GLYBURIDE AND METFORMIN HYDROCHLORIDE- glyburide and metformin hydrochloride tablet, film coated
Preferred Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GLYBURIDE AND METFORMIN HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for GLYBURIDE AND METFORMIN HYDROCHLORIDE TABLETS.

GLYBURIDE and METFORMIN HYDROCHLORIDE tablets, for oral use

Initial U.S. Approval: 2000

See full prescribing information for complete boxed warning.

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms include malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years old, radiological study with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue glyburide and metformin hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

INDICATIONS AND USAGE

Glyburide and metformin hydrochloride tablets are a combination of glyburide, a sulfonylurea, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

DOSAGE AND ADMINISTRATION

Adult Dosage:

- Give glyburide and metformin hydrochloride tablets in divided doses, twice daily, with meals. (2.1)
- For patients not treated with either glyburide (or another sulfonylurea) or metformin HCl, initiate treatment with another formulation with a dose of 1.25 mg glyburide and 250mg metformin HCl orally, once or twice daily with meals. (2.1)
- For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin HCl alone, the recommended starting dose is 2.5 mg/500 mg or 5 mg/500 mg orally twice daily with meals. (2.1)
- For patients previously treated with a combination therapy of glyburide (or another sulfonylurea) and metformin HCl, the starting dose should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin HCl already being taken. (2.1)
- Increase the dose gradually on the basis of glycemic control and tolerability, up to a maximum to a maximum dose of 20 mg glyburide/2000 mg metformin HCl daily. (2.1)

Renal Impairment:
Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.4)

- Do not use in patients with eGFR below 30 mL/minute/1.73 m^2(2.4)
- Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m^2(2.4)
- Assess risk/benefit if eGFR falls below 45 mL/minute/1.73 m^2(2.4)
- Discontinue if eGFR falls below 30 mL/minute/1.73 m^2(2.4)

Discontinuation for Iodinated Contrast Imaging Procedures:

- Glyburide and metformin hydrochloride tablets may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.5)

DOSAGE FORMS AND STRENGTHS

- Tablets: 1.25 mg glyburide and 250 mg metformin HCl (3)
- Tablets: 2.5 mg glyburide and 500 mg metformin HCl (3)
- Tablets: 5 mg glyburide and 500 mg metformin HCl (3)

CONTRAINDICATIONS

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) (4, 5.1)
- Hypersensitivity to metformin or glyburide. (4)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. (4)
- Concomitant administration of bosentan. (4, 7)

WARNINGS AND PRECAUTIONS

- Lactic Acidosis: See boxed warning. (5.1)
- Hypoglycemia: May be severe. Ensure proper patient selection, dosing, and instructions, particularly in at-risk populations (e.g., elderly, renally impaired) and when used with other anti-diabetic medications. (5.2)
- Potential Increased Risk of Cardiovascular Mortality with Sulfonylureas: Inform patient of risks, benefits and treatment alternatives. (5.3)
- Hemolytic anemia: Can occur if glucose 6-phosphate dehydrogenase (G6PD) deficient. Consider a non-sulfonylurea alternative. (5.4)
- Vitamin B_{12} Deficiency: Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.5)

ADVERSE REACTIONS

Most common (>5%) adverse reactions to glyburide and metformin hydrochloride diarrhea, headache, nausea/vomiting, abdominal pain, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rising Health, LLC at 1-833-395-6928 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7)
- The hypoglycemic action of glyburide and metformin hydrochloride may be potentiated by certain drugs. (7)
- Concomitant administration of colesevalam may led to reduced glyburide absorption. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Glyburide and metformin hydrochloride should be discontinued at least two weeks before expected delivery. (8.1)
- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metforminassociated 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 *Warnings and Precautions (5.1)*].

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, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided [see *Dosage and Administration (2.3), Contraindications (4)* and *Warnings and Precautions (5.1)*].

If metformin-associated lactic acidosis is suspected, immediately discontinue glyburide and metformin hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Glyburide and metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- Give glyburide and metformin hydrochloride tablets in divided doses, twice daily, with meals.
- For patients not treated with either glyburide (or another sulfonylurea) or metformin hydrochloride (HCl), initiate treatment with another formulation of glyburide and metformin HCl at a starting dose of 1.25 mg glyburide and 250mg metformin HCl orally, once or twice daily with meals.
- For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin HCl alone, the recommended starting dose of glyburide and metformin hydrochloride tablets is 2.5 mg/500 mg or 5 mg/500 mg orally twice daily with meals.

- For patients previously treated with a combination therapy of glyburide (or another sulfonylurea) and metformin HCl, the starting dose of glyburide and metformin hydrochloride tablets should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin HCl already being taken.
- Increase the dose gradually on the basis of glycemic control and tolerability, up to a maximum to a maximum dose of 20 mg glyburide/2000 mg metformin HCl daily.

