

ADRIDE®-M

Metformin Hydrochloride (ER) 500 mg and Glimepiride 2 mg Tablets

COMPOSITION

Each Uncoated Bi-layered tablet contains:
Metformin Hydrochloride USP 500 mg
(In Extended Release Form)
Glimepiride USP 2 mg
Excipients : Hypromellose, Microcrystalline cellulose, Colloidal anhydrous silica, Povidone K-90, Magnesium stearate, Purified Talc, Sodium starch Glycolate, Ferric oxide red, Povidone K-30

CLINICAL PHARMACOLOGY

ADRIDE-M contains two oral anti-hyperglycemic drugs glimepiride and metformin hydrochloride used in the management of type-2 diabetes (NIDDM).

Pharmacodynamics

Glimepiride: The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra-pancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride.

Metformin: Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), 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. Hence, the combination of glimepiride and metformin Extended Release complements each other and provides better glycemic control in management of type-2 diabetes and probably in the prevention of its associated macrovascular and microvascular complications.

Pharmacokinetics

Absorption

Glimepiride: After oral administration, glimepiride is completely absorbed from the GI tract. Studies have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean T max (time to reach Cmax) was slightly increased (12%) and the mean Cmax and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Metformin Extended Release: The absolute bioavailability of a metformin 500-mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of Metformin Extended Release, Cmax is achieved within 4-8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. Both high and low fat meals had the same effect on the pharmacokinetics of sustained release.

Distribution

Glimepiride: After intravenous dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg). Protein binding was greater than 99.5%.

Metformin Extended Release: Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. Distribution studies with metformin sustained release have not been conducted. At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 µg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism

Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxy derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytochrome enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent; whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

Metformin Extended Release: Metformin studies with metformin Extended Release have not been conducted. However, intravenous single-dose studies in normal subjects demonstrate that metformin immediate release does not undergo hepatic metabolism or biliary excretion.

Excretion

Glimepiride: When 14C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in the feces. No parent drug was recovered from urine or feces.

Metformin: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearance of metformin 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.

INDICATIONS

ADRIDE-M is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type-2 diabetes who are already treated with a combination of glimepiride and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to glimepiride alone and require additional glycaemic control.

DOSAGE & ADMINISTRATION

General

Dosage should be individualized on the basis of both effectiveness and tolerance. The combination should be given once daily with meals and should be started at a dose. The initial recommended dose is one tablet once daily with breakfast or first meal of the day. Starting dose for patients inadequately controlled on metformin monotherapy

ADRIDE-M may be initiated once daily, and gradually titrated after assessing the therapeutic response. Starting dose for patients who initially responded to glimepiride monotherapy and require additional glycaemic control based on the initial starting dose of glimepiride (1 or 2 mg). ADRIDE-M may be initiated once daily, and gradually titrated after assessing the therapeutic response.

Starting dose for patients switching from combination therapy of glimepiride plus metformin as separate tablets ADRIDE-M may be initiated based on the dose of glimepiride and metformin already being taken.

Maximum Recommended Dose

The maximum recommended dose for glimepiride is 8 mg daily. The maximum recommended daily dose for metformin Extended Release is 2550 mg in adults.

MODE OF ADMINISTRATION

Adride M should be swallowed without chewing with some liquid.

CONTRAINDICATIONS

Renal or hepatic dysfunction as suggested by serum creatinine levels >1.5 mg/dL, levels >2.1 mg/dL if there is a known creatinine clearance, which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. Hepatic impairment. Known hypersensitivity to this product or any of its components. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin. Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function.

WARNING & PRECAUTIONS

Cardiac effects: The administration of oral hypoglycemic drugs (tolbutamide) has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. In view of close similarities between the oral hypoglycemic drugs, this warning also applies for glimepiride.

Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Cardiac effects: The administration of oral hypoglycemic drugs (tolbutamide) has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. In view of close similarities between the oral hypoglycemic drugs, this warning also applies for glimepiride.

Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency and congestive heart failure. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

Medical emergency: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy, when it occurs