GLIPIZIDE AND METFORMIN HYDROCHLORIDE- glipizide and metformin hydrochloride tablet, film coated
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Zydus Pharmaceuticals USA Inc.

Glipizide and Metformin Hydrochloride Tablets, USP

WARNINGS: LACTIC ACIDOSIS

Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally > 5 mcg/mL [see PRECAUTIONS]

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, hepatic impairment, and mitochondrial disease.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided [see PRECAUTIONS].

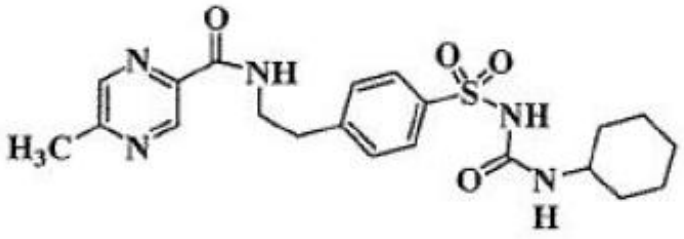
If metformin-associated lactic acidosis is suspected, immediately discontinue glipizide and metformin hydrochloride and institute general supportive measures in a hospital setting.
Prompt hemodialysis is recommended [see PRECAUTIONS].

DESCRIPTION

Glipizide and metformin hydrochloride tablets, USP contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes, glipizide and metformin hydrochloride.

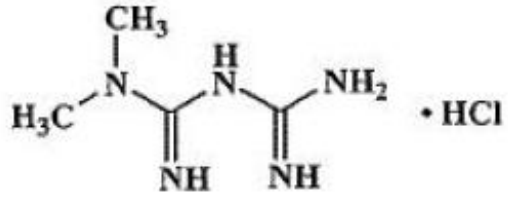
Glipizide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glipizide is 1-cyclohexyl-3-[[*p*-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]

sulfonyl]urea. Glipizide, USP white to almost white; crystalline powder with a molecular formula of $C_{21}H_{27}N_5O_4S$, a molecular weight of 445.55 and a pK_a of 5.9. The structural formula is represented below.



Glipizide

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 to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Metformin Hydrochloride

Each glipizide and metformin hydrochloride tablet intended for oral administration contains 2.5 mg glipizide with 250 mg metformin hydrochloride, 2.5 mg glipizide with 500 mg metformin hydrochloride, and 5 mg glipizide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide. Additionally each 2.5 mg/250 mg and 5 mg/500 mg tablet contains iron oxide red and each 2.5 mg/500 mg tablet contains polysorbate 80.

CLINICAL PHARMACOLOGY

Mechanism of Action:

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

Glipizide 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. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. The mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment.

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:

Glipizide and Metformin Hydrochloride Tablets:

In a single-dose study in healthy subjects, the glipizide and metformin components of glipizide and metformin hydrochloride tablets 5 mg/500 mg were bioequivalent to co-administered glipizide and metformin hydrochloride. Following administration of a single glipizide and metformin hydrochloride 5 mg/500 mg tablet in healthy subjects with either a 20% glucose solution or a 20% glucose solution with food, there was a small effect of food on peak plasma concentration (C_{max}) and no effect of food on area under the curve (AUC) of the glipizide component. Time to peak plasma concentration (T_{max}) for the glipizide component was delayed 1 hour with food relative to the same tablet strength administered fasting with a 20% glucose solution. C_{max} for the metformin component was reduced approximately 14% by food whereas AUC was not affected. T_{max} for the metformin component was delayed 1 hour after food.

Glipizide:

Gastrointestinal absorption of glipizide is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1 hour to 3 hours after a single oral dose. Glipizide does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes.

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:

Glipizide:

Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98% to 99% 1 hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 liters, indicative of localization within the extracellular fluid compartment. In mice, no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labeled drug.

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 hours to 48 hours and are generally <1 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Elimination:

Glipizide:

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates, and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine. The half-life of elimination ranges from 2 hours to 4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the 2 routes of administration, indicating that first-pass metabolism is not significant.

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.

Specific 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.

Renal Impairment

The metabolism and excretion of glipizide may be slowed in patients with impaired renal function (see **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION**).

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see **Table 1**; also, see **WARNINGS**).

Hepatic Impairment:

The metabolism and excretion of glipizide may be slowed in patients with impaired hepatic function (see **PRECAUTIONS**).

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

Geriatrics:

There is no information on the pharmacokinetics of glipizide 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**).

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

Subject Groups: Metformin Dose[a] (Numberof Subjects)	**C_{max}[b] (µg/mL)**	**T_{max}[c] (hrs)**	**Renal Clearnance (mL/min)**
Healthy, Nondiabetic Adults:			
500 mg SD[d] (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg SD (74)[e]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg t.i.d. for 19 doses[f] (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[f] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[g], 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}[h] 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)

[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] SD = single dose
[e] Combined results (average means) of 5 studies: mean age 32 years (range 23 to 59 years)
[f] Kinetic study done following dose 19, given fasting
[g] Elderly subjects, mean age 71 years (range 65 to 81 years)
[h] CL_{cr}= creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics:

No data from pharmacokinetic studies in pediatric subjects are available for glipizide. After administration of a single oral metformin hydrochloride 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed ˂5% between pediatric type 2 diabetic patients (12 years to 16 years of age) and gender- and weight-matched healthy adults (20 years to 45 years of age), all with normal renal function.

Gender:

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

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 glipizide.