2.2 Patients Receiving Colesevelam

- Administer glyburide and metformin hydrochloride tablets at least 4 hours prior to colesevelam for patients taking both drugs concomitantly [see *Drug Interactions (7)*].

2.3 Recommendations for Use in Renal Impairment

- Assess renal function prior to initiation of glyburide and metformin hydrochloride tablets and periodically thereafter.
- Glyburide and metformin hydrochloride tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
- Initiation of glyburide and metformin hydrochloride tablets in patients with an eGFR between 30 to 45 mL/minute/1.73 m^2 is not recommended.
- In patients taking glyburide and metformin hydrochloride tablets whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.
- Discontinue glyburide and metformin hydrochloride tablets if the patient's eGFR later falls below 30 mL/minute/1.73 m^2 [see *Warnings and Precautions (5.1)*].

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

- Discontinue glyburide and metformin hydrochloride tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 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 glyburide and metformin hydrochloride tablets if renal function is stable.

3 DOSAGE FORMS AND STRENGTHS

Glyburide and metformin hydrochloride tablets, USP are available as:

- *1.25 mg/250 mg Tablets:* Yellow, capsule shaped, biconvex, film-coated tablet with 'A' debossed on one side and '46' on the other side.
- *2.5 mg/500 mg Tablets:* Light pink, capsule shaped, biconvex, film-coated tablet with 'A' debossed on one side and '47' on the other side.
- *5 mg/500 mg Tablets:* Yellow, capsule shaped, biconvex, film-coated tablet with 'A' debossed on one side and '48' on the other side

4 CONTRAINDICATIONS

Glyburide and metformin hydrochloride tablets are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) [see *Warnings and Precautions (5.1)*].
- Hypersensitivity to metformin or glyburide.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Concomitant administration of bosentan [see *Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing 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 increased 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 glyburide and metformin hydrochloride. In glyburide 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 HCl 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 glyburide 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:

- *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 patient's renal function include [see *Dosage and Administration (2.1), Clinical Pharmacology (12.3)*]:

5.2 Hypoglycemia

All sulfonylurea drugs, including glyburide and metformin hydrochloride, are capable of producing severe hypoglycemia [see *Adverse Reactions (6)*]. Concomitant use of glyburide and metformin hydrochloride with other anti-diabetic medication can increase

the risk of hypoglycemia. A lower dose of glyburide and metformin hydrochloride may be required to minimize the risk of hypoglycemia when combining it with other anti-diabetic medications.

Educate patients to recognize and manage hypoglycemia. When initiating and increasing glyburide and metformin hydrochloride in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications) start with a lower dose. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of anti-diabetic medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

5.3 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 study designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with type 2 diabetes mellitus. The study involved 823 patients who were randomly assigned to 1 of 4 treatment groups.

UGDP reported that patients treated for 5 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 glyburide and of alternative modes of therapy.

Although only one 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.

5.4 Hemolytic Anemia

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with

sulfonylurea agents, including glyburide and metformin hydrochloride, can lead to hemolytic anemia. Avoid use of glyburide and metformin hydrochloride in patients with G6PD deficiency. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

5.5 Vitamin B_{12} Deficiency

In clinical studies of 29-week duration with metformin HCl tablets, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on glyburide and metformin hydrochloride and manage any abnormalities [see *Adverse Reactions (6.1)*].

5.6 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glyburide and metformin hydrochloride.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Lactic Acidosis [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Hypoglycemia [see *Warnings and Precautions (5.2)]*
- Cardiovascular mortality [see *Warnings and Precautions (5.3)*]
- Hemolytic anemia [see *Warnings and Precautions (5.4)*]
- Vitamin B_{12} Deficiency [*see Warnings and Precautions (5.5)*]

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In double-blind clinical studies with glyburide and metformin hydrochloride as initial therapy or as second-line therapy of 20 and 14 weeks, respectively (see section 14), a total of 642 patients received glyburide and metformin hydrochloride, 312 received metformin HCl, 324 received glyburide, and 161 received placebo. Adverse reactions are listed in Table 1.

Table 1: Adverse Reactions Occurring >5% in Double-Blind Clinical Studies of Glyburide And Metformin Hydrochloride Used as Initial (20 Weeks) or Second-Line (14 Weeks) Therapy

Adverse Reaction	Number (%) of Patients			
	Placebo	Glyburide	Metformin	Glyburide and Metformin

Reaction	N=161	N=324	HCl N=312	Hydrochloride N=642
Diarrhea	6%	6%	21%	17%
Headache	11%	11%	9%	9%
Nausea/vomiting	6%	5%	12%	8%
Abdominal pain	4%	3%	8%	7%
Dizziness	4%	6%	4%	6%

Hypoglycemia

The incidence of reported symptoms of hypoglycemia (such as dizziness, shakiness, sweating, and hunger), in the initial therapy study of glyburide and metformin hydrochloride are summarized in Table 2. For patients with a baseline HbA1c 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.

