congestive heart failure which is treated with medications, eg, digoxin (Lanoxin®) or furosemide (Lasix®)
- You drink alcohol excessively (all the time or short-term "binge" drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have certain x-ray procedures with injectable contrast agents
- You are going to have surgery
- You develop a serious condition, such as a heart attack, severe infection, or stroke
- You are ≥80 years of age and have NOT had your kidney function tested

Q12. What are the symptoms of lactic acidosis?

Some of the symptoms include: feeling very weak, tired or uncomfortable; unusual muscle pain; trouble breathing; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; or suddenly developing a slow or irregular heartbeat.

If you notice these symptoms, or if your medical condition has suddenly changed, stop taking glyburide and metformin hydrochloride tablets and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q13. What does my doctor need to know to decrease my risk of lactic acidosis?

Tell your doctor if you have an illness that results in severe vomiting, diarrhea, and/or fever, or if your intake of fluids is significantly reduced. These situations can lead to severe dehydration, and it may be necessary to stop taking glyburide and metformin hydrochloride tablets temporarily.

You should let your doctor know if you are going to have any surgery or specialized x-ray procedures that require injection of contrast agents. Glyburide and metformin hydrochloride tablets therapy will need to be stopped temporarily in such instances.

Q14. Can I take glyburide and metformin hydrochloride tablets with other medications?

Remind your doctor that you are taking glyburide and metformin hydrochloride tablets when any new drug is prescribed or a change is made in how you take a drug already prescribed. Glyburide and metformin hydrochloride tablets may interfere with the way some drugs work and some drugs may interfere with the action of glyburide and metformin hydrochloride tablets.

Do not take glyburide and metformin hydrochloride tablets if you are taking bosentan used for pulmonary arterial hypertension (PAH), which is high blood pressure in the vessels of the lungs.

Q15. What if I become pregnant while taking glyburide and metformin hydrochloride tablets?

Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take glyburide and metformin hydrochloride tablets during pregnancy.

Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of glyburide and metformin hydrochloride tablets if you are nursing a child.

Q16. How do I take glyburide and metformin hydrochloride tablets?

Your doctor will tell you how many glyburide and metformin hydrochloride tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of glyburide and metformin hydrochloride tablets and your dosage will be increased gradually until your blood sugar is controlled.

Q17. Where can I get more information about glyburide and metformin hydrochloride tablets?

This leaflet is a summary of the most important information about glyburide and metformin hydrochloride tablets. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type 2 diabetes as well as glyburide and metformin hydrochloride tablets and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.

Other brands listed are the trademarks of their respective owners.

The 2.5 mg/500 mg strength product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA 1088.

Manufactured by:

Cadila Healthcare Ltd.

Baddi, India

Rev.: 03/16

Revision Date: 11/03/16

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

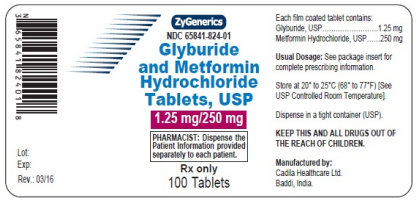
NDC 65841-824-01 in bottles of 100 tablets

Glyburide and Metformin Hydrochloride Tablets USP, 1.25 mg/250 mg

100 Tablets

Rx only

Zydus



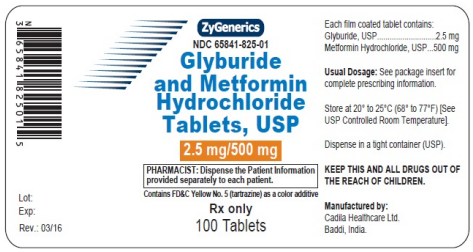
NDC 65841-825-01 in bottles of 100 tablets

Glyburide and Metformin Hydrochloride Tablets USP, 2.5 mg/500 mg

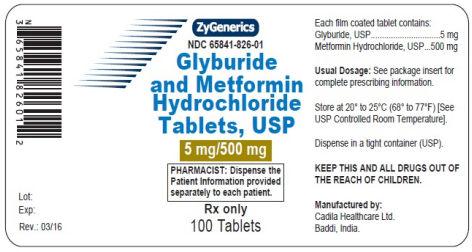
100 Tablets

Rx only

Zydus



NDC 65841-826-01 in bottles of 100 tablets
Glyburide and Metformin Hydrochloride Tablets USP, 5 mg/500 mg
100 Tablets
Rx only
Zydus



GLYBURIDE AND METFORMIN HYDROCHLORIDE

glyburide and metformin hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65841-824
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLYBURIDE (UNII: SX6KS8TVWC) (GLYBURIDE - UNII:SX6KS8TVWC)	GLYBURIDE	1.25 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	250 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM CARBONATE (UNII: H0G9379FGK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
POVIDONE K30 (UNII: U725QWY32X)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	CAPSULE	**Size**	13mm
Flavor		**Imprint Code**	653
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65841-824-06	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
2	NDC:65841-824-16	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
3	NDC:65841-824-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
4	NDC:65841-824-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
5	NDC:65841-824-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
6	NDC:65841-824-77	10 in 1 CARTON	04/07/2016	
6	NDC:65841-824-30	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206748	04/07/2016	

GLYBURIDE AND METFORMIN HYDROCHLORIDE

glyburide and metformin hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65841-825
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLYBURIDE (UNII: SX6KS8TVWC) (GLYBURIDE - UNII:SX6KS8TVWC)	GLYBURIDE	2.5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM CARBONATE (UNII: H0G9379FGK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C YELLOW NO. 5 (UNII: I753WB2F1M)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
POVIDONE K30 (UNII: U725QWY32X)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	YELLOW (tan to scarlet yellow)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	654
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65841-825-06	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
2	NDC:65841-825-16	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
3	NDC:65841-825-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
4	NDC:65841-825-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
5	NDC:65841-825-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
6	NDC:65841-825-77	10 in 1 CARTON	04/07/2016	
6	NDC:65841-825-30	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206748	04/07/2016	

GLYBURIDE AND METFORMIN HYDROCHLORIDE

glyburide and metformin hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65841-826
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLYBURIDE (UNII: SX6K58TVWC) (GLYBURIDE - UNII:SX6K58TVWC)	GLYBURIDE	5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM CARBONATE (UNII: H0G9379FGK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
POVIDONE K30 (UNII: U725QWY32X)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	YELLOW (pale yellow)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	655
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65841-826-06	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
2	NDC:65841-826-16	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
3	NDC:65841-826-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
4	NDC:65841-826-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
5	NDC:65841-826-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2016	
6	NDC:65841-826-77	10 in 1 CARTON	04/07/2016	
6	NDC:65841-826-30	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206748	04/07/2016	

Labeler - Zydus Lifesciences Limited (918596198)

Registrant - Zydus Lifesciences Limited (918596198)

Establishment

Name	Address	ID/FEI	Business Operations
Zydus Lifesciences Limited		677605858	ANALYSIS(65841-824, 65841-825, 65841-826) , MANUFACTURE(65841-824, 65841-825, 65841-826)