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 24-week, double-blind, active-controlled, multicenter international clinical trial, patients with type 2 diabetes, whose hyperglycemia was not adequately controlled with diet and exercise alone (hemoglobin A_{1c} [HbA_{1c}]>7.5% and ≤12%, and fasting plasma glucose [FPG]<300 mg/dL) were randomized to receive initial therapy with glipizide 5 mg, metformin 500 mg, glipizide and metformin hydrochloride tablets 2.5 mg/250 mg, or glipizide and metformin hydrochloride tablets 2.5 mg/500 mg. After 2 weeks, the

dose was progressively increased (up to the 12-week visit) to a maximum of 4 tablets daily in divided doses as needed to reach a target mean daily glucose (MDG) of ≤130 mg/dL. Trial data at 24 weeks are summarized in **Table 2**.

Table 2 Active-Controlled Trial of Glipizide and Metformin Hydrochloride Tablets in Patients with Inadequate Glycemic Control on Diet and Exercise Alone: Summary of Trial Data at 24 Weeks

	Glipizide Tablets 5 mg	**Metformin Tablets 500 mg**	**Glipizide and Metformin Hydrochloride Tablets 2.5 mg/250 mg**	**Glipizide and Metformin Hydrochloride Tablets 2.5 mg/500 mg**
Mean Final Dose	16.7 mg	1,749 mg	7.9 mg/791 mg	7.4 mg/1,477 mg
Hemoglobin A_{1c} (%)	**N=168**	**N=171**	**N=166**	**N=163**
Baseline Mean	9.17	9.15	9.06	9.10
Final Mean	7.36	7.67	6.93	6.95
Adjusted Mean Change from Baseline	-1.77	-1.46	-2.15	-2.14
Difference from Glipizide			-0.38[a]	-0.37[a]
Difference from Metformin			-0.70[a]	-0.69[a]
% Patients with Final HbA_{1c}<7%	43.5%	35.1%	59.6%	57.1%
Fasting Plasma Glucose (mg/dL)	**N=169**	**N=176**	**N=170**	**N=169**
Baseline Mean	210.7	207.4	206.8	203.1
Final Mean	162.1	163.8	152.1	148.7
Adjusted Mean Change from Baseline	-46.2	-42.9	-54.2	-56.5
Difference from Glipizide			-8.0	-10.4
Difference from Metformin			-11.3	-13.6

[a] $p < 0.001$

After 24 weeks, treatment with glipizide and metformin hydrochloride tablets 2.5 mg/250 mg and 2.5 mg/500 mg resulted in significantly greater reduction in HbA_{1c} compared to glipizide and metformin therapy. Also, glipizide and metformin hydrochloride tablets 2.5 mg/250 mg therapy resulted in significant reductions in FPG versus metformin therapy.

Increases above fasting glucose and insulin levels were determined at baseline and final study visits by measurement of plasma glucose and insulin for 3 hours following a standard mixed liquid meal. Treatment with glipizide and metformin hydrochloride tablets lowered the 3-hour postprandial glucose AUC, compared to baseline, to a significantly greater extent than did the glipizide and the metformin therapies. Compared to baseline, glipizide and metformin hydrochloride tablets enhanced the postprandial insulin response, but did not significantly affect fasting insulin levels.

There were no clinically meaningful differences in changes from baseline for all lipid

parameters between glipizide and metformin hydrochloride tablets therapy and either metformin therapy or glipizide therapy. The adjusted mean changes from baseline in body weight were: glipizide and metformin hydrochloride tablets 2.5 mg/250 mg, 0.4 kg; glipizide and metformin hydrochloride tablets 2.5 mg/500 mg, 0.5 kg; glipizide, 0.2 kg; and metformin, 1.9 kg. Weight loss was greater with metformin than with glipizide and metformin hydrochloride tablets.

Patients with Inadequate Glycemic Control on Sulfonylurea Monotherapy:

In an 18-week, double-blind, active-controlled U.S. clinical trial, a total of 247 patients with type 2 diabetes not adequately controlled ($HbA_{1c} \geq 7.5\%$ and $\leq 12\%$, and FPG < 300 mg/dL) while being treated with at least one-half the maximum labeled dose of a sulfonylurea (e.g., glyburide 10 mg, glipizide 20 mg) were randomized to receive glipizide (fixed dose, 30 mg), metformin (500 mg), or glipizide and metformin hydrochloride tablets 5 mg/500 mg. The doses of metformin and glipizide and metformin hydrochloride tablets were titrated (up to the 8-week visit) to a maximum of 4 tablets daily as needed to achieve MDG ≤ 130 mg/dL. Trial data at 18 weeks are summarized in **Table 3**.

Table 3 Glipizide and Metformin Hydrochloride Tablets in Patients with Inadequate Glycemic Control on Sulfonylurea Alone: Summary of Trial Data at 18 Weeks

	Glipizide Tablets 5 mg	**Metformin Tablets 500 mg**	**Glipizide and Metformin Hydrochloride Tablets 5 mg/500 mg**
Mean Final Dose	30 mg	1,927 mg	17.5 mg/1,747 mg
Hemoglobin A_{1c} (%)	**N=79**	**N=71**	**N=80**
Baseline Mean	8.87	8.61	8.66
Final Adjusted Mean	8.45	8.36	7.39
Difference from Glipizide			-1.06[a]
Difference from Metformin			-0.98[a]
% Patients with Final HbA_{1c}<7%	8.9%	9.9%	36.3%
Fasting Plasma Glucose (mg/dL)	**N=82**	**N=75**	**N=81**
Baseline Mean	203.6	191.3	194.3
Adjusted Mean Change from Baseline	7	6.7	-30.4
Difference from Glipizide			-37.4
Difference from Metformin			-37.2

[a] $p < 0.001$

After 18 weeks, treatment with glipizide and metformin hydrochloride tablets at doses up to 20 mg/2,000 mg per day resulted in significantly lower mean final HbA_{1c} and significantly greater mean reductions in FPG compared to glipizide and metformin therapy. Treatment with glipizide and metformin hydrochloride tablets lowered the 3-hour postprandial glucose AUC, compared to baseline, to a significantly greater extent

than did the glipizide and the metformin therapies. Glipizide and metformin hydrochloride tablets did not significantly affect fasting insulin levels.