Gastrointestinal Reactions

The incidence of gastrointestinal (GI) side effects (diarrhea, nausea/vomiting, and abdominal pain) in the glyburide and metformin hydrochloride initial therapy study are summarized in Table 2. Across all glyburide and metformin hydrochloride studies, GI symptoms were the most common adverse events with glyburide and metformin hydrochloride and were more frequent at higher dose levels. In controlled studies, <2% of patients discontinued glyburide and metformin hydrochloride therapy due to GI adverse events.

Table 2: Hypoglycemia or Gastrointestinal Adverse Reactions in a Placebo- and Active-Controlled Study of Glyburide and Metformin Hydrochloride as Initial Therapy (20 Weeks)

Variable	Placebo N=161	Glyburide Tablets N=160	Metformin HCl 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
Number (%) of patients with symptoms of hypoglycemia	3%	21%	3%	11%	38%
Number (%) of patients with gastrointestinal adverse events	24%	24%	43%	32%	38%

Dermatologic Reactions

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in 1.5% of glyburide-treated patients. These may be transient and may disappear despite continued use.

6.2 Postmarketing Adverse Reactions

The following adverse reactions have been identified during post-approval use of glyburide and metformin hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic: Angioedema, arthralgia, myalgia, and vasculitis have been reported.

Dermatologic: Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, which occasionally may present as purpura, hemolytic anemia, aplastic anemia, and pancytopenia, have been reported with sulfonylureas.

Hepatic: Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with postmarketing use of metformin. Cholestatic jaundice and hepatitis may occur rarely with glyburide, which may progress to liver failure. Liver function abnormalities, including isolated transaminase elevations, have been reported.

Metabolic: Hepatic porphyria reactions have been reported with sulfonylureas; however, these have not been reported with glyburide. Disulfiram-like reactions have been reported very rarely with glyburide. Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone.

Other Reactions: Changes in accommodation and/or blurred vision have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

7 DRUG INTERACTIONS

Table 3 presents clinically significant drug interactions with glyburide and metformin hydrochloride.

Table 3: Clinically Significant Drug Interactions with Glyburide and Metformin Hydrochloride

Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with glyburide and metformin hydrochloride may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate, zonisamide, acetazolamide and dichlorphenamide.
Drugs that Reduce Metformin Clearance	
	Concomitant use of drugs that interfere with common renal tubular

Clinical Impact:	transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [*see Clinical Pharmacology (12.3)*].
Intervention:	Consider the benefits and risks of concomitant use with glyburide and metformin hydrochloride.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention:	Warn patients against excessive alcohol intake while receiving glyburide and metformin hydrochloride.
Drugs that potentiate the hypoglycemic action of glyburide and metformin hydrochloride	
Clinical Impact:	Certain drugs may potentiate the hypoglycemic action of sulfonylureas, one of the components of glyburide and metformin hydrochloride.
Intervention:	Closely observe patient for hypoglycemia during co-administration and for loss of glycemic control when withdrawing these agents.
Examples:	Nonsteroidal anti-inflammatory agents and other highly protein-boind drugs, salicylcates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, beta-adrenergic blocking agents; potentially with ciprofloxacin, micronazole.
Bosentan	
Clinical Impact:	Increased risk of liver enzyme elevations was observed.
Intervention:	Concomitant administration is contraindicated.
Colesevalam	
Clinical Impact:	Concomitant administration may led to reduced glyburide absorption (AUC and Cmax: -32% and -47%, respectively).
Intervention:	Glyburide and metformin hydrochloride should be administered at least 4 hours prior to colesevelam.
Drugs Reducing Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving glyburide and metformin hydrochloride observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving glyburide and metformin hydrochloride, observe the patient closely for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a small number of published studies and postmarketing experience with glyburide use in pregnancy over decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal outcomes. However, sulfonylureas (including glyburide) cross the placenta and have been associated with neonatal adverse reactions such as hypoglycemia. Therefore, glyburide and metformin hydrochloride should be discontinued at least two weeks before expected delivery [see *Clinical Considerations*]. Limited data with metformin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see *Data*]. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy [see *Clinical Considerations*].

No evidence of harm to the fetus was observed when doses up to 500 times the maximum recommended human dose of 20 mg of glyburide, based on body surface area, were administered to rats and rabbits in reproduction studies.

No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 3- and 6- times, respectively, a 2000 mg clinical dose, based on body surface area [see *Data*].