There were no clinically meaningful differences in changes from baseline for all lipid parameters between glipizide and metformin hydrochloride tablets therapy and either metformin therapy or glipizide therapy. The adjusted mean changes from baseline in body weight were: glipizide and metformin hydrochloride tablets 5 mg/500 mg, 0.3 kg; glipizide, 0.4 kg; and metformin, 2.7 kg. Weight loss was greater with metformin than with glipizide and metformin hydrochloride tablets.

INDICATIONS AND USAGE

Glipizide 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

Glipizide and metformin hydrochloride tablets are contraindicated in patients with:

1. Severe renal impairment (eGFR below 30 mlL/min/1.73 m^2) (see **WARNINGS and PRECAUTIONS**).
2. Known hypersensitivity to glipizide or metformin hydrochloride.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS

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):747-830, 1970).

UGDP reported that patients treated for 5 years to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams 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 glipizide 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

General:

Glipizide and Metformin Hydrochloride Tablets:

Lactic Acidosis—There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (> 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increases lactate:pyruvate ratio; metformin plasma levels were generally > 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of glipizide and metformin hydrochloride. In glipizide and metformin hydrochloride treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue glipizide and metformin hydrochloride and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis,recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

o ***Renal Impairment***—The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patients renal function include (see **Dosage and Administration**, **Clinical Pharmacology**):

- Before initiating glipizide and metformin hydrochloride, obtain an estimated glomerular filtration rate (eGFR)
- Glipizide and metformin hydrochloride is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2. Initiation of glipizide and metformin hydrochloride is not recommended in patients with eGFR between 30-45 mL/min/1.73 m2 (see **Contraindications**)
- Obtain an eGFR at least annually in all patients taking glipizide and metformin hydrochloride. In patients at risk for the development of renal impairment (e.g., the

elderly), renal function should be assessed more frequently.
- In patients taking glipizide and metformin hydrochloride whose eGFR falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.

- ***Drug interactions***—The concomitant use of glipizide and metformin hydrochloride with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation. Consider more frequent monitoring of patients.
- ***Age 65 or Greater***—The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.
- ***Radiologic studies with contrast***—Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop glipizide and metformin hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mlL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism or heart failure, or in patients who will be administered intra-arterial iodinated contrast. Reevaluate eGFR 48 hours after the imaging procedure, and restart glipizide and metformin hydrochloride if renal function is stable.
- ***Surgery and other procedures***—With holding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension, and renal impairment. Glipizide and metformin hydrochloride should be temporarily discontinued while patients have restricted food and fluid intake.
- ***Hypoxic states***—Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue glipizide and metformin hydrochloride.
- ***Excessive 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 glipizide and metformin hydrochloride.
- ***Hepatic impairment***—Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of glipizide and metformin hydrochloride in patients with clinical or laboratory evidence of hepatic disease.
- ***Mitochondrial Diseases***— Metformin may increase the risk of lactic acidosis in patients with mitochondrial diseases such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD). Glipizide and metformin hydrochloride tablets are not recommended in patients with mitochondrial diseases such as MELAS syndrome and MIDD.

If a patient taking glipizide and metformin hydrochloride tablets develops elevated lactic acid levels (with or without accompanying neurologic signs and symptoms), discontinue glipizide and metformin hydrochloride tablets. Depending on the clinical context, consider evaluating the patient for MELAS, MIDD, or other mitochondrial disease.

Hypoglycemia:

Glipizide and metformin hydrochloride tablets are capable of producing hypoglycemia; 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 insufficiency may cause elevated drug levels of both glipizide and metformin hydrochloride. Hepatic insufficiency may increase drug levels of glipizide and 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.

Glipizide:

Renal and Hepatic Disease:

The metabolism and excretion of glipizide may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Hemolytic Anemia:

Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because glipizide and metformin hydrochloride tablets belong 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.

Vitamin B12 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 years to 3 years intervals may be useful.

Macrovascular Outcomes

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

Information for Patients:

Glipizide and Metformin Hydrochloride Tablets:

Patients should be informed of the potential risks and benefits of glipizide and metformin hydrochloride tablets 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 glipizide and metformin hydrochloride tablets 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 glipizide and metformin hydrochloride tablets, 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 glipizide and metformin hydrochloride tablets (see **Patient Information Leaflet** 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 (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Instruct patients to inform their doctor that they are taking glipizide and metformin hydrochloride tablets prior to any surgical or radiological procedure, as temporary discontinuation of glipizide and metformin hydrochloride tablets may be required until renal function has been confirmed to be normal (see Precautions).

Drug Interactions:

Glipizide and Metformin Hydrochloride Tablets:

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 glipizide and metformin hydrochloride tablets, the patient should be closely observed for loss of blood glucose control. When

such drugs are withdrawn from a patient receiving glipizide and metformin hydrochloride tablets, 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.

Glipizide:

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory agents, some azoles, 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 glipizide and metformin hydrochloride tablets, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide and metformin hydrochloride tablets, the patient should be observed closely for loss of blood glucose control. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide and metformin hydrochloride tablets with these drugs.

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. The effect of concomitant administration of fluconazole and glipizide has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received glipizide alone and following treatment with 100 mg of fluconazole as a single oral daily dose for 7 days, the mean percent increase in the glipizide AUC after fluconazole administration was 56.9% (range: 35% to 81%).