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes mellitus with an HbA1c >7 and has been reported to be as high as 20 to 25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes mellitus increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Fetal/Neonatal Adverse Reactions

Neonates of women with gestational diabetes who are treated with sulfonylureas during pregnancy may be at increased risk for neonatal intensive care admission and may develop respiratory distress, hypoglycemia, birth injury, and be large for gestational age. Prolonged severe hypoglycemia, lasting 4 to 10 days, has been reported in neonates born to mothers receiving a sulfonylurea at the time of delivery and has been reported with the use of agents with a prolonged half-life. Observe newborns for symptoms of hypoglycemia and respiratory distress and manage accordingly.

Dose adjustments during pregnancy and the postpartum period

Due to reports of prolonged severe hypoglycemia in neonates born to mothers receiving a sulfonylurea at the time of delivery, glyburide and metformin hydrochloride should be discontinued at least two weeks before expected delivery [see *Fetal/Neonatal Adverse Reactions*].

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Reproduction studies were performed in rats and rabbits at doses up to 500 times the maximum recommended human dose of 20 mg of glyburide based on body surface area comparisons and revealed no evidence of harm to the fetus.

Metformin did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 3 and 6 times a 2000 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.2 Lactation

Risk Summary

Breastfed infants of lactating women using glyburide and metformin hydrochloride should be monitored for symptoms of hypoglycemia [see *Clinical Considerations*]. Although glyburide was negligible in human milk in one small clinical lactation study; this result is not conclusive because of the limitations of the assay used in the study. There are no data on the effects of glyburide on milk production. Limited published studies report that metformin is present in human milk [see *Data*]. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for glyburide and metformin hydrochloride and any potential adverse effects on the breastfed child from glyburide and metformin hydrochloride or from the underlying maternal condition.

Clinical Considerations

Monitoring for adverse reactions

Monitor breastfed infants for signs of hypoglycemia (e.g., jitters, cyanosis, apnea, hypothermia, excessive sleepiness, poor feeding, seizures).

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with glyburide and metformin hydrochloride may result in ovulation in some anovulatory women.

8.4 Pediatric Use

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

8.5 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. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients are particularly susceptible to the hypoglycemic action of anti-diabetic agents. Hypoglycemia may be difficult to recognize in these patients.

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 hypoglycemia and lactic acidosis. Assess renal function more frequently in elderly patients [see *Dosage and Administration (2)* and *Warnings and Precautions (5.1)*].

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Glyburide and metformin hydrochloride is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 [see *Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1),* and *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Glyburide and metformin hydrochloride is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

Glyburide

Overdosage of sulfonylureas, including glyburide tablets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated with oral glucose. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment are medical emergencies requiring immediate treatment. The patient should be treated with glucagon or intravenous glucose. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of glyburide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of

glyburide, dialysis is unlikely to be of benefit.

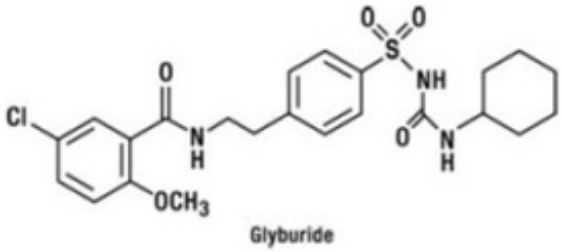
Metformin

Overdose of metformin has occurred, including ingestion of amounts greater than 50 g. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. 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.

11 DESCRIPTION

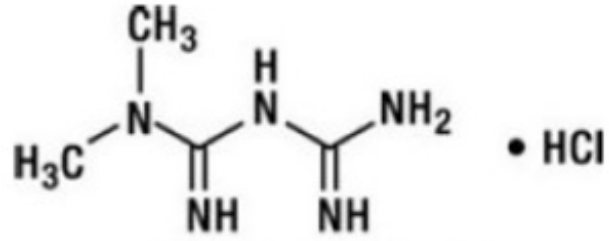
Glyburide and metformin hydrochloride tablets, USP for oral use contain glyburide USP and metformin hydrochloride USP.

Glyburide USP is a sulfonylurea and its chemical name is 1-[[p-[2-(5-chloro-*o*-anisamido) ethyl]phenyl]sulfonyl]-3-cyclo-hexylurea. Glyburide USP is a white to off-white crystalline compound with molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494.01. The structural formula is represented below.



Glyburide

Metformin hydrochloride USP is a biguanide in hydrochloride salt form and its chemical name is N,N-dimethylimidodicarbonimidic diamide monohydrochloride. It is a white to off-white crystalline compound with molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin is 6.68. The structural formula is as shown:



Metformin Hydrochloride

Glyburide and metformin hydrochloride tablets, USP are available in film-coated containing 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 film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, hypromellose, propylene glycol, polysorbate 80, talc, titanium dioxide and FD&C Yellow#6 aluminum lake. The 1.25 mg/250 mg and 5 mg/500 mg strengths also contain D&C Yellow#10 aluminum lake; The 2.5 mg/500 mg strength also contains FD&C Red#40 aluminum lake.

Meets USP Dissolution Test 2

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Glyburide primarily lowers blood glucose by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may decrease.

12.3 Pharmacokinetics

Absorption

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 standard particle-size glyburide coadministered with metformin. The pharmacokinetics of metformin HCl component of glyburide and metformin hydrochloride was consistent with that of metformin HCl coadministered with glyburide.

Effect of food: 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 effect of food on the pharmacokinetics of the metformin component of glyburide and metformin hydrochloride was indeterminate. However, food is known to decrease the extent of and slightly delay the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of

metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Glyburide

Single-dose studies with standard particle-size glyburide 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 standard particle-size glyburide products.

Metformin

The absolute bioavailability of a 500 mg metformin 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. 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.

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

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.

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

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 4) 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

Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either glyburide or metformin [see *Warnings and Precautions (8.7)*].

Renal Impairment

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

In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (Table 4); [see *Dosage and Administration (2), Contraindications (4),* and *Warnings and Precautions (5.1)*].

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 (Table4); [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.1)*].

Table 4: Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin HCl

Subject Groups: Metformin HCl Dose[a] (number of subjects)	**C_{max}[b] (mcg/mL)**	**T_{max}[c] (hrs)**	**Renal Clearance (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:	2.45 (±0.70)	2.71 (±1.05)	412 (±98)

850 mg SD (12)			
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

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).

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 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.

No evidence of impaired fertility was observed when doses up to 500 times the maximum recommended human dose of 20 mg of glyburide, based on body surface area comparisons, were administered to rats in reproduction studies.

Metformin

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommendation human daily dose of 2000 mg on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

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

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons.

14 CLINICAL STUDIES

Patients with Inadequate Glycemic Control on Diet and Exercise Alone

In a 20-week, double-blind, placebo-controlled, multicenter U.S. clinical study, involving 806 drug-naive patients with type 2 diabetes, whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] below 240 mg/dL, baseline hemoglobin A_{1c} [HbA1c] between 7% and 11%), were randomized to receive initial therapy with placebo, 2.5 mg glyburide, 500 mg metformin HCl, 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 to a maximum of 4 tablets daily as needed to reach a target FPG of 126 mg/dL. Study data at 20 weeks are summarized in Table 5.

Table 3: Mean Change in Hemoglobin A1c and Fasting Plasma Glucose in Patients Receiving Placebo, Glyburide, Metformin HCl or Glyburide and Metformin Hydrochloride at 20 Weeks

	Placebo	**Glyburide 2.5 mg tablets**	**Metformin HCl 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[a]	−1.31[a]
Difference from				−0.24[b]	−0.29[b]

Glyburide					
Difference from Metformin				−0.44[b]	−0.49[b]
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[a]	−44.7[a]
Difference from Glyburide				−5.8[c]	−4.5[c]
Difference from Metformin				−20.3[c]	−18.9[c]
Final HbA1c 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%

[a] p<0.001
[b] p<0.05
[c] p=NS

Mean baseline body weight was 87 kg, 87 kg, 89 kg, 89 kg and 87 kg in the placebo, glyburide 2.5mg, metformin 500mg, glyburide and metformin hydrochloride 1.25mg/250mg and 2.5mg/500mg arms, respectively. Mean change in body weight from baseline to week 20 was -0.7 kg, +1.7 kg, -0.6 kg, +1.4 kg and +1.9 in the placebo, glyburide, metformin, glyburide and metformin hydrochloride 1.25mg/250mg and 2.5mg/500mg arms, respectively.

Patients with Inadequate Glycemic Control on Sulfonylurea Alone

In a 16-week, double-blind, active-controlled U.S. clinical study, a total of 639 patients with type 2 diabetes not adequately controlled (mean baseline HbA1c 9.5%, mean baseline FPG 213 mg/dL) while being treated with at least one-half the maximum dose of a sulfonylurea (e.g., glyburide 10 mg, glipizide 20 mg) were randomized to receive glyburide (fixed dose, 20 mg), metformin HCl (500 mg), glyburide and metformin hydrochloride 2.5 mg/500 mg, or glyburide and metformin hydrochloride 5 mg/500 mg. The doses of metformin HCl and glyburide and metformin hydrochloride were titrated to a maximum of 4 tablets daily as needed to achieve FPG <140 mg/dL. Study data at 16 weeks are summarized in Table 6.