In studies assessing the effect of colesevelam on the pharmacokinetics of glipizide ER in healthy volunteers, reductions in glipizide $AUC_{0-\infty}$ and C_{max} of 12% and 13%, respectively, were observed when colesevelam was coadministered with glipizide ER. When glipizide ER was administered 4 hours prior to colesevelam, there was no significant change in glipizide $AUC_{0-\infty}$ or C_{max}, –4% and 0%, respectively. Therefore, glipizide and metformin hydrochloride tablets should be administered at least 4 hours prior to colesevelam to ensure that colesevelam does not reduce the absorption of glipizide.

Metformin Hydrochloride:

Furosemide:

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. 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 co-

administered chronically.

Nifedipine:

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration 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.

Drugs that reduce metformin clearance:

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. 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.

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

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

Other:

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with glipizide and metformin hydrochloride may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving glipizide and metformin hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Glipizide:

A 20-month study in rats and an 18 month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

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 maximum recommended human daily (MRHD) dose of 2000 mg of the metformin component of glipizide and metformin hydrochloride tablets 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 glipizide and metformin hydrochloride tablets based on body surface area comparisons.

Pregnancy:

Teratogenic Effects:

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, glipizide and metformin hydrochloride tablets should not be used during pregnancy unless clearly needed (see below).

There are no adequate and well-controlled studies in pregnant women with glipizide and metformin hydrochloride tablets or its individual components. No animal studies have been conducted with the combined products in glipizide and metformin hydrochloride tablets. The following data are based on findings in studies performed with the individual products.

Glipizide:

Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5 to 50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to

the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits, no teratogenic effects were found.

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 times and 6 times the MRHD dose of 2000 mg of the metformin component of glipizide and metformin hydrochloride tablets 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 days 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 glipizide and metformin hydrochloride tablets be used during pregnancy. However, if it is used, glipizide and metformin hydrochloride tablets should be discontinued at least 1 month before the expected delivery date (see **Pregnancy; Teratogenic Effects**).

Nursing Mothers:

Although it is not known whether glipizide 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 glipizide and metformin hydrochloride tablets, taking into account the importance of the drug to the mother. If glipizide and metformin hydrochloride tablets are discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use:

Safety and effectiveness of glipizide and metformin hydrochloride tablets in pediatric patients have not been established.

Geriatric Use:

Of the 345 patients who received glipizide and metformin hydrochloride tablets 2.5 mg/250 mg and 2.5 mg/500 mg in the initial therapy trial, 67 (19.4%) were aged 65 and older while 5 (1.4%) were aged 75 and older. Of the 87 patients who received glipizide and metformin hydrochloride tablets in the second-line therapy trial, 17 (19.5%) were aged 65 and older while 1 (1.1%) was at least aged 75. No overall differences in effectiveness or safety were observed between these patients and younger patients in either the initial therapy trial or the second-line therapy trial, 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.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the

higher risk of lactic acidosis. Assess renal function more frequently in elderly patients (see also **WARNINGS, PRECAUTION** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Glipizide and Metformin Hydrochloride Tablets:

In a double-blind 24 week clinical trial involving glipizide and metformin hydrochloride tablets as initial therapy, a total of 172 patients received glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg, 173 received glipizide and metformin hydrochloride tablets, 2.5 mg/500 mg, 170 received glipizide, and 177 received metformin. The most common clinical adverse events in these treatment groups are listed in **Table 4**.

Table 4 Clinical Adverse Events >5% in any Treatment Group, by Primary Term, in Initial Therapy Study

Adverse Event	Number (%) of Patients			
	Glipizide Tablets 5 mg N=170	Metformin Tablets 500 mg N=177	Glipizide and Metformin Hydrochloride Tablets 2.5 mg/250 mg N=172	Glipizide and Metformin Hydrochloride Tablets 2.5 mg/500 mg N=173
Upper respiratory infection	12 (7.1)	15 (8.5)	17 (9.9)	14 (8.1)
Diarrhea	8 (4.7)	15 (8.5)	4 (2.3)	9 (5.2)
Dizziness	9 (5.3)	2 (1.1)	3 (1.7)	9 (5.2)
Hypertension	17 (10)	10 (5.6)	5 (2.9)	6 (3.5)
Nausea/vomiting	6 (3.5)	9 (5.1)	1 (0.6)	3 (1.7)

In a double-blind 18 week clinical trial involving glipizide and metformin hydrochloride tablets as second-line therapy, a total of 87 patients received glipizide and metformin hydrochloride tablets, 84 received glipizide, and 75 received metformin. The most common clinical adverse events in this clinical trial are listed in **Table 5**.

Table 5 Clinical Adverse Events >5% in any Treatment Group, by Primary Term, in Second-Line Therapy Study

Adverse Event	Number (%) of Patients		
	Glipizide Tablets[a] 5 mg N=84	Metformin Tablets[a] 500 mg N=75	Glipizide and Metformin Hydrochloride Tablets[a] 5 mg/500 mg N=87
Diarrhea	11 (13.1)	13 (17.3)	16 (18.4)
Headache	5 (6)	4 (5.3)	11 (12.6)
Upper respiratory infection	11 (13.1)	8 (10.7)	9 (10.3)

Musculoskeletal pain	6 (7.1)	5 (6.7)	7 (8)
Nausea/vomiting	5 (6)	6 (8)	7 (8)
Abdominal pain	7 (8.3)	5 (6.7)	5 (5.7)
UTI	4 (4.8)	6 (8)	1 (1.1)

[a] The dose of glipizide was fixed at 30 mg daily; doses of metformin and glipizide and metformin hydrochloride tablets were titrated.