Table 4: Mean Change in Hemoglobin A1c and Fasting Plasma Glucose in Patients Receiving Glyburide, Metformin HCl or Glyburide and Metformin Hydrochloride at 16 Weeks

	Glyburide 5 mg tablets	**Metformin HCl 500 mg tablets**	**Glyburide and Metformin Hydrochloride 2.5 mg/500 mg**	**Glyburide and Metformin Hydrochloride 5 mg/500 mg**

			tablets	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[a]	−1.70[a]
Difference from Metformin			−1.90[a]	−1.91[a]
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	221.0	233.8	169.6	161.1
Difference from Glyburide			−51.3[a]	−59.9[a]
Difference from Metformin			−64.2[a]	−72.7[a]
Final HbA1c 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%

[a] p<0.001

Weight gain due to glyburide was comparable in all three exposed groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Glyburide and Metformin Hydrochloride Tablets USP, 5 mg/500 mg: Yellow, capsule shaped, biconvex, film-coated tablet with ‘A’ debossed on one side and ‘48’ on the other side.

Bottles of 30	NDC 68788-8341-3
Bottles of 60	NDC 68788-8341-6
Bottles of 90	NDC 68788-8341-9
Bottles of 100	NDC 68788-8341-1
Bottles of 120	NDC 68788-8341-8

Store at 20° to 25°C (68º to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in light-resistant containers.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Lactic Acidosis:

Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its

development. Advise patients to discontinue glyburide and metformin hydrochloride immediately and to promptly notify their healthcare provider practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about importance of regular testing of renal function while receiving glyburide and metformin hydrochloride. Instruct patients to inform their doctor that they are taking glyburide and metformin hydrochloride prior to any surgical or radiological procedure, as temporary discontinuation may be required [see *Warnings and Precautions (5.1)*].

Hypoglycemia:

Inform patients that hypoglycemia may occur when taking glyburide and metformin hydrochloride. Explain to patients the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development [see *Warnings and Precautions (5.2)*].

Cardiovascular Mortality:

Inform patients that 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. Inform patients of the potential risks and benefits of glyburide and of alternative modes of therapy [see *Warnings and Precautions (5.3)*].

Vitamin B_{12} Deficiency:

Inform patients about importance of regular hematological testing while receiving glyburide and metformin hydrochloride [see *Warnings and Precautions (5.5)*].

Females of Reproductive Age:

Inform females that treatment with glyburide and metformin hydrochloride may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [see *Use in Specific Populations (8.3)*].

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Revised: 02/2019

PATIENT INFORMATION

Glyburide and Metformin Hydrochloride Tablets USP, for oral use

(glye’ bure ide and met for’ min hye” droe klor’ ide)

What is the most important information I should know about glyburide and metformin hydrochloride tablets?

Glyburide and metformin hydrochloride tablets can cause serious side

effects, including:

Lactic Acidosis. Metformin hydrochloride, a medicine in glyburide and metformin hydrochloride tablets, can cause a rare, but serious, side effect called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital.

Stop taking glyburide and metformin hydrochloride tablets and call your healthcare provider right away if you get any of the following symptoms of lactic acidosis:

- feel very weak and tired
- have unusual sleepiness or sleep longer than usual
- have unusual (not normal) muscle pain
- feel cold, especially in your arms and legs
- have trouble breathing
- feel dizzy or lightheaded
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis if you:

- have severe kidney problems. **“See “Do not take glyburide and metformin hydrochloride tablets if you:”**
- have liver problems.
- drink a lot of alcohol (very often or 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 certain x-ray tests with injectable dyes or contrast agents.
- have surgery or other procedures for which you need to restrict the amount of food and liquid you eat and drink.
- have congestive heart failure.
- have a heart attack, severe infection, or stroke.
- are 65 years of age or older.

Tell your healthcare provider if you have any of the problems in the list above.

Tell your healthcare provider that you are taking glyburide and metformin hydrochloride tablets before you have surgery or x-ray tests.

Your healthcare provider may need to stop glyburide and metformin hydrochloride tablets for a while if you have surgery or certain x-ray tests.

Glyburide and metformin hydrochloride tablets can have other serious side effects. See **“What are the possible side effects of glyburide and metformin hydrochloride tablets?”**

What is glyburide and metformin hydrochloride tablets?

- Glyburide and metformin hydrochloride tablets are a prescription medicine that contains glyburide (sulfonylurea) and metformin hydrochloride. Glyburide and

metformin hydrochloride tablets is used with diet and exercise to help control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- It is not known if glyburide and metformin hydrochloride tablets are safe and effective in children under 18 years of age.

Do not take glyburide and metformin hydrochloride tablets if you:

- have severe kidney problems.
- are allergic to metformin hydrochloride, glyburide or any of the ingredients in glyburide and metformin hydrochloride tablets. See the end of this Patient Information leaflet for a complete list of ingredients in glyburide and metformin hydrochloride tablets.
- have a condition called metabolic acidosis, including diabetic ketoacidosis (high levels of certain acids called “ketones” in your blood or urine).
- take bosentan.

Before taking glyburide and metformin hydrochloride tablets tell your healthcare provider about all medical conditions, including if you:

- have a history or risk for diabetic ketoacidosis. See **“Do not take glyburide and metformin hydrochloride tablets if you:”**
- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are 65 year of age or older.
- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking.
- have or any members of your family have glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- are taking insulin or another sulfonylurea medicine.
- are pregnant or plan to become pregnant. It is not known if glyburide and metformin hydrochloride tablets will harm your unborn baby. You should not take glyburide and metformin hydrochloride tablets during the last 2 weeks of your pregnancy. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are a woman who has not gone through menopause (premenopausal) who does not have periods regularly or at all. Glyburide and metformin hydrochloride tablets can cause the release of an egg from an ovary in a woman (ovulation). This can increase your chance of getting pregnant.
- are breastfeeding or plan to breastfeed. It is not known if glyburide one of the medicines in glyburide and metformin hydrochloride tablets passes into your breast milk. Metformin the other medicine in glyburide and metformin hydrochloride tablets can pass into your breastmilk. Talk with your healthcare provider about the best way to feed your baby while you take glyburide and metformin hydrochloride tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Glyburide and metformin hydrochloride tablets may affect the way other medicines

work, and other medicines may affect how glyburide and metformin hydrochloride tablet works.

How should I take glyburide and metformin hydrochloride tablets?

- Take glyburide and metformin hydrochloride tablets exactly as your healthcare provider tells you.
- glyburide and metformin hydrochloride tablets should be taken 2 times each day with meals to help decrease an upset stomach side effect and avoid hypoglycemia.
- If you are taking colesevelam and glyburide and metformin hydrochloride tablets, take your glyburide and metformin hydrochloride tablets at least 4 hours before taking your colesevelam.
- Your healthcare provider should do blood tests to check how well your kidneys are working before and during your treatment with glyburide and metformin hydrochloride tablets.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1c.
- Low blood sugar (hypoglycemia) can happen more often when glyburide and metformin hydrochloride tablets is taken with certain other diabetes medicines. Talk to your healthcare provider about how to prevent, recognize, and manage low blood sugar. See **“What are the possible side effects of glyburide and metformin hydrochloride tablets?”**
- Check your blood sugar as your healthcare provider tells you to.
- If you take too much glyburide and metformin hydrochloride, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking glyburide and metformin hydrochloride tablets?

- Do not drink a lot of alcoholic drinks while taking glyburide and metformin hydrochloride tablets. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase the chance of getting lactic acidosis.
- Do not drive, operate machinery, or do other dangerous activities until you know how glyburide and metformin hydrochloride tablets affects you.

What are the possible side effects of glyburide and metformin hydrochloride tablets?

Glyburide and metformin hydrochloride tablets can cause serious side effects, including:

- See **“What is the most important information I should know about glyburide and metformin hydrochloride tablets?”**
- **low blood sugar (hypoglycemia). Low blood sugar is a serious, but common side effect of glyburide and metformin hydrochloride tablets.** If you take glyburide and metformin hydrochloride tablets with another medicine that can cause low blood sugar, such as insulin, you have a higher risk of getting low blood sugar. The dose of insulin or other diabetic medicines may need to be lowered while you take glyburide and metformin hydrochloride tablets. Signs and symptoms of low blood sugar may include:

- headache
- hunger
- dizziness
- drowsiness
- fast heartbeat
- sweating
- weakness
- confusion
- blurred vision
- irritability
- shaking or feeling jittery
- anxiety
- slurred speech
- mood changes

- **increased risk of cardiovascular deaths.** Taking oral hypoglycemic medicines like glyburide and metformin hydrochloride tablets to treat diabetes have increased the risk of death from heart disease or stroke compared to treating diabetes with diet alone or diet and insulin.
- **hemolytic anemia.** People with G6PD deficiency who take glyburide and metformin hydrochloride tablets may develop hemolytic anemia (fast breakdown of red blood cells).
- **low vitamin B_{12} (vitamin B_{12} deficiency).** Using glyburide and metformin hydrochloride tablets may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} levels before. Your healthcare provider may do blood tests to check your vitamin B_{12} levels.

The most common side effects of glyburide and metformin hydrochloride tablets include:

- diarrhea
- vomiting
- headache
- stomach pain
- nausea
- dizziness

These are not all the possible side effects of glyburide and metformin hydrochloride tablets.

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

How should I store glyburide and metformin hydrochloride tablets?