Hypoglycemia:

In a controlled initial therapy trial of glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg and 2.5 mg/500 mg the numbers of patients with hypoglycemia documented by symptoms (such as dizziness, shakiness, sweating, and hunger) and a fingerstick blood glucose measurement ≤50 mg/dL were 5 (2.9%) for glipizide, 0 (0%) for metformin, 13 (7.6%) for glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg, and 16 (9.3%) for glipizide and metformin hydrochloride tablets, 2.5 mg/500 mg. Among patients taking either glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg or glipizide and metformin hydrochloride tablets, 2.5 mg/500 mg, 9 (2.6%) patients discontinued glipizide and metformin hydrochloride tablets due to hypoglycemic symptoms and 1 required medical intervention due to hypoglycemia. In a controlled second-line therapy trial of glipizide and metformin hydrochloride tablets, 5 mg/500 mg, the numbers of patients with hypoglycemia documented by symptoms and a fingerstick blood glucose measurement ≤50 mg/dL were 0 (0%) for glipizide, 1 (1.3%) for metformin, and 11 (12.6%) for glipizide and metformin hydrochloride tablets. One (1.1%) patient discontinued glipizide and metformin hydrochloride tablets therapy due to hypoglycemic symptoms and none required medical intervention due to hypoglycemia (see **PRECAUTIONS**).

Gastrointestinal Reactions:

Among the most common clinical adverse events in the initial therapy trial were diarrhea and nausea/vomiting; the incidences of these events were lower with both glipizide and metformin hydrochloride tablets dosage strengths than with metformin therapy. There were 4 (1.2%) patients in the initial therapy trial who discontinued glipizide and metformin hydrochloride tablets therapy due to gastrointestinal (GI) adverse events. Gastrointestinal symptoms of diarrhea, nausea/vomiting, and abdominal pain were comparable among glipizide and metformin hydrochloride tablets, glipizide and metformin in the second-line therapy trial. There were 4 (4.6%) patients in the second-line therapy trial who discontinued glipizide and metformin hydrochloride tablets therapy due to GI adverse events.

Glipizide

Gastrointestinal Reactions

Cholestatic and hepatocellular forms of liver injury accompanied by jaundice have been reported rarely in association with glipizide; glipizide and metformin hydrochloride tablets should be discontinued if this occurs.

OVERDOSAGE

Glipizide:

Overdosage of sulfonylureas, including glipizide, 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 hours to 48 hours, since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

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 glipizide 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 glipizide/2,000 mg metformin. Glipizide 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 glipizide), 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 glipizide 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}, 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 glipizide and metformin hydrochloride tablets therapy in patients taking concomitant glipizide (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.

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

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

For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of glipizide and metformin hydrochloride tablets is 2.5 mg/250 mg once a day with a meal. For patients whose FPG is 280 mg/dL to 320 mg/dL a starting dose of glipizide and metformin hydrochloride tablets 2.5 mg/500 mg twice daily should be considered. The efficacy of glipizide and metformin hydrochloride tablets in patients whose FPG exceeds 320 mg/dL has not been established. Dosage increases to achieve adequate glycemic control should be made in increments of 1 tablet per day every 2 weeks up to maximum of 10 mg/1,000 mg or 10 mg/2,000 mg glipizide and metformin hydrochloride tablets per day given in divided doses. In clinical trials of glipizide and metformin hydrochloride tablets as initial therapy, there was no experience with total daily doses ˃10 mg/2,000 mg per day.

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

For patients not adequately controlled on either glipizide (or another sulfonylurea) or metformin alone, the recommended starting dose of glipizide and metformin hydrochloride tablets 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 glipizide and metformin hydrochloride tablets should not exceed the daily doses of glipizide 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/2,000 mg per day.

Patients previously treated with combination therapy of glipizide (or another sulfonylurea) plus metformin may be switched to glipizide and metformin hydrochloride tablets 2.5 mg/500 mg or 5 mg/500 mg; the starting dose should not exceed the daily dose of glipizide (or equivalent dose of another sulfonylurea) and metformin already being taken. The decision to switch to the nearest equivalent dose or to titrate should be based on clinical judgment. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of glipizide and metformin hydrochloride tablets should be titrated as described above to achieve adequate control of blood glucose.

Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of glipizide and metformin hydrochloride and periodically thereafter.

Glipizide and metformin hydrochloride is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.

Initiation of glipizide and metformin hydrochloride in patients with an eGFR between 30 mL/minute/1.73 m^2 to 45 mL/minute/1.73 m^2 is not recommended.

In patients taking glipizide and metformin hydrochloride whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.

Discontinue glipizide and metformin hydrochloride if the patient's eGFR later falls below 30 mL/minute/1.73 m^2. (See **WARNINGS**.)

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue glipizide and metformin hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 mL/min/1.73 $m^2$and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart glipizide and metformin hydrochloride if renal function is stable.

Specific Patient Populations:

Glipizide and metformin hydrochloride tablets are not recommended for use during pregnancy or for use in pediatric patients. The initial and maintenance dosing of glipizide 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 glipizide 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 and PRECAUTIONS**).

HOW SUPPLIED

Glipizide and Metformin Hydrochloride Tablets USP, 2.5 mg/250 mg are pink-colored, biconvex, modified capsule-shaped, film-coated tablet, debossed with "ZE68" on one side and plain on other side and are supplied as follows:

NDC 68382-184-16 in bottle of 90 tablets with child-resistant closure

NDC 68382-184-01 in bottle of 100 tablets

NDC 68382-184-10 in bottle of 1000 tablets

NDC 68382-184-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

Glipizide and Metformin Hydrochloride Tablets USP, 2.5 mg/500 mg are white-colored, biconvex, modified capsule-shaped, film-coated tablet, debossed with "ZE67" on one side and plain on other side and are supplied as follows:

NDC 68382-185-16 in bottle of 90 tablets with child-resistant closure

NDC 68382-185-01 in bottle of 100 tablets

NDC 68382-185-10 in bottle of 1000 tablets

NDC 68382-185-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

Glipizide and Metformin Hydrochloride Tablets USP, 5 mg/500 mg are pink-colored,

biconvex, modified capsule-shaped, film-coated tablet, debossed with "ZE66" on one side and plain on other side and are supplied as follows:

NDC 68382-186-16 in bottle of 90 tablets with child-resistant closure

NDC 68382-186-01 in bottle of 100 tablets

NDC 68382-186-10 in bottle of 1000 tablets

NDC 68382-186-77 in unit-dose blister cartons of 100 (10 x 10) unit-dose tablets

Storage:

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

Dispense in a tight container.

Manufactured by:

Zydus Lifesciences Ltd.

Ahmedabad, India

Distributed by:

Zydus Pharmaceuticals (USA) Inc.

Pennington, NJ 08534

Rev.: 06/26

Patient Information Leaflet

Glipizide and Metformin Hydrochloride

(**glip'-i-zyde and met-for'-min hye"-dro-klor'-ide**)

Tablets, USP

WARNING:

A small number of people who have taken metformin hydrochloride have developed a serious condition called lactic acidosis. Tell your doctor if you have severe kidney problems. (see Question Nos. 9 to 12).

Q1. Why do I need to take Glipizide and Metformin Hydrochloride Tablets?

Your doctor has prescribed glipizide 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 glipizide and metformin hydrochloride tablets you should first try to control your diabetes by exercise and weight loss. Even if you are taking glipizide and metformin hydrochloride tablets, you should still exercise and follow the diet recommended for your diabetes.

Q5. Does Glipizide and Metformin Hydrochloride Tablet work differently from other glucose-control medications?

Yes, it does. Glipizide and metformin hydrochloride tablet combines 2 glucose lowering drugs, glipizide and metformin. These 2 drugs work together to improve the different metabolic defects found in type 2 diabetes. Glipizide 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 glipizide and metformin hydrochloride tablets, your doctor may prescribe injectable insulin or take other measures to control your diabetes.

Q7. Can Glipizide and Metformin Hydrochloride Tablets cause side effects?

Glipizide 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 glipizide and metformin hydrochloride tablets (see **Question Nos. 9-13**).

Q8. What are the most common side effects of Glipizide and Metformin Hydrochloride Tablets?

The most common side effects of glipizide 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 glipizide and metformin hydrochloride tablets with meals can help reduce these side effects.

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 Glipizide and Metformin Hydrochloride Tablets can cause?

People who have a condition known as glucose-6-phosphate dehydrogenase (G6PD) deficiency and who take glipizide and metformin hydrochloride 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 Glipizide and metformin hydrochloride tablets.

Glipizide and metformin hydrochloride tablets rarely cause serious side effects.

Metformin, one of the medicines in glipizide and metformin hydrochloride can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with glipizide and metformin hydrochloride if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as MELAS syndrome and MIDD.

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your glipizide and metformin hydrochloride for a while if you have any of these things.

Glipizide and metformin hydrochloride can have other serious side effects. See **"What are the possible side effects of glipizide and metformin hydrochloride?"**

Q10. Can I take Glipizide and Metformin Hydrochloride Tablets with other medications?

Remind your doctor that you are taking glipizide and metformin hydrochloride tablets when any new drug is prescribed or a change is made in how you take a drug already prescribed.

Glipizide and metformin hydrochloride tablets may interfere with the way some drugs work and some drugs may interfere with the action of glipizide and metformin hydrochloride tablets.

Q11. What if I become pregnant while taking Glipizide 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 glipizide 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 glipizide and metformin hydrochloride tablets if you are nursing a child.

Q12. How do I take Glipizide and Metformin Hydrochloride Tablets?

Your doctor will tell you how many glipizide 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 glipizide and metformin hydrochloride tablets and your dosage will be increased gradually until your blood sugar is controlled.

Q13. Where can I get more information about Glipizide and Metformin Hydrochloride Tablets?

This leaflet is a summary of the most important information about glipizide 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 glipizide 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.

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

Manufactured by:

Zydus Lifesciences Ltd.

Ahmedabad, India

Distributed by:

Zydus Pharmaceuticals (USA) Inc.