- Store glyburide and metformin hydrochloride tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep glyburide and metformin hydrochloride tablets and all medicines out of the reach of children.

General information about the safe and effective use glyburide and

metformin hydrochloride tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use glyburide and metformin hydrochloride tablets for a condition for which it was not prescribed. Do not give glyburide and metformin hydrochloride tablets to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about glyburide and metformin hydrochloride tablets that is written for health professionals.

What are the ingredients in glyburide and metformin hydrochloride tablets?

Active ingredients: glyburide and metformin hydrochloride.

Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, hypromellose, propylene glycol, polysorbate 80, talc, titanium dioxide and FD&C Yellow#6 aluminum lake. The 1.25 mg/250 mg and 5 mg/500 mg strengths also contain D&C Yellow#10 aluminum lake; The 2.5 mg/500 mg strength also contains FD&C Red#40 aluminum lake.

For more information, call Rising Health, LLC at 1-833-395-6928.

Distributed by:
Rising Health, LLC
Saddle Brook, NJ 07663

Made in India
Code: TS/DRUGS/19/1993

This Patient Package Insert has been approved by the U.S. Food and Drug Administration

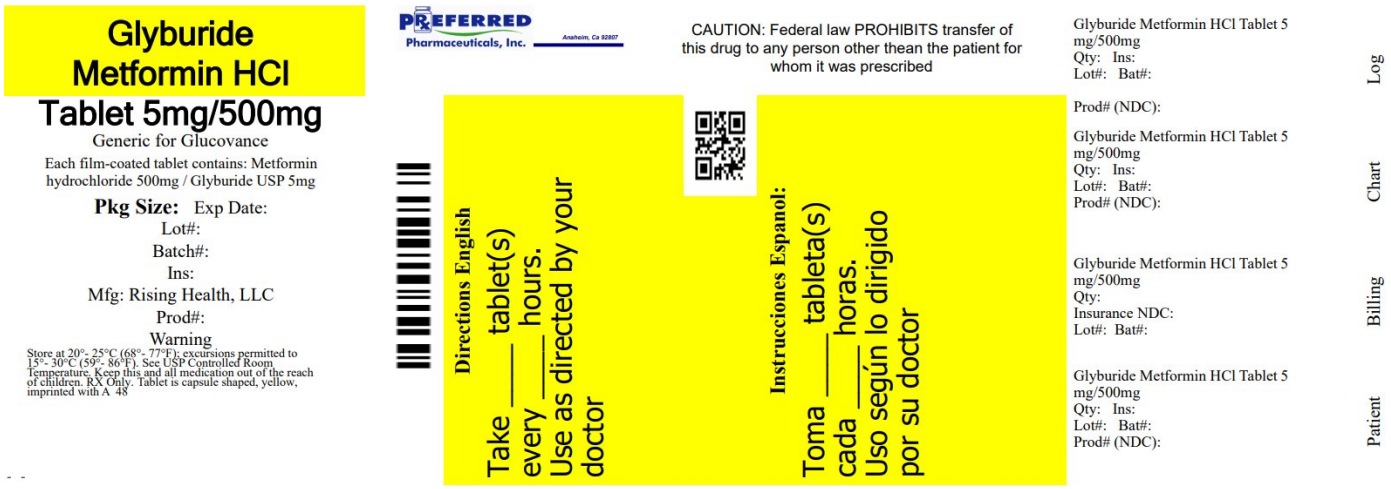
Revised: 02/2019

Repackaged By: Preferred Pharmaceuticals Inc.

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 5 mg/500 mg

Rising® **NDC 68788-8341**
Glyburide and
Metformin
Hydrochloride
Tablets, USP
5 mg/500 mg
Rx only

Repackaged By: Preferred Pharmaceuticals Inc.



GLYBURIDE AND METFORMIN HYDROCHLORIDE

glyburide and metformin hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68788-8341(NDC:57237-025)
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
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE K90 (UNII: RDH86HJV5Z)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	CAPSULE (Biconvex)	**Size**	17mm

Flavor		**Imprint Code**	A;48
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68788-8341-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/10/2023	
2	NDC:68788-8341-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	02/10/2023	
3	NDC:68788-8341-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	02/10/2023	
4	NDC:68788-8341-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/10/2023	
5	NDC:68788-8341-8	120 in 1 BOTTLE; Type 0: Not a Combination Product	02/10/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077870	02/10/2023	

Labeler - Preferred Pharmaceuticals Inc. (791119022)

Registrant - Preferred Pharmaceuticals Inc. (791119022)

Establishment

Name	Address	ID/FEI	Business Operations
Preferred Pharmaceuticals Inc.		791119022	REPACK(68788-8341)

Revised: 5/2024 Preferred Pharmaceuticals Inc.