Pennington, NJ 08534

Rev.: 06/26

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

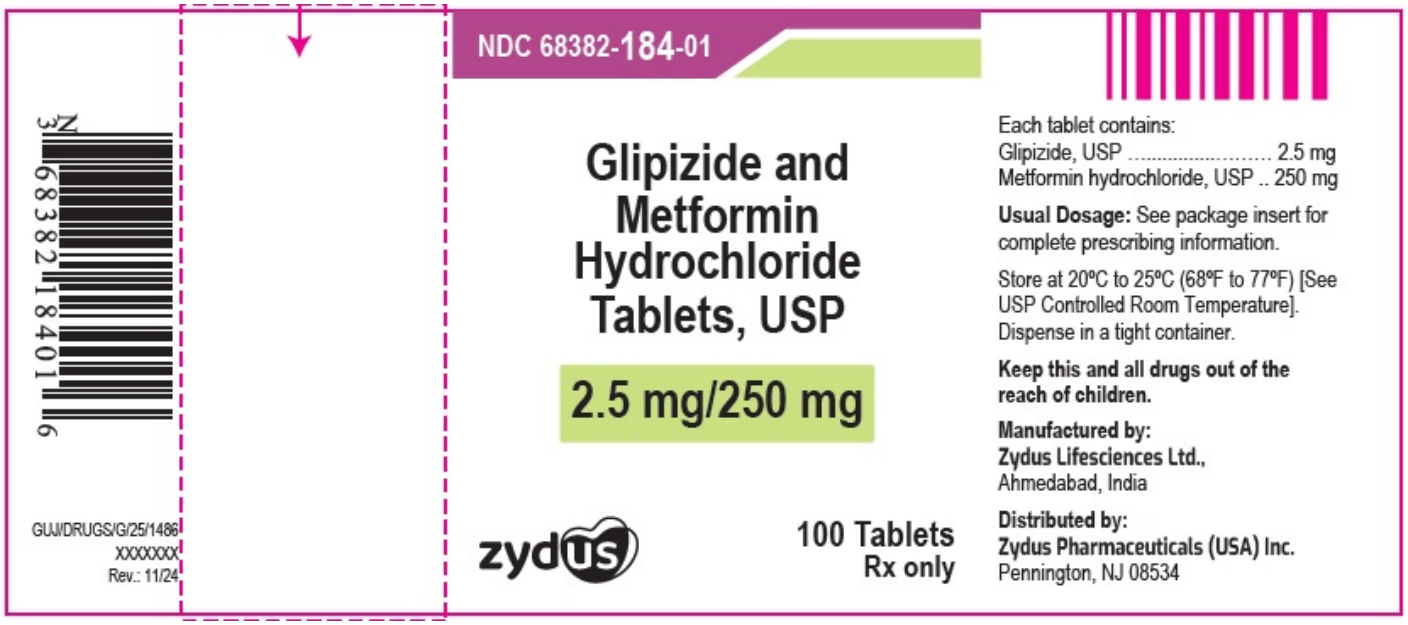
NDC 68382-184-01 in bottle of 100 tablets

Glipizide and Metformin Hydrochloride Tablets USP, 2.5 mg/250 mg

R_x only

100 tablets

ZYDUS



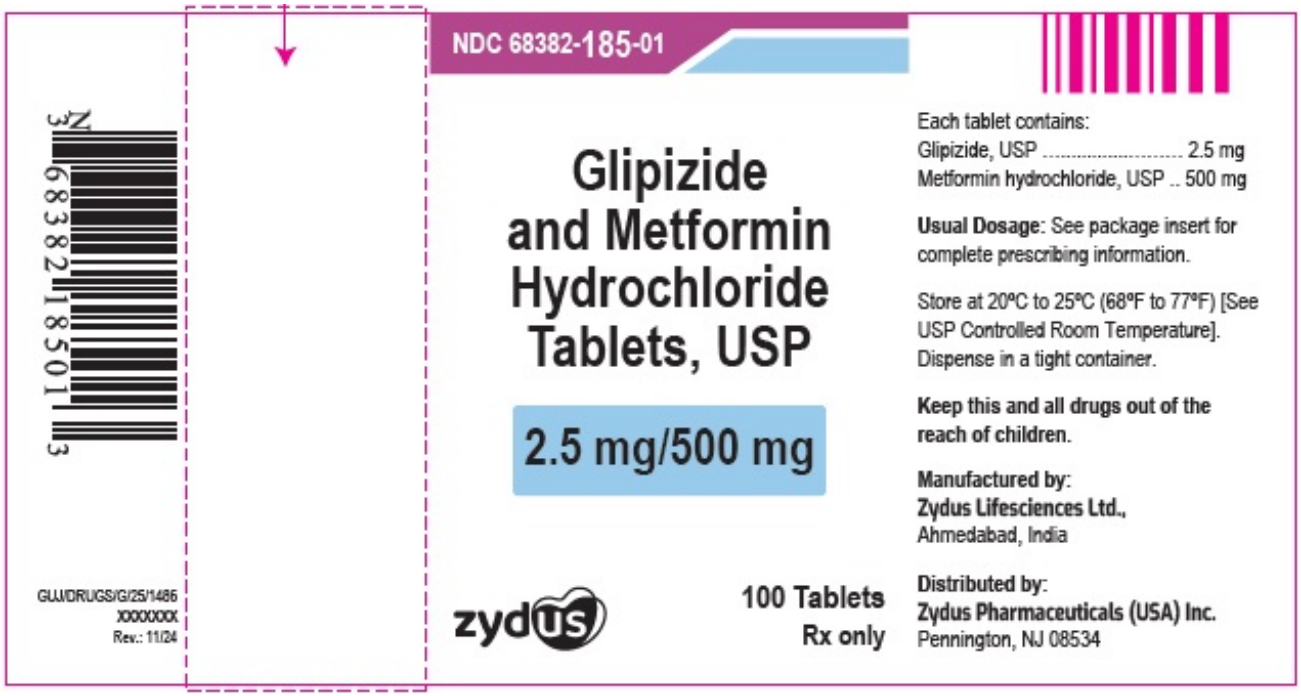
NDC 68382-185-01 in bottle of 100 tablets

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

R_x only

100 tablets

ZYDUS



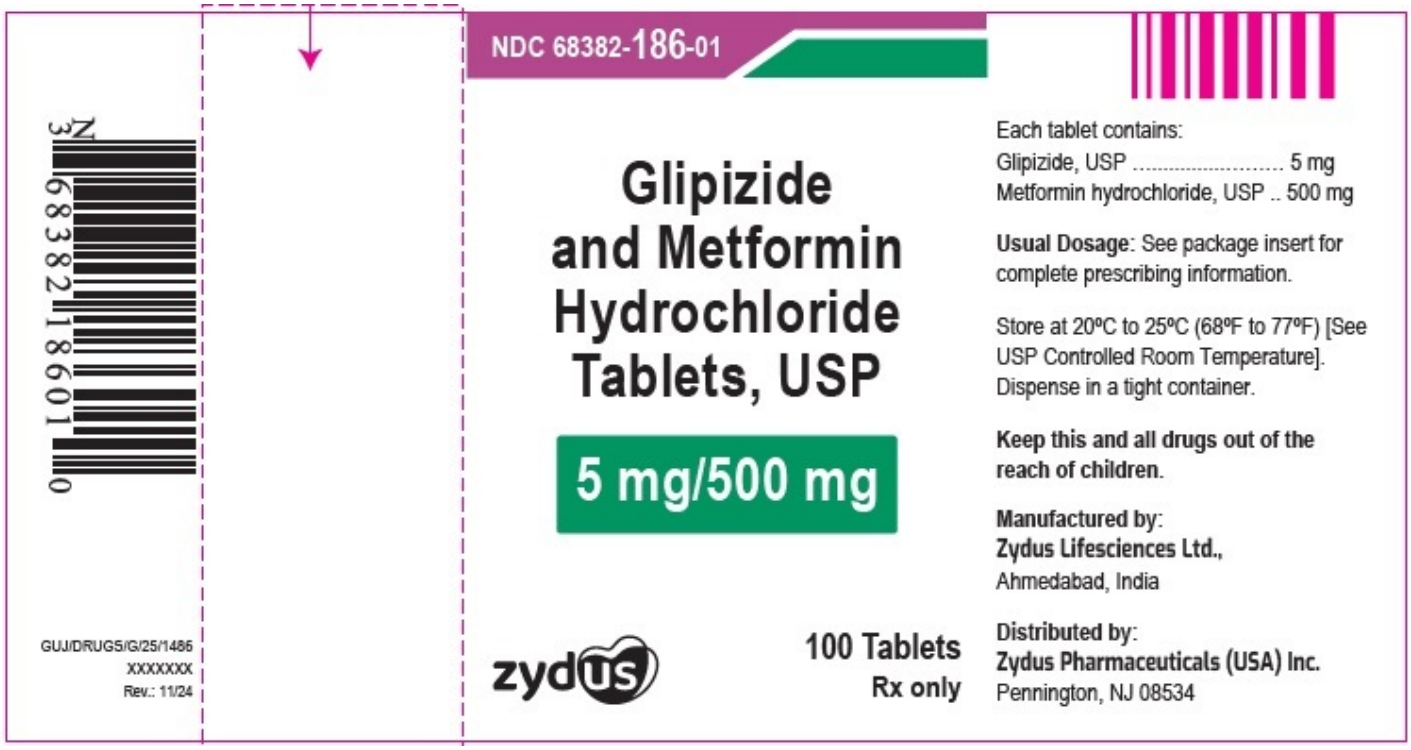
NDC 68382-186-01 in bottle of 100 tablets

Glipizide and Metformin Hydrochloride Tablets USP, 5 mg/500 mg

R_x only

100 tablets

ZYDUS



GLIPIZIDE AND METFORMIN HYDROCHLORIDE

glipizide and metformin hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68382-184
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
GLIPIZIDE (UNII: X7WDT95N5C) (GLIPIZIDE - UNII:X7WDT95N5C)	GLIPIZIDE	2.5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	PINK (PINK)	**Score**	no score
Shape	CAPSULE (CAPSULE)	**Size**	11mm
Flavor		**Imprint Code**	ZE68
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68382-184-16	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
2	NDC:68382-184-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
3	NDC:68382-184-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
4	NDC:68382-184-77	10 in 1 CARTON	05/05/2016	
4	NDC:68382-184-30	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	ANDA078905	05/05/2016	

GLIPIZIDE AND METFORMIN HYDROCHLORIDE

glipizide and metformin hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68382-185
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLIPIZIDE (UNII: X7WDT95N5C) (GLIPIZIDE - UNII:X7WDT95N5C)	GLIPIZIDE	2.5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN -	METFORMIN	500 mg

UNII:9100L32L2N)	HYDROCHLORIDE	500 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	WHITE (WHITE)	**Score**	no score
Shape	CAPSULE (CAPSULE)	**Size**	15mm
Flavor		**Imprint Code**	ZE67
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68382-185-16	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
2	NDC:68382-185-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
3	NDC:68382-185-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
4	NDC:68382-185-77	10 in 1 CARTON	05/05/2016	
4	NDC:68382-185-30	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	ANDA078905	05/05/2016	

GLIPIZIDE AND METFORMIN HYDROCHLORIDE

glipizide and metformin hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68382-186
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLIPIZIDE (UNII: X7WDT95N5C) (GLIPIZIDE - UNII:X7WDT95N5C)	GLIPIZIDE	5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	PINK (PINK)	**Score**	no score
Shape	CAPSULE (CAPSULE)	**Size**	15mm
Flavor		**Imprint Code**	ZE66
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68382-186-16	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
2	NDC:68382-186-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
3	NDC:68382-186-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/05/2016	
4	NDC:68382-186-77	10 in 1 CARTON	05/05/2016	
4	NDC:68382-186-30	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	ANDA078905	05/05/2016	

Labeler - Zydus Pharmaceuticals USA Inc. (156861945)

Registrant - Zydus Pharmaceuticals USA Inc. (156861945)

Establishment

Name	Address	ID/FEI	Business Operations
Zydus Lifesciences Limited		918596198	ANALYSIS(68382-184, 68382-185, 68382-186) , MANUFACTURE(68382-184, 68382-185, 68382-186)

Revised: 6/2026 Zydus Pharmaceuticals USA Inc.